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Impact of antenatal exposure to a mixture of persistent organic pollutants on intellectual development☆,☆☆,☆☆☆,☆☆☆☆

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ABSTRACT

Objective: Strong experimental evidence exists that several endocrine disrupting chemicals (EDCs) have neurobehavioral toxicity. However, evidence of associations between prenatal exposure and child's cognitive development is inconsistent. Moreover, toxicants are generally analyzed one by one without considering aggregate effects. We examined here the impact of a prenatal exposure to a mixture of persistent organic pollutants (POPs) on intellectual abilities in preschool children, and compared their effects to those described in the literature.

Methods: Sixty-two children were included in a longitudinal cohort. Four organochlorine pesticides, four polychlorinated biphenyls (PCBs) and seven perfluorinated compounds (PFCs) were measured in cord blood. Intellectual abilities were assessed at 6 years of age using the Wechsler Preschool and Primary Scale of Intelligence 4th ed. (WPPSI-IV). We examined the associations between a mixture of POPs and cognitive performances using principal components approach (PCA) and weighted quantile sum (WQS) regression taking sex difference into account.

Results: No negative correlation was found when analyses were performed on boys and girls together. In sex-stratified analyses, lower scores in full scale intelligence quotient (FSIQ) and fluid reasoning index (FRI) were observed in boys most exposed to a mixture of POPs. Increase of the WQS index was also associated with lower verbal comprehension index (VCI) scores in girls only. No other negative correlation was found using both WQS and PCA models.

Conclusion: Our study suggests deleterious associations between antenatal exposure to a mixture of POPs and sex-specific cognitive level, clarifying some trends described in the literature.

1. Introduction

Endocrine Disrupting chemicals (EDCs) are exogenous substances present in the environment which alter the functions of the endocrine system, causing adverse health effects in an intact organism, or its offspring, or (sub) population (Becher et al., 2012). Among them, persistent organic pollutants (POPs) are a group of synthetic compounds that are or have been widely used in consumer, agricultural and industrial products. This widespread utilization resulted in ubiquitous detection of organochlorine pesticides, such as 4,4′-dichlorodiphenyldichloroethylene (4,4′-DDE), polychlorinated biphenyls (PCBs) and perfluoroalkyl compounds (PFCs) in the serum of the general population in Europe and in the US (Patterson et al., 2014). Although the use or production of some of those compounds has been banned or restricted, these POPs are bioaccumulative and have a long half-life. Thus, they are still detected in wildlife and humans worldwide

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(Patterson et al., 2014). These compounds are also detected in the blood of pregnant women and in the amniotic fluid and umbilical cord blood indicating the fetal contamination by POPs crossing the placenta (Bradman et al., 2003).

Neurodevelopment is a complex process that starts as early as the second gestational week and continues through adolescence in humans (Sadler, 2005). Vital biological processes take place during in utero and early postnatal life to ensure normal brain development (Rice and Barone, 2000). It is recognized that disruption of these processes, in particular by environmental risk factors (e.g. ante or perinatal infection, neonatal maladaptation, trauma and poor stimulation), is deleterious for the nervous system development and is linked to cognitive deficits and socioemotional, or behavioural maladjustment in children (Carlsson et al., 2021).

Exposure to endocrine disrupting chemicals during this critical period of human development increases the risk of adverse health effects including neurodevelopmental disorders as illustrated by a growing number of epidemiological studies conducted worldwide and indicating association between perinatal exposure to POPs and cognitive impairment.

Accidental mass poisonings due to ingestion of PCB-contaminated cooking oil in Japan in 1968 and Taiwan in 1979 illustrated the neurobehavioral toxicity of PCBs as it resulted in a number of clinical morbidities, including adverse neurodevelopment in response to prenatal exposure (Chen et al., 1992; Chen et al., 1994). These incidents were the basis for classifying PCBs and other organochlorine compounds as suspected developmental neurotoxicants. Epidemiological studies suggest that prenatal exposure impairs the development of cognitive abilities. Most papers found associations between developmental exposure to PCBs and impairment of at least one cognitive domain, as attested by poorer scores on overall intelligence (Jacobson et al., 1990, 1996, 2002; Guo et al., 1995; Patadin et al., 1999; Boersma, 2001; Walkowiak et al., 2001; Vreugdenbil et al., 2002; Lai et al., 2002; Stewart et al., 2008; Park et al., 2010; Forns et al., 2012; Tatsuta et al., 2014; Lyall et al., 2018; Ruel et al., 2019) and verbal functions (Jacobson et al., 1990, 1996; Forns et al., 2012). To a lesser extent, other cognitive functions, such as memory (Jacobson et al., 1990; Forns et al., 2012), attention (Neugebauer et al., 2015) and perceptual performance (Forns et al., 2012), also appear to be negatively impacted (Appendix C).

Given their extreme persistence in the environment, PFCs are currently one of the main public health concerns regarding EDCs. However, there are relatively few studies concerning the impact of prenatal exposure to PFCs on intellectual development (Appendix B). Most studies have shown that children who were most exposed to PFC during the fetal period have a lower mental score at 3 years of age (Goudarzi et al., 2016; Oh et al., 2021; Luo et al., 2022a; Zhou et al., 2023). Developmental exposure to PFCs has been associated with an absence (Spratel et al., 2020; Carrizosa et al., 2021) or even a beneficial effect (Lyall et al., 2018; Stein et al., 2013; Harris et al., 2018; Vuong et al., 2019) on intellectual abilities in older children. Nevertheless, in Taiwan, prenatal exposure to PFUnDA was associated with lower Full-Scale Intelligence Quotient (FSIQ) scores in children at age 5 years and prenatal exposure to seven types of PFCs were associated with a reduction of child's IQ scores with, PFNA only reaching significance (Wang et al., 2015). In a U.S. birth cohort study, verbal IQ scores were lower among children exposed to higher prenatal concentrations of PFOA, although the dose-response pattern appeared non-linear with weaker associations observed for the third and fourth quartiles (Harris et al., 2018). Finally, in a more recent study, Goodman et al. reported that an antenatal exposition to PFOA, PFOS or PFHxS was inversely associated with performance IQ on the WPPSI at 3–4 years, but only in males (Goodman et al., 2023).

A limited number of studies also suggested some neurotoxicity of the widespread insecticide dichlorodiphenyltrichlorethan (DDT). A significant negative association was found between cord serum and 4.4′-DDE levels, which indicated DDT contamination and cognitive development before 3 years of age in a small spanish cohort (Ribas-Fito et al., 2003). Among older children, a reduction in the overall cognitive development has been highlighted at 3.5–5 years of age (Torres-Sanchez et al., 2013). However, although the risk of a clinical diagnosis of intellectual disability seems higher in patients exposed to 4,4′-DDE (Lyall et al., 2017), many other studies did not found impairment in mental development (Forns et al., 2012; Ruel et al., 2019; Gladen et al., 1988; Rogan et al., 1991; Eskenazi et al., 2006, 2018; Torres-Sanchez et al., 2007, 2009; Bahena-Medina et al., 2011; Jusko et al., 2012; Yamazaki et al., 2017; Vermeir et al., 2021) or global cognitive score (Jusko et al., 2012; Vermeir et al., 2021; Ribas-Fito et al., 2006; Gladen et al., 1991; Roze et al., 2009; Kyriklaki et al., 2016; Kalloo et al., 2021) (Appendix A).

IQ point loss, even moderate, can have far-reaching socio-economic consequences for the general population. Each year in Europe, it is estimated that 13.0 million IQ points are lost, with 59 300 cases of intellectual disability attributable to prenatal organophosphate exposure. The cost related to this contamination ranges from €46.8 to 195 billion annually (Trasande et al., 2015). Thus, estimating the burden and disease related to exposure to other EDCs remains essential.

However, the majority of studies investigating the associations between prenatal exposure to these chemicals and cognitive neurodevelopment in children have focused on single exposure models (Lazarevic et al., 2019). This approach has some limitations (Braun et al., 2016). First, the use of a large number of individual parameters would create some false positive results when performing multiple comparisons. Secondly, as co-occurring chemical exposures may interact with each other and have additive or synergistic effects, this approach may underestimate the realistic toxicity associated with chemical mixtures in the natural environment. Finally, correlations between chemicals with common sources, exposure pathways, or metabolic processes, can induce multicollinearity when analyzed simultaneously. Consequently, it may be difficult to assess the relative importance of individual exposures, and therefore to separate potential etiological agents from co-pollutant confounders and redundant variables.

Therefore, the present study aimed at investigating associations between mixture of prenatal POPs concentration and intellectual abilities at 6 years of age using two adapted statistical approaches. As intelligence is a complex construct resulting from the interactions between different cognitive skills (verbal, visuo-spatial, working memory, processing speed), general but also specific cognitive domains were analyzed and compared to the current literature. As previous studies have reported sex-specific associations between cognitive outcomes and a number of environmental chemicals included in our analysis (Kern et al., 2017), girls and boys scores will be examined together and separately.

2. Methods

2.1. Study participants

The EPOPEE (*Effet des Polluants Organiques Persistants sur l'Evolution des Enfants*) cohort was created from children born between 2014 and 2016 in the University Hospital of Liege (Belgium).

Recruitment process and quantification of pollutants in cord blood were already described in Dufour et al. (2018). Briefly, every woman admitted for delivery was asked to participate in a study on neonatal asphyxia biomarkers as first intention, and impact of EDCs on thyroid function as second intention. Umbilical cord blood samples were collected from 281 participants who gave their consent, centrifugated and stored at −80 °C immediately after delivery. Exclusion criteria included insufficient serum volume (<0.5 ml), absence of TSH level record, and congenital hypothyroidism. All patients were born vaginally at term, without notable antenatal or perinatal history. Subsequently, parents of the children of this cohort were contacted in order to take part in the current study and to complete a cognitive assessment. Of the 212 original participants 62 were available for testing at 6 years of age (M = 5.75; SD = 0.32) before entering elementary school. This study has been approved by the local biomedical Ethics Committee.

2.2. Exposure

Four organochlorine pesticides, namely β-hexachlorohexane (β-HCH), hexachlorobenzene (HCB), trans-nonachlor and 4,4′-dichlorodiphenyldichloroethylene (4,4′-DDE), 4 PCBs (PCBs-118, -138, −153, and −180), and 7 PFCs (perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroheptanoic acid (PFHpA) and perfluoroundecanoic acid (PFUdA)) were analyzed in cord blood. The detailed analytical method has been described in a previous publication (Dufour et al., 2018). For each of them, the limit of quantification (LOQ) was determined during the validation process and was defined as the smallest concentration measured with a maximal incertitude not exceeding 40%.

In order to consider representative toxicants in our population, substances for which less than 20% of the values were above the LOQ were eliminated from the analysis (namely β-HCH, HCB, trans-nonachlor, PCB 118, PFDA, PFHpA and PFUdA). Values below the LOQ of each POPs, were replaced by a random value from a triangular distribution between zero and the LOQ. Finally, a logarithmic transformation was performed to reduce dispersion and satisfy normality assumptions of our models.

2.3. Cognitive ability assessment

Children's cognitive abilities were assessed using the Wechsler Preschool and Primary Scale of Intelligence 4th ed. (WPPSI-IV; Wechsler Intelligence Scale for Children) , a test validated in French and used to measure the intelligence quotient (IQ) of children from 2.5 to 7.7 years old.

The WPPSI-IV provides a general measure of intellectual efficiency, namely the Full IQ Scale (FSIQ),which relies on 10 core subtests. These subtests (listed with their respective composite) are used to calculate five indexes: (1)Verbal Comprehension Index (VCI) (Information, Similarities) which explores general knowledge and verbal conceptual reasoning, (2)Visual Spatial Index (VSI) (Block Design, Object Assembly) which analyses visuo-spatial and constructive abilities requiring manipulation, (3) Fluid Reasoning Index (FRI) (Matrix Reasoning, Picture Concepts) which tests non-verbal analogical and conceptual reasoning, (4) Working Memory Index (WMI) (Picture Memory, Zoo Locations) which assesses visual and verbal short-term memory and the executive component, (5) Processing Speed Index (PSI) (Bug Search, Cancellation) which examines processing speed though visual target identification tasks involving visual attention. All indices and FSIQ have a population mean of 100 ± 15, with higher scores indicating better performance.

2.4. Covariates

Information on covariates was obtained from questionnaires completed by the parents during the tests and from maternal birth records. These data included maternal age at delivery, pre-pregnancy body mass index (BMI), parity, duration of breastfeeding, parental education assessed by the level of study achieved, parental smoking status, maternal alcohol consumption during pregnancy, gestational age, child birth weight, age at the moment of testing and child sex. Children's thyroid function assessed by thyroid stimulating hormone (TSH) measurement performed 3 days after birth was also considered.

Among these covariates, only those associated with IQ scores were selected ($p < 0.05$). To identify these covariates, Student T-tests were performed to assess the effect of dichotomic variables on IQ measures (e.g. parental smoking status), while univariate regression models were used for continuous variables (e.g. birth weight).

2.5. Statistical analysis

Principal Component Analysis (PCA) was first used to reduce the set of original variables and to extract a smaller number of principal components (PCs)(Lazarevic et al., 2019; Frenoy et al., 2022). PCs explaining at least 50% of the variance cumulatively were selected and used to predict the outcome of interest by means of classic regression models (Agay-Shay et al., 2015; O'Rourke and Hatcher, 2013).

Using the R package "gWQS", generalized Weighted quantile sum (WQS) approach was used to summarize the overall exposure to the mixture of POPs by estimating a body burden index (the WQS index) (Renzetti et al., 2019). This score was achieved through 100 times bootstrap sampling on the full data with constraints of negative coefficient. The final index was included in a regression model to evaluate the overall effect of the mixture on the outcomes of interest (Zhang et al., 2019; Carrico et al., 2015). At the end, to select the chemicals effectively associated with the outcome, significant components in the index were identified by comparing the average weight for each component to a sectioned threshold parameter, τ. In our analysis conducted with 8 components, we used $\tau = 1/8 = 0.125$. This second analysis was only performed in children in whom all POPs were measured ($n = 55$). In order to demonstrate the stability of our data and to approach the repeated holdout strategy described by Tanner et al. (2020), the standard WQS analysis was repeated (rh = 100) to simulate a distribution of validated results from the underlying population. The mean and the coefficient inference (95% confidence intervals (CI)) of the WQS index β coefficient and the chemical weights in relevant situations were considered (Supplementary data – Table 6).

Finally, to examine the effect of gender on the associations between co-exposure to POPs and IQ scores, we included an interaction term between gender and the mixture index in the WQS model; this make it possible to estimate the direct effect of the multiplicative interaction of these variables and to conduct an explicit hypothesis test (Supplementary data Table 7). However, interpreting the beta coefficients and the contribution of each POP to the overall mixture effect is complicated due to the infinite ways such an effect could be obtained with changes in chemical exposure; we therefore chose to examine associations in boys and girls independently.

The statistical analyses were performed using RStudio (version 3.4.2; R Project for Statistical Computing). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Descriptive analyses

In total, 30% of the 212 children of the original cohort participated in this follow-up study. There was no difference between the participating and non-participating groups regarding POP detected levels.

Table 1 summarizes the characteristics of the studied cohort. Mothers averaged 30 years old at delivery, and generally did not smoke or consume alcohol during pregnancy. Over half of the women were primiparous. The average duration of breastfeeding was 8 months. Most included parents had at least a high school diploma. All children were born at term with an average weight of 3312g. Fifty-four percent of the 62 participants were males. The average age of children at testing was 5 years and 9 months.

Almost all children in our cohort scored within the normal range, with a mean FSIQ slightly above average (M = 106.54, SD = 11.48). The mean standard score for all indexes fell within the normal range (VCI: M = 111.82, SD = 12.22; VSI: M = 102.64, SD 14.36; FRI: M = 104.73, SD = 10.40; WMI: M = 102.32, SD = 16.32; PSI: M = 102.58, SD = 10.88). The population profile was relatively homogeneous with better abilities in verbal skills, especially for the Similarities subtest.

Table 1
Demographic characteristics and cognitive scores.

Variable	N	N (%)	Mean	SD	Min	Q1	Med	Q3	Max
Sex (male)	62	34 (54)							
Age during tests (years)	62		5.75	0.32	5.08	5.47	5.79	6.02	6.28
Pre-pregnancy BMI (kg/m^2)	61		23.67	4.51	16.35	20.32	22.48	26.62	37.26
Maternal age at delivery (years)	62		30.4	4.4	20.0	28.0	30.0	33.0	42.0
Parity (multiparous)	62	31 (50)							
Gestational age (days)	62		276	9	252	270	278	284	289
Birth weight (kg)	62		3.31	0.50	2.29	2.98	3.30	3.60	5.02
TSH (mUI/L)	61		5.18	3.15	0.10	3.10	4.60	6.70	16.60
Alcohol during pregnancy (>1 serving/month)	62	5 (8)							
Breast feeding (months)	61	53 (87)	8	10	1	3	4	9	52
Smoking parents	62								
None		46 (74)							
Only the father		5 (8)							
Only the mother		6 (10)							
Both		5 (8)							
Parental educational level (> high school)	62								
Mother		45 (72)							
Father		38 (61)							
Both		32 (52)							
Full Scale IQ (FSIQ)	62		106.54	11.48	73	100	107	113	129
Verbal Comprehension Index (VCI)	62		111.82	12.22	89	102	111	120	142
Visual Spatial Index (VSI)	62		102.64	14.36	79	94	100	112	155
Fluid Reasoning Index (FRI)	62		104.73	10.40	89	98	101	109	132
Working Memory Index (WMI)	62		102.32	16.32	70	90	100	114	146
Processing Speed Index (PSI)	62		102.58	10.88	77	97	103	111	123

POP levels are summarized in Table 2. Among organochlorine pesticides, only DDE has a significant detection rate (18%) and was considered for further analysis (Bahena-Medina et al., 2011). PCBs were detected in 84 % of the samples. PCB 118 was never detected while PCBs 138, 153 and 180 were detected in 24 %, 52 % and 78 % of the samples respectively. Finally, PFCs were found in 98 % of the samples. PFOS was detected in 81 % of samples and had the highest serum concentration (mean: 1.16 ng/ml), followed by PFOA (mean: 0.79 ng/ml) detected in 93 % of the samples. The concentrations of PFHxS and PFNA were one order of magnitude lower than those of PFOS, and were detected in 66% and 93% of the sample respectively.

3.2. Selection of covariates

Results showed that FSIQ and FRI significantly varied with birth weight and smoking status of the parents, VCI was related to mother smoking status only, FSIQ and VCI were associated to mother and father education level, and FSIQ was correlated to breast feeding duration. No adjustment factor was found to be related to VSI, WMI and PSI.

3.3. POPs and cognitive outcome

3.3.1. Principal components approach

Pairwise Pearson's correlation coefficients between individual chemical concentrations are shown on Fig. 1A. Analyses indicated that several POP concentrations are highly correlated. To identify uncorrelated components representing the exposure to substances, a PCA was performed on the matrix of log-transformed POP concentrations. Among the PCs highlighted by the analysis, we selected the first three accounting for 24 %, 17 % and 15 % of the total variance respectively; together these PCs explained 56% of the variability. Loading factors for each chemical on each component are presented in Fig. 1B. The first component (Comp 1) captured the largest part of explained variance with high factor loading for PFCs and, to a lesser extent, for 4,4′-DDE and PCB 180 concentrations. The second component (Comp 2) was characterized by high loading factors for all PCBs with a small correlation with 4,4′-DDE. Finally, the third component (Comp 3) exhibited high factor load for 4,4′-DDE.

Finally, multiple linear regression were fitted, with the identified component scores as main exposure variables in the same model. Analyses were performed on the FSIQ and its five indices. All these models were adjusted for the covariates selected above. No negative correlation between exposure to POPs and cognitive tests was observed. Positive correlations were highlighted between the first component and the VSI in the total population. In sex-stratified analyses, positive correlations were found between the first component and the VSI and WMI scores in girls only. Results are presented in Table 3.

3.3.2. WQS model

An increase of the WQS index was associated with lower FSIQ (Coeff = −5.13, SE = 1.91, and p = 0.014) and FRI (Coeff = −2.53, SE = 0.99, and p = 0.018) scores in boys only. A worse VCI score was also identified

Table 2
Exposed population and summary of POPs levels (ng/mL); undetected values have been replaced by values below the limit of quantification (LOQ).

Variable	N	N (%) > LOQ	LOQ	Mean	SD	Min	Q1	Med	Q3	Max
Pesticides										
4,4′-DDE	58	18 (31)	0.41	<LOQ	0.21	<LOQ	<LOQ	<LOQ	0.44	0.96
PCBs										
PCB153	58	30 (52)	0.07	0.07	0.03	<LOQ	<LOQ	0.07	0.09	0.19
PCB138	58	14 (24)	0.15	<LOQ	0.10	<LOQ	<LOQ	<LOQ	<LOQ	0.70
PCB180	58	45 (78)	0.05	0.06	0.02	<LOQ	0.05	0.06	0.07	0.18
PFCs										
PFHxS	59	39 (66)	0.15	0.23	0.18	<LOQ	<LOQ	0.18	0.30	0.94
PFOA	59	55 (93)	0.25	0.79	0.47	<LOQ	0.42	0.75	0.95	2.94
PFNA	59	49 (83)	0.10	0.19	0.11	<LOQ	0.11	0.17	0.24	0.53
PFOS	59	48 (81)	0.50	1.16	1.24	<LOQ	0.61	0.85	1.34	9.21

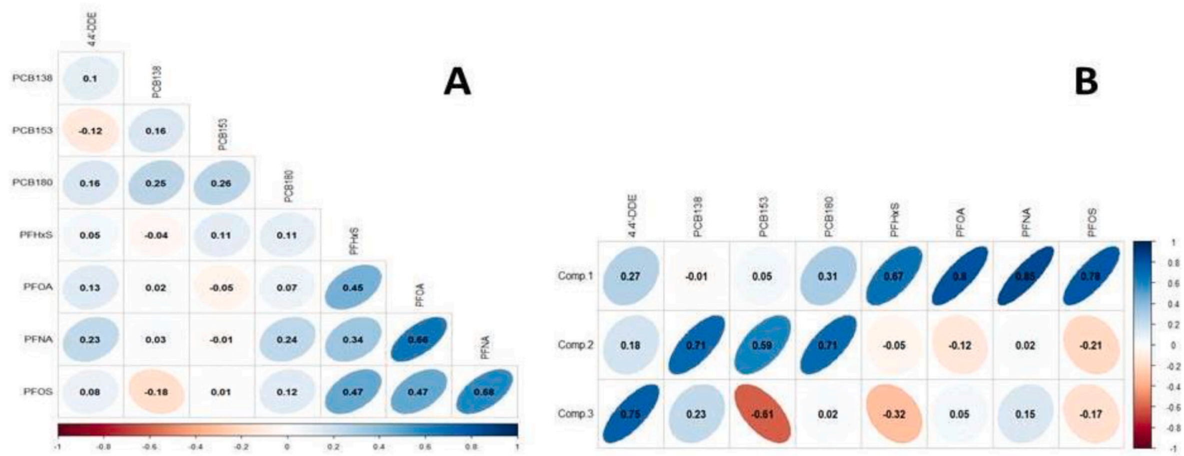

Fig. 1. Pairwise Pearson's correlation coefficients between individual POPs (A) and between the three components and POPs (B); positive correlations are highlighted in blue and negative correlations in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Adjusted multivariate regression between PCA components and IQ scores. Statistically significant results ($p < 0.05$) are in bold.

	FSIQ Coeff (SE)	VCI Coeff (SE)	VSI Coeff (SE)	FRI Coeff (SE)	WMI Coeff (SE)	PSI Coeff (SE)
Comp 1	−0.08 (0.87)	−1.70 (1.04)	**2.64 (1.22)**	−0.05 (0.95)	1.34 (1.37)	−0.59 (0.94)
Girls	1.17 (1.18)	−2.02 (1.48)	**3.81 (1.73)**	1.50 (1.18)	**4.64 (2.10)**	−0.18 (1.37)
Boys	−0.54 (1.21)	−2.19 (1.36)	2.06 (1.61)	−1.51 (1.45)	−0.25 (1.63)	−0.45 (1.28)
Comp 2	0.39 (1.13)	0.23 (1.34)	−1.90 (1.67)	−0.11 (1.19)	−1.05 (1.82)	0.96 (1.27)
Girls	1.41 (1.16)	0.81 (1.79)	2.87 (2.13)	0.73 (1.41)	3.75 (2.57)	1.24 (1.57)
Boys	−1.69 (1.66)	1.13 (1.86)	2.45 (2.26)	−1.03 (1.84)	1.05 (2.26)	−1.92 (1.80)
Comp 3	0.01 (1.28)	0.30 (1.51)	2.50 (1.65)	−0.58 (1.40)	1.34 (2.13)	−0.43 (1.46)
Girls	2.20 (1.51)	1.02 (2.26)	−1.19 (2.75)	1.57 (1.76)	1.34 (3.34)	0.24 (1.99)
Boys	−2.30 (2.02)	0.08 (2.13)	0.38 (3.08)	−2.98 (2.36)	−4.12 (2.91)	−2.75 (2.31)

in girls only (Coeff = −2.42, SE = 1.16, and p = 0.048). (Table 4).

DDE, PFOA, PCB180 and PFOS mostly impacted the FSIQ score in boys. Their weights were 0.391, 0.273, 0.152 and 0.128 respectively. For the FRI score in boys, DDE, PFOA and PCB138 had the greatest weight with 0.449, 0.277 and 0.138, respectively. Finally, PFHxS, PFOA and PFOS had the most deleterious effects on VCI score in girls with a weight of 0.305, 0.232 and 0.207 respectively (Table 5).

Table 4
Associations between WQS index and IQ scores. Statistically significant results ($p < 0.05$) are in bold.

	FSIQ Coeff (SE)	VCI Coeff (SE)	VSI Coeff (SE)	FRI Coeff (SE)	WMI Coeff (SE)	PSI Coeff (SE)
WQS	−0.52 (1.62)	−1.35 (0.75)	1.08 (1.04)	0.01 (0.78)	−0.82 (1.10)	−0.45 (0.78)
Girls	1.12 (2.27)	**−2.42 (1.16)**	0.59 (1.69)	1.59 (1.01)	0.49 (1.99)	−1.02 (1.27)
Boys	**−5.13 (1.91)**	−1.94 (0.96)	−0.53 (1.47)	**−2.53 (0.99)**	−1.88 (1.28)	−1.35 (1.00)

Table 5
Weights from weighted quantile sum regression for pollutant index and risk of lower FSIQ score in boys (A), VCI score in girls (B) and FRI score in boys (C). Weights above 0.125 are in bold.

A. Increased risk of lower FSIQ in boys	
Chemical	Weight
DDE	**0.391**
PFOA	**0.273**
PCB180	**0.152**
PFOS	**0.128**
PFHxS	0.029
PCB153	0.022
PFNA	0.004
PCB138	0.002
B. Increased risk of lower VCI in girls	
Chemical	Weight
PFHxS	**0.305**
PFOA	**0.232**
PFOS	**0.207**
DDE	0.101
PCB138	0.071
PCB153	0.043
PFNA	0.028
PCB180	0.012
C. Increased risk of lower FRI in boys	
Chemical	Weight
DDE	**0.449**
PFOA	**0.277**
PCB138	**0.138**
PFHxS	0.062
PCB180	0.048
PFNA	0.014
PFOS	0.008
PCB153	0.004

4. Discussion

4.1. Impact of mixture on intellectual development

We investigated the relationship between prenatal exposure to eight POPs and intellectual development in 6 year-old children assessed by the WPPSI-IV. In our study, a mixture of organochlorine pesticides, PCBs and PFCs were found to have deleterious effects on global cognition in boys using WQS model.

Recent reviews suggest associations of DDE (Davis et al., 2019) and PCBs (Pessah et al., 2019) with several aspects of cognition, including poorer on overall intelligence, while evidence for adverse effects of prenatal PFCs exposure on cognition is inconclusive (Carrizosa et al., 2021). However, only a limited number of studies attempted to quantify the impact of aggregate exposure to multiple chemicals on intellectual development. Considering literature focusing on the POPs analyzed in our study (Appendices A, B and C), Luo et al. showed that PFCs mixture was associated with a significant decrease in cognitive and language abilities in two year-old children assessed with the Bayley Scales of Infant Development (BSID) using quantile-based g-computation and WQS approaches (Luo et al., 2022b). The assigned weights indicated that PFNA was the largest contributor to the mixture effect. Although this toxicant does not seem to have much impact in our analysis, two other prospective cohort studies showed that prenatal PFNA exposure was negatively associated with lower verbal IQ in children at 4 and 8 years, respectively (Wang et al., 2015; Spratlen et al., 2020). PFNA detection rates and average concentrations were much higher in these studies compared to ours. Tanner et al. (2020) explored whether early pregnancy exposure to a mixture of 26 persistent and nonpersistent EDCs was associated with IQ in 718 children aged 7 years using WQS model. This study found that higher exposure to the EDCs mixture, including some PFCs, was associated with a lower IQ, only in boys, supporting our results. However, bisphenol F (BPF) made the largest contribution to the index with a weight of 18%; other chemicals of concern included PFOA (6%), PFOS (5%) and PFHxS (4%). Although no other epidemiologic study has assessed the impact of BPF on childhood neurodevelopment, bisphenol A has demonstrated deleterious impact on child cognition (Lin et al., 2017). Thereby, BPF may potentiate the mixture effect observed in this study. Kalloo et al. studied the impact of chemical mixture exposure during pregnancy on cognitive abilities in school-aged children. Whereas prenatal 4.4′-DDE alone did not seem to impair cognitive abilities, its association with phenols, phthalates, several metals, other pesticides, some PCBs and PFCs had deleterious effects on all measures of IQ at 5 and 8 years when analyzed with k-means clustering (Kalloo et al., 2021). In a Norwegian article studying the impact of exposure to PFCs on cognitive development, PCA model did not show significant effect on verbal or nonverbal IQ measured using Standfort-Binet test (Skogheim et al., 2020) while a similar American study found negative association between a mixture and verbal IQ measured using WPPSI-R at 4 years (Spratlen et al., 2020). In this last study, the principal component was dominated by positive loadings for PFNA whose detection rate and concentration were at least twice as high as those found in our population.

Results of our WQS approach also indicated a deleterious effect of a mixture on FRI scores in boys. FRI assesses the child's ability to use his reasoning skills to infer the analogical or conceptual relationships between images. Our results are consistent with those of Guo et al. who were the first to show that accidental contamination in Taiwan had more impact on fluid reasoning (Raven's Matrices) in Yu-Cheng boys at age 6, 7 and 8[10]. A link can also be made with the results of Goodman et al. who showed that exposure to a mixture of PFCs was inversely associated with non verbal IQ only in 3–4 year-old boys, using the WPPSI-III test and a WQS approach (Goodman et al., 2023). In this study, the mixture was dominated by PFHxS, PFOA and PFOS. More detailed analysis of visual integration and abstraction capabilities could be interesting.

Finally, our analysis revealed a negative correlation between a prenatal exposure to a mixture of PFCs and verbal abilities in girls. These results are in agreement with those of Jeddy et al., where maternal serum concentrations of selected PFCs were also negatively associated with early language development in 15 and 38 month-old girls. In this study, vocabulary was mostly impacted, although there was no consistent pattern of association across all measured PFCs and endpoints (Jeddy et al., 2017). The results of Zhou et al. showed a decreased score in communication at 6 months on the Age and Stage Questionnaire (ASQ)(Zhou et al., 2023); most associations remained significant in boys in sex-stratified models, but results were no more significant at 12 and 24 months. Finally, Luo et al. also demonstrated a negative impact of prenatal PFCs on language scores of BSID at 2 years (Luo et al., 2022a). In older children, an English study performed on children aged 7 years demonstrated negative associations between prenatal exposures to PFOA and PFOS and performances at the Boston Naming Test, a visual confrontation naming test which measures the word retrieval or word finding performance of a subject (Oulhote et al., 2019). More recently, Oh et al. showed a negative correlation between prenatal PFOA exposure and language scores subtests of the Mullen Scales of Early Learning test at 2 and 3 years. However, these results are inconsistent with some other studies that did not demonstrate specific language impairment following PFCs exposure (Harris et al., 2018; Skogheim et al., 2020).

Overall, these results lead us to speculate that mixtures might have greater and more complex action on cognitive abilities than individual compounds. The aggregate effect of these chemicals might be more impactful because some of these toxics act via shared biological pathways or affect multiple pathways implicated in neurodevelopment. For instance, organochlorine pesticides, PCBs and PFCs pass through the placenta, enter the fetus, and have a direct toxic action on the developmental brain (Seralini and Jungers, 2021). Moreover, these molecules can impact thyroid and gonadal hormone homeostasis (Patisaul, 2021; Prezioso et al., 2018), as well as epigenetic processes, such as DNA methylation (Lister et al., 2013; Leung et al., 2018), which are known to be critical for the brain development.

The potentially deleterious effect of a combination of POPs, particularly PFCs, on intellectual function has been raised by our data. DDE seems to have the most important deleterious impact in our study. This EDC, like PCBs, is relatively less represented in recent literature and its effects in mixtures are probably underestimated. Moreover, unlike highly PCBs-exposed populations who retained lower intellectual skills (Lai et al., 1994), most studies carried out on populations that are also less exposed no longer demonstrated such significant effects (Gladen et al., 1988, 1991; Rogan et al., 1991; Roze et al., 2009; Koopman-Esseboom et al., 1996; Daniels et al., 2003; Winneke et al., 1998, 2005; Nakajima et al., 2006, 2017; Wilhelm et al., 2008; Lynch et al., 2012; Boucher et al., 2014; Berghuis et al., 2018; Kim et al., 2018; Gray et al., 2005; Zhang et al., 2017). This threshold effect, or the lower sensitivity of the WPPSI to detect subtle effects on certain cognitive functions such as attention or memory, could explain the lack of major impact of PCBs in our study.

4.2. Sex difference

In our study, we showed that the impact of maternal POP concentrations on cognitive scores was consistently greater in boys compared to girls.

By definition, EDCs increase the risk of childhood neurodevelopmental disorders by interfering with hormone signaling or metabolism. The thyroid axis constitutes a major target because of its involvement in neuronal migration, synaptogenesis, and myelination during gestation and early childhood (Zoeller and Rovet, 2004). However, many POPs, such as PFCs (Du et al., 2013) and PCBs (Thaddeus et al., 2015), also act on the steroid axis which plays a critical role in brain organization of the neuroendocrine circuitry that coordinates sex-specific physiology. Numerous neurons express steroid hormone receptors during different stages of development, making them likely targets of chemicals (Dickerson and Gore, 2007). Therefore, considering hormonal and metabolic differences observed between girls and boys, POPs impinging on steroid sensitive circuitry in the brain could exert effects on cognition in a gender dependent manner (Kern et al., 2017).

Furthermore, many other biological mechanisms may explain the heightened vulnerabilities of the male brain to toxics, in comparison to the female brain. Some animal and human studies have shown differences especially in oxidative processes, neuroprotection phenomena, and POP pharmacokinetics (accumulation, distribution, clearance) between males and females (Kern et al., 2017; Dzierlenga et al., 2020).

In addition, some epigenetic mechanisms are hormonally regulated and may modulated the effects of early life POPs exposures on long term health outcomes (Baccarelli and Bollati, 2009).

Finally, the timing of exposure may also have a big influence on whether or not the chemical remains biologically active. This is probably most important during fetal development due to the incomplete formation of the blood-brain barrier and the maturation of key endocrine systems which are therefore extremely sensitive to disruption by chemicals with hormone-like activity (Rice and Barone, 2000).

Numerous articles have suggested sex-specific effects of EDCs on cognitive function. For example, 2 studies showed greater vulnerability of intellectual functioning to PCBs in boys. The first documented that accidental contamination in Taiwan had more impact on Raven's Matrices tests in Yu-Cheng boys (Guo et al., 1995). In the second, lower scores on the Snijders-Oomen non-verbal intelligence tests (SON) were found in boys exposed to PCBs. However, these last results were linked to PCB 118 (Vermeir et al., 2021), which was not selected in our study due to lack of detection in our population. Concerning PFCs, in the World Trade Center birth cohort, child sex modified the association between PFOS and the mental development index measured using the BSID at 2 years, with the observed relationship being positive for females and negative for males (Spratlen et al., 2020). In the study of Goodman et al. (2023), every doubling of PFOA, PFOS or PFHxS was inversely associated with performance IQ measured by WPPSI-III at age 3 in males only. In the same study, every quartile increase in the WQS index was associated with poorer performance IQ in males, PFHxS contributing the largest weight to the index. In Liew et al., a no dose-response pattern sex-specific correlations were also found: in girls, the second quartile of PFOA and the third quartile of PFNA were associated with higher IQ scores on WPPSI-R at 5 years compared with the lowest quartile; in boys, the second quartile of PFHxS appeared to be associated with lower IQ (Liew et al., 2018). A deleterious effects of mixtures of PFCs has been reported on FSIQ at age 7 in boys in the studies of Tanners (Tanner et al., 2020). Finally, in Vuong et al., prenatal PFOA was positively correlated to FSIQ of the Wechsler Intelligence Scale for Children (WISC) at age 8 in girls only (Vuong et al., 2019).

In contrast, the Hokkaido Study found a lower mental developmental index of the Bayley Scale in girls only at 6 but not at 18 months (Goudarzi et al., 2016). Oh et al. observed also sex-specific correlation with negative association between PFHxS and Composite Scores of the Mullen Scales of Early Learning (MSEL), a standardized developmental test, at 12 months of age in girls only (Oh et al., 2021). Gaspar et al. demonstrated an impairment on FSIQ of the WISC at age 7 exclusively in girls exposed to 4,4′-DDE (Gaspar et al., 2015), while this toxicant is curiously the one that has the most deleterious impact on intelligence in boys in our mixture.

Furthermore, other studies have found no consistent pattern between PFCs and sex-specific neurodevelopmental effects (Harris et al., 2018).

To conclude, although more evidence and systematic analyses are required to specify the differential impact of chemicals on intellectual development, our finding of male vulnerability to prenatal toxic exposure appears to be consistent with most research examining sex-specific effects of POPs (Guo et al., 1995; Vermeir et al., 2021; Liew et al., 2018; Sioen et al., 2013), and the broader literature on developmental neurotoxicity of some others EDs (Azar et al., 2021; Green et al., 2019) and metals (Desrochers-Couture et al., 2018; Gade et al., 2021).

4.3. Positive correlation

We observed significant positive associations between PC1 (i.e., higher PFCs exposure overall) and better VSI and WMI scores. These "protective" associations between various PFCs and cognitive,outcomes are surprising but in line with some previous studies mentioned above (Carrizosa et al., 2021; Stein et al., 2013; Spratlen et al., 2020; Liew et al., 2018). It has been suggested that some seafood-related contaminants such as PFCs and PCBs (Winneke et al., 2005, ; Manzano-Salgado et al., 2016) could act as a proxy for fish nutrients, manifesting protective associations actually related to the benefits of seafood consumption. PFCs may also exert neuroprotective effects by activating human peroxisome proliferator-activated receptor (PPAR) which have anti-oxidant and anti-inflammatory actions (Maloney and Waxman, 1999; Villapol, 2018; Liu et al., 2015).Even if these positive associations between some PFCs and cognition were not reported in all studies, it certainly warrants further investigation.

4.4. Statistical analysis

Assessing the impact of EDCs through the existing literature remains challenging. Differences in population demographics, covariate adjustment, toxic choices, exposure levels and timing, single versus multi-pollutant analyses, statistical tools used, or random error may explain diverging results across studies for these chemicals. At any rate, these different findings indicate that co-occurring chemical exposures modeling might identify some outcomes that are missed in single regression models that do not adjust for or take into account co-exposure effects.

We chose two complementary dimension reduction techniques since they provided interpretable profiles of cumulative environmental chemical exposure that could be used to predict health outcomes. While PCA and WQS allow analysis of uncorrelated substrate mixtures, they create non-overlapping exposure profiles whose analysis is complementary. More specifically, PCA reduces the number of features by creating vectors that explain variation in related features, whereas WQS gives a weight to each substrate based on its impact on the variable of interest. PCA is therefore more representative of the exposome of the population studied whereas the WQS allows more easily generalizations on the effect of certain mixtures.

Given these complementary but different models, our results on PCA and WQS were expected to differ. These observations are in agreement with those of other studies exploring multiple complementary statistical approaches (Kalloo et al., 2020).

4.5. Strength and limitations

One strength of our study is its prospective design. We measured several of the most frequently detected POPs to assess their effects on intellectual development. Given their persistent nature, a single sample can be considered representative of long term exposure, unlike non-persistent compounds. Measurement were done on the child's cord blood, which represents direct exposure of the subject during a period of high vulnerability for brain development. We use standardized tests with trained examiners to assess main cognitive outcomes, including FSIQ and its indexes. We conducted our analyses using two validated and complementary statistical approaches to study the joint effect of a mixture of POPs, taking into consideration the main confounding factors. The selection of relevant chemicals and the use of PCA and WQS reduce the number of variables studied and, therefore, the risk of association by chance.

The main limitation of this study includes the relatively small number of patients and the low participation rate in the context of Covid epidemic. A selection bias is not excluded. The results of the present study need to be confirmed with a larger cohort. In this respect, the study of a larger cohort would make it possible to control for postnatal environmental risk factors such as the importance of intellectual stimulation, or levels of chemical contamination.

The average IQ of our population was in the upper average range (mean 106.54), which might be partly explained by the higher education level of the parents. Indeed, although parents' IQ has not been evaluated, there is some evidence of increased heritability and decreased shared environmental variance of intelligence at higher levels of parental education (Dong et al., 2023). As some of the findings reported in the literature review might hold only for more vulnerable subgroups, it is possible that optimal child stimulation can help compensate for subtle negative influence related to POPs exposure. Moreover, co-exposure to other unmeasured contaminants could be accountable for some of the correlations highlighted. For example, strong association between PCBs and mercury makes it less likely to observe independent relationships between PCBs and cognitive outcomes after statistically controlling for the other contaminants (Stewart et al., 2003).

Finally, IQ measurement paves the way for more in-depth investigation of cognitive development. Other complementary analyses remain essential in order to determine more subtle effects of early exposure to a mixture of POPs on more specific cognitive domains such as motor abilities, attention, learnings and memory skills. Since EDC exposures may contribute substantially to neurobehavioral disease, with a high probability of significant costs (Trasande et al., 2015), and potential risk of multi-transgenerational effects (Coperchini et al., 2024), a better understanding of EDCs' effects on human health is crucial to developing future regulatory strategies to prevent exposure and ensure the health of today's children and future generations (Duh-Leong et al., 2023).

5. Conclusion

Intelligence is a lifelong trait that has a strong influence on educational attainment, career success, mental well-being, adult morbidity, and life expectancy (Wraw et al., 2018). Understanding the influence of environmental factors on children's cognitive outcomes is an important area of inquiry. In addition, it is fundamental to emphasize the importance of using mixture methods to assess the effect of co-exposure to multiple toxics.

In this prospective birth cohort study, an exposition to prenatal EDC mixture was associated with decreased scores of intellectual abilities in pre-school children with a sex-dependent effect. FSIQ and FRI scores are negatively impacted by POPs in boys only, while language abilities are lower in girls exposed to a mixture of PFCs. Our findings support the hypothesis that EDCs are negatively associated with child neurodevelopment.

Though POP levels have been steadily decreasing since their regulation, their persistence in the environment and in human tissue make them a continuing public health concern. Further studies are required to confirm and clarify the observed results.

CRediT authorship contribution statement

Christophe Barrea: Writing – original draft, Methodology, Funding acquisition, Data curation, Conceptualization. **Patrice Dufour:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Pirard Catherine:** Writing – review & editing, Data curation. **Corinne Charlier:** Writing – review & editing, Funding acquisition, Data curation. **Fanny Brevers:** Investigation, Data curation. **Laurence Rousselle:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Conceptualization. **Anne-Simone Parent:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114422.

Appendices.

Appendix A

Summary of literature regarding the impact of DDE on mental and intellectual development – Abbreviations: Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), Collaborative Perinatal Project (CPP), INfancia y Medio Ambiente (INMA), Sapporo/Hokkaido Study (SHS), Venda Health Examination of Mothers, Babies and their Environment (VHEMBE), Development at Adolescence and Chemical Exposure (DACE), Flemish Environment and Health Study (FLESH), Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens (COMPARE), Rhea Mother-Child Cohort (RMC), Early Markers for Autism (EMA), Health Outcome and Measure of the Environment (HOME); Bayley Scales of Infant Development (BSID), Griffiths Mental Development Scales (GMDS), McCarthy Scales of Children's Abilities (MSCA), Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC), Snijders-Oomen Niet-verbale intelligentie test (SON, a non-verbal intelligence test)

Cohort, location and year of enrollment	References	Sample size	DDE exposition	Age of assessment (years)	Outcome measures	Primary findings
North Carolina, USA 1978–1982	Gladen et al., 1988 Rogan et al., 1991	802	Cord blood Median = 3.95 ppb	0.5 1, 1.5 and 2	BDSI (mental score) BDSI (mental score)	↑ MDI score No correlation
Spain 1997–1999	Ribas-Fito et al., 2003	92	Cord blood Median = 0.85 ng/ml	11.08 (13 months)	BDSI (mental score) GMDS	↓ MDI score ↓ Social and Performance scores
CHAMACOS, USA 1999–2000	Eskenazi et al., 2006	330	Maternal serum Mean = 1436.9 ng/g of lipid	0.5, 1 and 2	BSID (mental score)	No correlation
Mexico 2001–2005	Torres-Sanchez et al., 2007 Torres-Sanchez et al., 2009	270	Maternal serum Mean = 6.8 ng/ml)	0.08 (1 month), 0.25, 0.5, 1, 2, 1.5, 2 and 2.5	BSID II (mental score)	No correlation
Morelos, Mexico 2001–2009	Bahena-Medina et al., 2011	265	Maternal serum Mean = 7.27 ng/ml	0.08 (1 month)	BSID II (mental score)	No correlation

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Cohort, location and year of enrollment	References	Sample size	DDE exposition	Age of assessment (years)	Outcome measures	Primary findings
CPP, USA 1959–1965	Jusko et al., 2012	1100	Maternal serum Median = 24.5 ng/ml	0.66 (8 months)	BSID II (mental score)	No correlation
INMA, Spain 2003–2008	Forns et al., 2012	1801	Cord blood Median = 1.19 ng/g lipid	1.17 (14 months)	BSID II (mental score)	No correlation
SHS, Japan 2002–2005	Yamazaki et al., 2017	164	Maternal serum Median = 634 pg/g wet	0.5 and 1.5	BSID II (mental score)	No correlation
VHEMBE, South Africa 2012–2013	Eskenazi et al., 2018 ()	752	Maternal serum Median = 240.4 ng/g lipid	1 and 2	BSID III (mental score)	No correlation
DACE, Nehterlands 1998–2002	Ruel et al., 2019	87	Maternal serum Median = 88.0 ng/g lipid	1.5	BSID II (mental score)	No correlation
FLESH, Belgium 2002–2006	Vermeir et al., 2021	112	Cord blood Mean 198.2 ng/g lipid	3	BSID II (mental score)	No correlation
North Carolina, USA 1978–1982	Gladen et al., 1991	645	Cord blood Median = 3.95 ppb	3, 4 and 5	MSCA	No correlation
Spain 1997–1999	Ribas-Fito et al., 2006	475	Cord blood Median = 1.01 ng/ml	4	MSCA	↓ Memory scores
COMPARE, Netherlands 2001–2002	Roze et al., 2009	62	Maternal serum Median = 94.7 ng/g lipid	5.5	WPPSI	No correlation
CPP, USA 1959–1965	Jusko et al., 2012	1100	Maternal serum Median = 24.5 ng/ml	7	WISC	No correlation
Mexico 2001–2005	Torres-Sanchez et al., 2013	203	Maternal serum Mean = 6.8 ng/ml)	3.5, 4, 4.5 and 5	MSCA	↓ global cognition, verbal comprehension, quantitative and memory components
CHAMACOS, USA 1999–2000	Gaspar et al., 2015	595	Maternal serum Mean = 606.4 ng/g of lipid	7 and 10	WISC	↓ Full Scale IQ and Processing Speed at age 7 years in girls, but not boys
RMC, Greece 2007–2008	Kyriklaki et al., 2016	689	Maternal serum Mean = 2.9 ng/ml	4	MSCA	No correlation
EMA, USA 2000–2003	Lyall et al., 2017	181	Maternal serum Median = 218 ng/g lipid	0–18	ID diagnosis	↑ risk of ID vs control
FLESH, Belgium 2002–2006	Vermeir et al., 2021	206	Cord blood Mean = 198.2 ng/g lipid	3	SON	No correlation
HOME, USA 2003–2006	Kalloo et al., 2021	253	Maternal serum Median = 67 ng/g lipid	5–8	WISC/WPPSI	No correlation with DDE alone; combined Mixture (with phenols, phthalates, pesticides, and perfluoroalkyl substances) ↓ global cognition (k-means clustering)

Appendix B

Summary of literature regarding the impact of PFCs on mental and intellectual development – Abbreviations: World Trade Center (WTC), Markers of Autism Risk in Babies - Learning Early Signs (MARBLES), INfancia y Medio Ambiente (INMA), Shanghai Birth Cohort Study (SBCS), Shanghai Maternal-Child Pairs study (MGPG), Danish National Birth Cohort (DNBC), Early Markers for Autism (EMA), Health Outcome and Measure of the Environment (HOME), Mother, Father and Child Study (MoBa), Maternal-Infant Research on Environmental Chemicals (MIREC); Bayley Scales of Infant Development (BSID), Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT), Mullen Scales of Early Learning (MSEL), Age and Stage Questionnaire (ASQ), Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC), Kaufman Brief Intelligence Test (KBIT), Wide Range Assessment of Memory and Learning (WRAML), McCarthy Scales of Children's Abilities (MSCA).

Cohort, location and year of enrollment	References	Sample size	PFC exposition	Age of assessment (years)	Outcome measures	Primary findings
Hokkaido study, Japan 2002–2005	Goudarzi et al., 2016	173	Maternal plasma The medians of PFOS and PFOA were 5.7 and 1.2 ng/ml respectively	0.5 and 1.5	BSID II (mental score)	PFOA ↓ MDI at 6 months of age in girls only
WTC USA 2001–2002	Spratlen et al., 2020	302	Cord blood The means of PFOS, PFOA, PFNA, PFHxS, PFDS were 6.27, 2.37, 0.45, 0.69, 0.13 ng/ml respectively	1, 2 and 3	BSID II (mental score)	PFOS ↑ MDI at 2 years in females PFOA, PFHxS and PC1 ↑ MDI at 3 years of age
MARBLES, USA 2009–2014	Oh et al., 2021	302	Maternal serum The medians concentrations of PFOS, PFOA, PFNA and PFHxS were 2.8, 0.9, 0.5 and 0.4 ng/ml respectively	0.5, 1, 2 and 3	MSEL	PFOA ↓ Composite score (=FSIQ) at 2 and 3 years of age PFHxS ↓ Composite score at 1 year of age in girls only PFOA ↓ Visual reception at 3 years of age PFOA and PFNA ↓ Receptive language at 2 years of age PFOA ↓ Expressive language at 2 and 3 years of age
INMA Project, Spain 2004–2008	Carrizosa et al., 2021	1240	Maternal serum The medians of PFOA, PFOS, PFHxS and PFNA were 2.4, 6.1, 0.6 and 0.7 ng/ml respectively	1.2 (14 months)	BSID (mental score)	No association
SBCS, Shangai 2013–2016	Luo et al., 2022a	2257	Maternal serum The medians of PFOA, PFOS, PFNA, PFDeA, PFUnDA, PFHxS, PFDoA, PFBS, PFHpA, PFOSA were 11.9, 9.56, 1.74, 1.73, 1.42, 0.54, 0.17, 0.04, 0.06, 0.08 ng/ml respectively	2	BSID III (mental score)	PFOS, PFNA, PFDeA and PFUnDA ↓ MDI PFOA ↑ MDI Mixture ↓ MDI (quantile-base g-computation) WQS (PFNA, PFDeA) ↓ MDI
MGPG, Shanghai 2016–2017	Zhou et al., 2023	1285	Cord serum The medians of PFOA, PFOS, PFDA, PFNA, PFTrA, PFDoA, PFHxS, PFBA, 8 and 6:2Cl-PFESA were 4.61, 2.70, 0.24, 0.34, 0.08, 0.25, 1.13, 0.09, 0.04, 2.12 μg/L respectively	2, 6, 12 and 24 months	ASQ-III	PFOA, PFOS, PFDA, PFNA ↓ developmental score at 6 months (global, communication and gross-motor) PFHxS ↓ developmental score at 6 months (communication and gross-motor) Mixture ↓ communication at 6 months in overall population and boys (quantile-base g-computation)
C8 Health Project USA 2005–2006	Stein et al., 2013	320	Estimated in utero PFOA The median of PFOA were 43.7 ng/ml	6–12 years	WISC-IV	PFOA ↑ Full Scale IQ
Taiwan 2000–2001	Wang et al., 2015	120	Maternal serum The medians of PFOS, PFOA, PFUnDA, PFNA, PFHxS, PFDeA and PFDoDA were 13.25, 2.5, 3.42, 1.59, 0.69, 0.44 and 0.38 ng/ml respectively	5 and 8	WPPSI-R	PFUnDA and PFNA ↓ full scale IQ
Project Viva, USA 1999–2002	Harris et al., 2018	1116	Maternal serum The medians of PFOA, PFOS, PFHxS, PFNA, EtFOSAA and MeFOSAA were 5.6, 24.9, 2.4, 0.6, 1.2 and 1.9 ng/ml respectively	7.7	KBIT-2 WRAML2	PFOA ↓ Verbal IQ Score PFOS ↑ Non-Verbal IQ PFOA, PFOS, PFNA and PFHxS ↑ Design Memory Score PFNA ↑ Picture Memory Score
DNBC, Danish 1996–2002	Liew et al., 2018	1592	Maternal serum The medians of PFOS, PFOA, PFHxS, PFNA, PFHpS, PFDA, PFOSA and PFHpA were 28.10, 4.28, 1.07, 0.46, 0.37, 0.17, 2.32 and 0.07 ng/ml respectively	5	WPPSI-R	The second quartile of PFOA and the third quartile of PFNA ↑ IQ in girls The second quartile of PFHxS ↓ IQ in boys
EMA, USA 2000–2003	Lyall et al., 2018	155 vs 373controls	Maternal serum The medians concentrations of PFOS, PFOA, PFOSA, PFNA, PFHxS, PFDeA, Me-PFOSA-AcOH and Et-PFOSA-AcOH were 15.9, 3.28, 0.10, 0.47, 1.35, 0.16, 1.11 and 0.75 ng/ml respectively	0–18	ID diagnosis	PFNA ↑ Verbal IQ
HOME Study, USA 2003–2006	Vuong et al., 2019	221	Maternal serum The means of PFOA, PFOS, PFHxS, PFNA were 5.2, 12.4, 1.4 and 0.9 ng/ml respectively	8	WISC-IV	PFOA ↑ FSIQ in girls only
SELMA, Sweden 2007–2010	Tanner et al., 2020	718	Maternal serum The means of PFOA, PFOS, PFNA, PFDA, PFUnDA and PFHxS were 0.20, 0.06, 0.01, 0.02, 0.02, 0.03	7	WISC-IV	Mixture ↓ IQ scores in boys (WQS)
WTC USA 2001–2002	Spratlen et al., 2020	302	Cord blood The means of PFOS, PFOA, PFNA, PFHxS, PFDS were 6.27, 2.37, 0.45, 0.69, 0.13 ng/ml respectively	4 and 6	WPPSI-R	Mixture ↓ verbal IQ at 4 years (PCA)
MoBa, Norway 1999–2008	Skogheim et al., 2020	944	Maternal serum The means of PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFHpS, PFOS were 2.61, 0.45, 0.19, 0.25, 0.79, 0.16 and 12.32 ng/ml respectively	3.5	Standfort-Binet	No association with verbal and nonverbal IQ

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Cohort, location and year of enrollment	References	Sample size	PFC exposition	Age of assessment (years)	Outcome measures	Primary findings
INMA Project, Spain 2004–2008	Carrizosa et al., 2021	1240	Maternal serum The medians of PFOA, PFOS, PFHxS and PFNA were 2.4, 6.1, 0.6 and 0.7 ng/ml respectively	4–5	MSCA	No association
MIREC, Canada 2008–2011	Goodman et al., 2023	2001	Maternal serum The means of PFOA, PFOS and PFHxS were 1.70, 4.40, 1.09 μg/L respectively	3–4	WPPSI-III	PFOA, PFOS, PFHxS and mixture ↓ performance IQ only in males (WQS)

Appendix C

Summary of literature regarding the impact of PCBs on mental and intellectual development – Abbreviations: Dutch Mother-Child Study (DMCS), European Background PCB Study (EBS), Collaborative Perinatal Project (CPP), Duisburg Birth Cohort (DBC), INfancia y Medio Ambiente (INMA), Cord Blood Monitoring Program (CBMP), Development at Adolescence and Chemical Exposure (DACE), New York State Angler Cohort Study (NYSAC), Sapporo-Hokkaido Study (SHS), Children's Health and Environmental Chemicals in Korea (CHECK), Flemish Environment and Health Study (FLEHS), Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens (COMPARE), Tohoku Study of Child Development (TSCD), Rhea Mother-Child Cohort (RMCC), Health Outcome and Measures of the Environment (HOME), Early Markers for Autism (EMA), Development at Adolescence and Chemical Exposure (DACE); Bayley Scales of Infant Development (BSID), McCarthy Scales of Children's Abilities (MSCA), Wechsler Intelligence Scale for Children (WISC), Stanford-Binet Intelligence Scales (SBIS), Raven's Colored Progressive Matrices (RCPM), Ravens Standard Matrices (RSM), Kaufman Assessment Battery for Children (K-ABC), Snijders-Oomen Niet-verbale intelligentie test (SON, a non-verbal intelligence test)

Cohort, location and year of enrollment	References	Sample size	PCB exposition	Age of assessment (years)	Outcome measures	Primary findings
North Carolina, USA 1978–1982	Gladen et al., 1988 Rogan et al., 1991	802	cord blood Median ΣPCBs (total) = 4.27 ppb	0.5, 1, 1.5 and 2	BSID (mental score)	No correlation
Taïwan Cohort 1978–1985	Lai et al., 1994	117	PCB contamination during the "oil disease"	0.5, 1, 1.5 and 2	BSID (mental score)	Yucheng children scored lower than their controls
DMCS, Netherlands 1990–1992	Koopman-Esseboom et al., 1996	207	Maternal blood Mean ΣPCBs (118, 138, 153, 180) = 2.2 ng/g	0.25 (3 months), 0.58 (7 months) and 1.5	BSID (mental score)	No correlation
EBS, Germany 1993–1995	Walkowiak et al., 2001	171	Cord blood Mean ΣPCBs (118, 153, 180) = 218 ng/g lipid	0.58 (7 months), 1.5 and 2.5	BSID (mental score)	Negative effect in relation to the sum of PCB 138, 153 and 180 in breast milk (2 weeks postpartum) rather than in cord plasma
CPP, USA 1959–1965	Daniels et al., 2003	1207	Maternal blood Median ΣPCBs (28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203) = 2.7 μg/L wet	0.67 (8 months)	BSID (mental score)	No correlation
Spain 1997–1999	Ribas-Fito et al., 2003	102	Cord blood Median ΣPCBs (28, 52, 101, 118, 138, 153, 180) = 1.9 ng/ml)	1,08 (13 months)	BSID (mental score) GMDS	No correlation No correlation
Hokkaido, Japan 2002–2004	Nakajima et al., 2006	134	Maternal blood Median ΣPCBs (total) = 22.9 ng/g lipid	0.5	BSID (mental score)	No correlation
DBC, Germany 2000–2002	Wilhelm et al., 2008	179	Maternal blood Median ΣPCBs (118, 126, 156) = 5.71 pg/g lipid	1 and 2	BSID II (mental score)	No correlation
Slovakia 2002–2004	Park et al., 2010	760	Maternal blood Median ΣPCBs (138, 153, 170, 183) = 414 ng/g lipid) - Median ΣPCBs (118, 156) = 21 ng/g lipid	1,33 (16 months)	BSID II (mental score)	Dioxin-like mono-ortho PCBs (118, 156) ↓ MDI score
INMA Project, Spain 2003–2008	Forns et al., 2012	1801	Maternal blood Median ΣPCBs (138, 153, 180) = 102.72 ng/g lipid	1,17 (14 months)	BSID II (mental score)	No correlation
CBMP, Canada 1993–1996	Boucher et al., 2014	89	Cord blood Median PCB 153 = 78.1 ng/g lipid	0,92 (11 months)	BSID II (mental score)	No correlation
DACE, Netherlands 1998–2002	Ruel et al., 2019	181	Maternal serum Median ΣPCBs (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) = 296.8 ng/g lipid	1.5 and 2.5	BSID II (mental score)	PCB-153 ↓ MDI at 18 months, not at 30 months

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Cohort, location and year of enrollment	References	Sample size	PCB exposition	Age of assessment (years)	Outcome measures	Primary findings
NYSAC II, USA 1996–1999	Lynch et al., 2012	44	Maternal serum Median Σ 74 PCBs = 991.7 ng/g lipid	2	BSID II (mental score)	No correlation
SHS, Japan 2002–2004	Nakajima et al., 2017	190	Maternal serum Mean TEQ ΣPCBs (77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 170, 180, 189) = 18.8 pg/g lipid	0,5 and 1,5	BSID II (mental score)	No correlation
CHECK, Korea 2011–2012	Kim et al., 2018	140	Maternal serum Median ΣPCBs (74, 99, 105, 114, 118, 138, 153, 156, 157, 167, 170, 180, 189, 194) = 27.3 ng/g lipid	1,5	BSID II (mental score)	No correlation
FLEHS, Belgium 2002–2006	Vermeir et al., 2021	206	Cord serum Mean ΣPCB (138, 153, 180) = 87.9 ng/g lipid – Mean PCB118 and 170 = 14.9 and 8.9 ng/g lipid respectively	3	BSID II (mental score)	No correlation
Michigan Study, USA 1980–1981	Jacobson et al., 1990 , Jacobson et al., 1996 and Jacobson et al., 2002	81	Cord blood Mean ΣPCBs (total) = 2.5 ng/ml serum	4 11	MSCA WISC	↓ General Cognitive Index, Verbal, Quantitative and Memory scores ↓ Full scale, ↓ verbal IQ, ↓ freedom from distractibility
North Carolina, USA 1978–1982	Gladen et al., 1991	645	cord blood Median ΣPCBs (total) = 4.27 ppb	3,4 and 5	MSCA	No association
Taïwan Cohort 1978–1985	Lai et al., 2002 Guo et al., 1995	117	PCB contamination during the “oil disease”	2, 3, 4, 5 6, 7, 8, 9, 10, 11, 12 and 13 5, 6, 7, 8 and 9	SBIS WISC-R RCPM and RSM	↓ FIQ, VIQ and PIQ up to 11 years ↓ performances from 5 up to 8 years
DMCS, Netherlands 1990–1992	Patadin et al., 1999 ; Boersma, 2001 and Vreugdenbil et al., 2002	395	Maternal serum Median ΣPCBs (118, 138, 153, 180) = 2.04 μg/l	3 6	K-ABC MSCA	↓ Overall cognitive, sequential and simultaneous processing scales ↓ cognitive abilities when parental and home characteristics were less optimal. These effects were not measurable in children raised in more optimal environments.
EBS, Germany 1993–1995	Walkowiak et al., 2001 and Winneke et al., 2005	87	Cord blood Mean ΣPCBs (118, 153, 180) = 218 ng/g lipid	3.5 6	K-ABC K-ABC	Associations slightly positive between cord blood PCB and the Mental Processing Composite-Index No association
Oswego Study, USA 1991–1994	Stewart et al., 2003	194	Cord blood Median ΣPCBs (total) = 0.52 ng/g wet	3.17 (38 months) and 4.5	MSCA	↓ General Cognitive Index, Perceptual and Quantitative Scales at 3 years but not 4 years
Oswego Study, USA 1991–1994	Stewart et al., 2008	156	Placental PCB Mean ΣPCBs (total) = 1.50 ng/g wet	9	WISC	↓ Full Scale IQ, Verbal IQ, Verbal Comprehension Index and Freedom from Distractibility; In contrast to placental PCBs, cord bloods PCBs were unrelated to IQ
CPP, USA 1959–1965	Gray et al., 2005	894	Maternal blood Median ΣPCBs (28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203) = 2.85 μg/l wet	7	WISC	No correlation
COMPARE, Dutch 2001–2002	Roze et al., 2009	62	Maternal serum Median PCB 153 = 63 ng/g lipid	5	WPPSI	No correlation
INMA, Spain 2003–2008	Forns et al., 2012	422	Cord blood Median ΣPCBs (118, 138, 153, 180) = 0.71 ng/ml wet	4	MSCA	PCB153 ↓ General cognitive, Verbal, Quantitative, Perceptual-performance and Memory scales
TSCD, Japan 2001–2004	Tatsuta et al., 2014	387	Cord blood Median ΣPCBs (total) = 46.5 ng/g lipid	3,5	K-ABC	Highly chlorinated PCB homologs (PCB 206, 207 and 208) ↓ sequential and mental processing score; no effect of ΣPCBs
RMCC, Greece 2007–2008	Kyriklaki et al., 2016	689	Maternal blood Median ΣPCBs (118, 138, 153, 156, 170, 180) = 320.8 pg/ml	4	MSCA	↓ in working memory tasks
HOME, USA 2003–2006	Zhang et al., 2017	239	Maternal blood Median ΣPCBs (118, 138, 153, 180) = 31.30 ng/g lipid	8	WISC	No correlation
EMA, USA 2000–2003	Lyall et al., 2017	181	Maternal serum Median ΣPCBs (28, 99, 118, 138, 153, 158, 170, 180, 187, 194, 196, 199, 203) = 57.9 ng/g lipid	14 to 17	ID diagnosis	Dioxine-like PCB138/158 ↑ intellectual disability compared to control

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Cohort, location and year of enrollment	References	Sample size	PCB exposition	Age of assessment (years)	Outcome measures	Primary findings
DACE, Netherlands 1998–2002	Berghuis et al., 2018	101	Maternal serum Median ΣPCBs (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) = 319 ng/g lipid	14,4	WISC	Higher levels of PCB-183 were near-significantly associated with lower intelligence (P < 0.10).
FLEHS, Belgium 2002–2006	Vermeir et al., 2021	206	Cord serum Mean ΣPCB (138, 153, 180) = 87.9 ng/g lipid – Mean PCB118 and 170 = 14.9 and 8.9 ng/g lipid respectively	3	SON	PCB118 ↓ reasoning, performance and total IQ in boys only

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