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Neuromotor effects of early-life exposure to a mixture of endocrine disruptors in Belgian preschool children

Christophe Barrea[1,2,5*], Patrice Dufour[3], Pirard Catherine[3], Corinne Charlier[3], Fanny Brevers[4], Anne-Simone Parent[1,2†] and Laurence Rousselle[4†]

Abstract

Objective Children gradually develop motor skills that enable them to move efficiently in various daily activities such as self-care, academics and sports. The impact of prenatal exposure to endocrine disruptors (EDCs) on these performances remains understudied and current results are inconsistent. This study aims at examining the neuromotor function of Belgian preschoolers exposed in utero to a mixture of some of these chemicals.

Methods From 2014 to 2016, 66 children (35 boys and 31 girls) were recruited for a longitudinal cohort study. Two polychlorinated biphenyls (PCBs) and four perfluoroalkyl substances (PFASs) were measured in cord serum. A standardized motor evaluation, the Movement Assessment Battery for Children II (MABC-II), and a clinical sensori-motor assessment examining minor neurological dysfunction were administered at 6 years of age. The impact of the mixture of EDCs on neuromotor outcome measures was evaluated using two validated statistical models. Sex-specific analyses were also conducted.

Results Using a principal component analysis, a negative association was identified between a mixture of PCB-153 and – 180 and the Total Clinical examination score in the whole population (β (95% CI) = -15.8 (-26.51; -5.09), $p = 0.005$). After stratification by sex, negative associations were observed between the Gross Motor score of the MABC-II test and prenatal exposure to a mixture of PFASs and PCB-180, specifically in boys. This association was consistent across both the weighted quantile sum regression model (β (95% CI) = -2.36 (-3.42; -0.62), $p = 0.023$) and the principal component approach (β (95% CI) = -1.09 (-2.15; -0.13), $p = 0.044$).

Conclusion Our findings suggest that the neuromotor function of young children is adversely influenced by prenatal exposure to toxicants in a sex-specific manner.

Keywords Endocrine disrupting chemicals, Mixture, Motor, Minor neurological dysfunction, Preschool, Sex-stratified effect

†Anne-Simone Parent and Laurence Rousselle contributed equally to this work.

*Correspondence:
Christophe Barrea
christophe.barrea@chuliege.be
[1]Department of Paediatrics, University of Liege (ULg), CHU, Liege 4000, Belgium
[2]GIGA Neurosciences, Neuroendocrinology Unit, University of Liege (ULg), CHU, Liege 4000, Belgium
[3]Laboratory of Clinical, Forensic and Environmental Toxicology, University of Liege (ULg), CHU, Liege 4000, Belgium
[4]Research Unit for a Life-Course Perspective on Health and Education, University of Liege (ULg), Liege 4000, Belgium
[5]CHU University of Liege, 1, Avenue de l'Hôpital, Liège 4000, Belgium

Introduction

The effects of endocrine disruptors (EDCs) on neurodevelopment represent a growing concern in modern societies. Among these toxics, persistent organic pollutants are man-made chemicals historically used for a wide variety of industrial purposes such as flame-retardants, solvents, and pesticides. They are widespread and stable environmental toxicants, highly resistant to biotransformation and environmental degradation. Despite the fact that the production and use of these chemicals has been banned or limited by law, exposure to many of these compounds such as polychlorinated biphenyls (PCBs) and perfluoroalkyl substances (PFASs) persists [1, 2]. More importantly, these contaminants cross the placenta during pregnancy and bioaccumulate in foetal tissues [3].

According to the Developmental Origins of Health and Disease (DOHaD) hypothesis [4], environmental exposure to EDCs may lead to potential health effects, including a range of deficiencies in motor development, The fetal and early popstnatal periods are particularly vulnerable to such effects due to rapid brain development [5]. During the first weeks of life, neurological assessment is primarily based on the evaluation of active and passive muscle tone. Infants with hypotonic phenotypes are known to have lower psychomotor development at 2–3 years of age [6]. In school-aged children, motor skills range from gross motor coordination and balance to fine motor performance, which are necessary for daily personal care, academic achievements and athletic activities [7]. Consequently, poor movement performance often leads to reduced participation to educational activities and learning abilities, with long-term detrimental impacts on self-confidence and academic success [8, 9]. In this context, a neuromotor assessment looking for minor neurological dysfunction (MND) has been systematically carried out in some countries to identify children at-risk of motor developmental disorders as early as possible. MND is defined as neurological dysfunctions, such as choreiform dyskinesia, mild diffuse hypotonia, or mild impairment of fine manipulative ability, which is not attributable to a brain injury such as cerebral palsy [10]. MND is well predictive of increased neurodevelopmental disorder. Furthermore, MND in school-aged children is associated with neurodevelopmental disorders, such as developmental coordination disorder or learning disabilities [11–13]. As it is widely accepted that performance at the beginning of primary school partly predicts later school careers, this evaluation usually takes place before entering elementary school.

Some EDCs are suspected to alter neuromotor development. Studies in different animal models have shown an impairment of motor function associated with prenatal exposure of EDCs [14–16] and suggested possible sex-related differences that could make males particularly vulnerable [17–19]. In humans, results are less consistent. The neurotoxicity of EDCs was first recognized through accidental poisoning incidents in Yusho (Japan 1968) and Yu-Cheng (Taiwan 1979): babies exposed to PBCs *in utero* exhibited slowness, lack of endurance, hypotonia, jerkiness, and clumsy movement [20]. The children of Yu-Cheng were closely monitored, and a number of adverse outcomes were associated with PCBs poisoning, including lower Bayley Scales of Infant Development (BSID) psychomotor scores, which assesses body control, large muscle coordination, fine hands and fingers movements, and dynamic movement [21]. Compared to unexposed infants they also showed delay on 32 of 33 developmental milestones, including turning pages, holding pencils, imitating drawn circles, and catching a ball [22]. At 7–12 years of age, Chen et al. 1994 [23] did not report anomalies on the standard neurological examination but observed subtle signs consisting of mirror movements, mild to moderate deficits in finger-thumb opposition, and choreiform movements. In the years following the Yusho and Yu-Cheng poisonings, several epidemiological studies were conducted to investigate the impact of antenatal environmental exposure to PCBs and other EDCs on motor functioning. Although most studies reported either null or inverse associations, the epidemiological findings to date remained inconclusive [24–27]. These inconsistencies might be explained, to some extent, by the different methodological approaches and population-specific effects, potentially resulting from dose-dependent responses [26]. Various assessment tools were used, including neurological examination, neurodevelopmental evaluations as well as more specific motor tests. Furthermore, humans are typically exposed to mixtures of environmental endocrine–disrupting chemicals simultaneously, yet most studies focused on single chemicals or a class of similar chemicals. By neglecting the influence of EDC mixtures, prior research may have failed to capture the synergic and/or cumulative health effects of EDCs, due to correlated co-pollutants [28]. Finally, some authors investigated sex-specific associations between prenatal exposure to EDCs and neurodevelopmental outcomes in children [29–33].

The main goal of this study was to evaluate the neuromotor effects of early-life exposure to a mixture of EDCs in preschool children using two validated statistical approaches. Given the evidence of sex-specific effect reported in the literature, analyses were performed both on the whole population and within sex-stratified subgroups.

Methods

Study participants

Participants were part of the EPOPEE (*Effet des Polluants Organiques Persistants sur l'Evolution des Enfants*) study described elsewhere [34].

Briefly, mother-child pairs from the general population were recruited through the maternity of the University Hospital of Liege (Belgium) between 2014 and 2016. Umbilical cord blood samples were collected, centrifugated and stored at -80 °C immediately after delivery. Inclusion criteria include the absence of ante/perinatal disease, prematurity and chronic affection.

Of the 212 original participants, 77 gave their consent to participate in the motor and clinical evaluation at 6 years of age, before starting elementary school. Finally, only 66 of them had enough cord blood to perform a dosage of all EDCs studied and were selected for the present study. This study was approved by the local biomedical Ethics Committee of the University Hospital of Liege.

Exposure

EDCs in cord blood were measured using a detailed analytical method described in Dufour et al. [35]. Briefly, 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) were analysed following the methodology outlined by Pirard et al. [36]. The concentrations of seven PFASs ((perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroheptanoic acid (PFHpA) and perfluoroundecanoic acid (PFUdA)) were determined based on the protocol described by Karrman et al. [37]. The analytical methods were validated according the total error approach in order to meet the ISO17025 standards and the guidelines of the French Society of Pharmaceutical Science and Technique [38]. For each EDC, the limit of quantification (LOQ) was determined during the validation process and defined as the lowest concentration measurable with a maximal uncertainty not exceeding 40%.

Only EDCs with a detection rate above the LOQ in more than 50% of sample were included in the analysis [39]. This resulted in the selection of two PCBs (PCBs-138 and −180) and four PFASs (PFOS, PFOA, PFHxS and PFNA). As recommended by Lubin et al. [40], values below the detection limit were replaced using multiple imputation techniques to create five imputed datasets (K = 5) [41, 42].

Finally, a logarithmic transformation was applied to reduce the dispersion and satisfy normality assumptions of our models.

Motor outcome

Motor outcome was assessed using the Movement Assessment Battery for Children II (MABC-II), a standardized test of motor skills for children 4 to 12 years of age [43]. This test, widely used in practice and in research, yields a score for total movement performance based on separate scores for fine motor skills (manual dexterity), ball skills (object control), and static and dynamic balance (postural control). Standardized scores for each subtest as well as the total score range from 0 to 20, with higher score indicating better performance. In our study, the last two subtests were combined to have a global measure of gross motor skills. The MABC-II assesses motor skills in children aged 3 to 6 years through a set of age-appropriate tasks. In addition, each child was tested for signs of minor neurological dysfunction using the standardized protocol developed by Willems G. et al. [44] (Appendix C). This clinical sensori-motor assessment, inspired by the works of Kalverboer A.F [45]. and Bax M [46], was specifically created to offer a comprehensive school-entrant medical examination and to highlight children at risk of developing motor or learning disorders. The Willems examination consists of 89 items including motor tasks, as well as sensory evaluation. Each item receives a score of 2, 1 or 0 depending on whether the test was passed, hesitant, or failed. Medical elements were also considered and scored from 2 to 0 according to their deviation from the norm. This assessment gives an overall score out of 500 points which is predictive of learning disabilities, a lower score indicating a higher risk of learning difficulties, mainly when entering primary school. In our study, a motor-specific clinical score which focused only on motor items (max score = 150) was also taken into consideration.

The MABC-II and the clinical evaluation were performed in a standardized manner by the first author, blinded to EDC exposure.

Covariates

Data regarding the parents and child were obtained through a general questionnaire completed during the first study visit. Additional information was collected from hospital medical records. These data included maternal age at delivery, parity, duration of breastfeeding, parental education (categorized as having a diploma higher than high school or not), parental smoking status, maternal alcohol consumption during pregnancy, gestational age, child birth weight, age during testing and child's sex. Children's thyroid function was assessed by measuring thyroid stimulating hormone (TSH) levels in a dried blood spot collected three days after birth.

The main confounders were selected based on prior knowledge, according to Directed Acyclic Graph theory [47] (maternal and paternal education, maternal age,

maternal and paternal smoking, multiparity, gestational age, birth weight and gender) (Appendix D). Furthermore, models were adjusted for child's age as this parameter greatly influences the outcome. Some parameters (peri/antenatal disease and the presence of a chronic affection), used as exclusion criteria, were not included in the models. Finally, other covariates (alcohol consumption during pregnancy, thyroid function, breastfeeding) were selected a priori based on previous literature as they greatly influence the development of cognitive functions [48, 49].

The associations between each variable and the outcome were then evaluated: Student tests were used to test group differences for binary variables, while univariate regression models were carried out to assess the effects of continuous variables on outcome measures (Appendix E). Variables associated with motor scores at a significant level of $p < 0.20$ were included as covariates in the final analysis [50]. The results indicated that all tests were influenced by parental educational level and smoking status. There was an effect of age on the Total and Motor specific clinical scores of the clinical examination, as well as the Global and the Fine Motor scores of the MABC-II. Additionally, the Total score of the Clinical examination and all scores of the MABC-II were influenced by the age of the mother at delivery. The sex of the child and the breast-feeding duration impacted the Fine Motor score of the MABC-II. Lastly, only the Global score of the MABC-II was influenced by multiparity (Table 1).

Statistical analysis

We computed descriptive statistics for exposure and outcome variables, as well as model covariates.

Two different statistical models were employed to explore the association between MABC-II and Clinical examination scores and prenatal exposure to a mixture of EDCs. Given that some chemicals are correlated, classic regression models were rejected because they are subject to dimensionality and collinearity issues.

So, we first specifically used Principal Components Approach (PCA) to reduce the the set of original variables and to extract a smaller number of principal components (Comp). Components explaining at least 50% of the variance cumulatively were selected [51]. Multiple linear regression models were then used to investigate the association between each component and Global Motor and Clinical examination scores while controlling for relevant covariates [26].

Secondly, generalized Weighted Quantile Sum (WQS) regression was used to quantify the cumulative effect of EDCs exposures and to estimate the relative contribution of individual components of the mixture to the outcomes of interest [52]. To achieve this, the overall exposure to the mixture of EDCs was summarized by estimating a body burden index (the WQS index). We used quartiles of exposures with 100 bootstrap samples, a 60% validation dataset, and a negative coefficient constraint. The final index was then included in a regression model to evaluate the overall effect of the mixture on the outcomes of interest. To identify the chemicals most strongly associated with the outcome, significant components of the WQS index were determined by comparing the average weight for each component against a sectioned threshold parameter, τ. In our analysis conducted with six components, we used $\tau = 1/6 = 0.167$. To ensure the stability of our data and to approximate the repeated holdout strategy described by Tanner et al. [53], the standard WQS analysis was repeated ($rh = 100$) to simulate a distribution of validated results from the underlying population. The mean and confidence intervals (95% CI) for the WQS index β coefficient and the chemical weights in relevant situation were considered (Appendix F).

Finally, given the concern about the hormonally active property of some EDCs [54] and the sex-specific effects observed in animal models [17, 19], analyses were conducted on both the total and sex-stratified populations.

All analyses were performed using R software version 4.1.2 [55]. The miWQS package was used for WQS regression analysis [56]. The MIPCA package [57] was applied as a preliminary step to perform multiple imputation before running PCA model with the FactoMineR package [58]. Statistical significance was set at a p-value of 0.05.

Table 1 Selected covariates for each cognitive test; student tests were used for binary variables, while univariate regression models were carried out for continuous variables

Cognitive testing		Selected covariates
Clinical examination	Total score	Mother and father smoking status and educational level, age of the child during the test, age of the mother at delivery.
	Motor specific clinical score	Mother and father smoking status, father educational level, age of the child during the test
MACB-II	Global score	Multiparity, mother and father smoking status and educational level, age of the child during the test, age of the mother at delivery.
	Fine Motor	Sex of the child, mother and father smoking status and educational level, age of the child during the test, age of the mother at delivery, breast feeding duration
	Global Motor	Mother and father smoking status and educational level, age of the mother at delivery.

Table 2 Demographic characteristics and cognitive scores

Variable	*N*	*N* (%)	Mean	SD	Min	Q1	Med	Q3	Max
Sex (male)	66	35 (53)							
Age during tests (years)	66		5.72	0.34	5.08	5.44	5.73	6.01	6.41
Maternal age at delivery (years)	66		30	5	18	28	30	33	42
Parity (multiparous)	66	33 (50)							
Gestational age (days)	66		276	9	252	270	278	284	289
Birth weight (kg)	66		3.31	0.50	2.28	2.98	3.30	3.62	5.01
TSH (mUI/L)	66		5.32	3.19	0.10	3.30	4.55	7.07	16.6
Alcohol during pregnancy (> 1 serving/month)	66	5 (8)							
Breast feeding	66	53 (80)							
Smoking parents	66								
Smoking father		12 (18)							
Smoking mother		13 (20)							
Parental educational level (> high school)	66								
Mother		44 (67)							
Father		38 (58)							
Clinical evaluation									
Total score	66		342	51	174	306	351	377	439
Motor specific clinical score	66		94	17	30	86	95	104	122
MABC-II									
Total score	66		8	5	1	5	8	10	15
Fine Motor score	66		9	3	1	6	10	11	14
Gross Motor score	66		17	8	9	14	16	20	28

Table 3 Detection rate above the limit of quantification (LOQ), geometric mean concentrations, standard deviation (SD) and quartiles of the EDCs considered in the study. Concentrations were expressed in ng/mL

Variable	*N*	*N* (%) > LOQ	LOQ (ng/mL)	Mean (ng/mL)	SD	Min (ng/mL)	Q1 (ng/mL)	Med (ng/mL)	Q3 (ng/mL)	Max (ng/mL)
PCBs										
PCB-153	66	36 (55)	0.07	0.07	0.03	< LOQ	< LOQ	0.08	0.08	0.19
PCB-180	66	51 (77)	0.05	0.06	0.03	< LOQ	0.05	0.06	0.07	0.18
PFASs										
PFHxS	66	42 (64)	0.15	0.20	0.15	< LOQ	< LOQ	0.17	0.27	0.89
PFOA	66	62 (94)	0.25	0.79	0.48	< LOQ	0.41	0.73	0.99	2.94
PFNA	66	52 (79)	0.10	0.18	0.12	< LOQ	0.11	0.15	0.24	0.53
PFOS	66	51 (77)	0.50	1.07	1.20	< LOQ	0.56	0.81	1.24	9.21

Results

Descriptive analyses

General characteristics of the study sample are summarized in Table 2. In total, 66 participants were included in the analysis, with a slightly larger proportion of boys (53%). All children were born at full term with an average weight of 3307 g. Half of them were the first child of their mother, and a majority were breastfed (80%). The average age of the children at testing was 5 years and 9 months. The average maternal age was 30 years old at delivery. Mother generally did not smoke or consume alcohol during pregnancy. More than half of the mothers (67%) and the fathers (58%) had education attainment higher than high school.

Table 2 presents an overview of children's motor and clinical outcomes. The mean (± SD) for Total Clinical examination score and Motor specific clinical score were 342 (± 51) and 94 (± 17) respectively. Only one child had a Total score under 200. Concerning the motor evaluation with the MABC-II test, 55% of the population had a Global score in the normal range [7–13]; 36% and 9% of the participants were respectively under vs. above the average range. The mean (± SD) for global MABC-II score, Fine Motor score and Gross Motor score were 8 (± 5), 9 (± 3) and 17 (± 8) respectively. Note that there was a significant correlation between the Motor specific clinical score and all scores of the MABC-II test ($p < 0.001$).

Six chemicals were detectable in more than 50% of the study population. The median concentration, geometric mean concentration, and distribution of these chemicals are shown in Table 3. PCBs were detected in 83% of the samples and included PCB-153 and –180 with a detection rate of 55% and 77% respectively. Finally, in 98% of the samples, at least one PFAS was found. PFOA was the

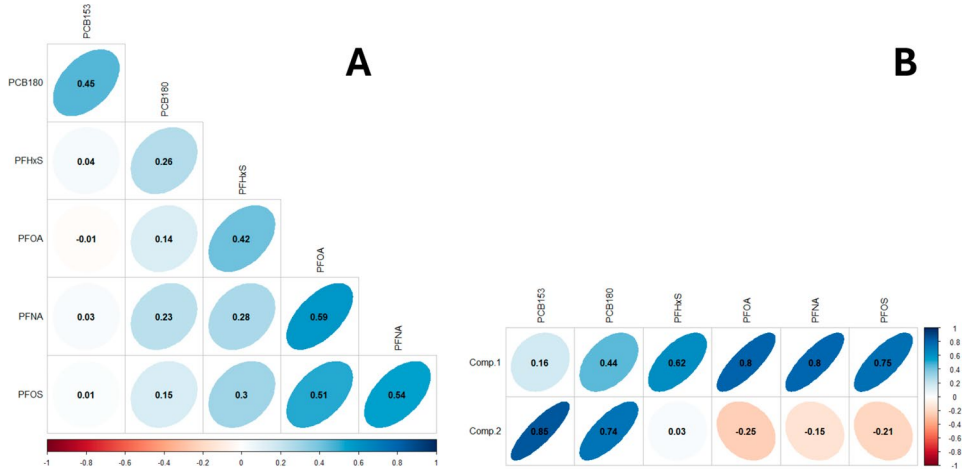

Fig. 1 Pairwise Pearson's correlation coefficients between individual EDCs (**A**) and between the two components and EDCs (**B**); positive correlations are highlighted in blue and negative correlations in red

Table 4 Adjusted multivariate regression coefficient β (95% confidence intervals (CI)) between PCA components and the clinical examination score or MABC-II test in preschool children. Component 1 (Comp1) included all PFASs and PCB-180; component 2 (Comp2) included PCBs-153 and – 180. Statistically significant results ($p < 0.05$) are indicated in bold

	Clinical Examination				**MABC-II**					
	Total Score		**Motor specific clinical score**		**Total Score**		**Fine Motor**		**Gross Motor**	
	β	**(95% CI)**	**β**	**(95% CI)**	**β**	**(95% CI)**	**β**	**(95% CI)**	**β**	**(95% CI)**
Comp 1	-0.69	(-9.40 ; 8.02)	1.02	(-1.81 ; 3.85)	-0.03	(-0.61 ; 0.56)	0.33	(-0.18 ; 0.84)	-0.25	(-1.01 ; 0.51)
Girls	10.40	(-1.48 ; 22.28)	3.26	(-0.78 ; 7.29)	0.94	(-0.01 ; 1.90)	0.91	(-0.08 ; 1.74)	0.77	(-0.47. 2.01)
Boys	-9.80	(-22.48 ; 2.88)	-0.08	(-4.10 ; 3.95)	-0.63	(-1.40 ; 0.13)	0.05	(-0.61 ; 0.71)	**-1.09**	**(-2.15 ; -0.13)**
Comp 2	**-15.80**	**(-26.51 ; -5.09)**	-0.72	(-4.26 ; 2.82)	-0.06	(-0.80 ; 0.69)	-0.32	(-0.99 ; 0.34)	-0.25	(-1.21 ;0.72)
Girls	-10.76	(-25.00 ; 3.48)	-1.24	(-6.26 ; 3.78)	0.04	(-1.18 ; 1.25)	-0.19	(1.38. 1.00)	-0.075	(-1.74. 1.59)
Boys	-15.35	(-34.17 ; 0.46)	-0.45	(-5.67 ; 4.78)	0.09	(-1.13 ; 1.31)	-0.17	(-1.20 ; 0.86)	-0.10	(-1.66 ; 1.46)

most represented PFASs (mean: 0.79 ng/mL), followed by PFNA (mean: 0.18 ng/mL), PFOS (mean: 1.07 ng/mL) and PFHxS (mean: 0.20 ng/mL).

No significant differences between girls and boys were found regarding exposure to EDCs and neuromotor scores (Appendix G).

EDCs and neuromotor outcomes

Principal components approach

Pairwise Pearson correlations among cord blood concentrations of chemicals are shown in Fig. 1A. Analyses indicated that several EDC concentrations are moderately correlated.

PCA identified two main components accounting respectively for the 40.9% and 23.2% of the total variance. Loading factors for each chemical on each component are presented in Fig. 1B. The first component (Comp1) was characterized by significant loading factors for all PFASs and PCB-180. The second component (Comp2) had high loading factors for PCBs-153 and – 180.

Adjusted multivariate regression analysis were conducted to examine the relationship between PCA components and motor outcomes (clinical evaluation and MABC-II assessment). In boys and girls taken together, Comp2 was negatively associated with the Total clinical examination score (β (95% CI) = -15.8 (-26.51; -5.09), $p = 0.005$). Additionally, sex-specific analyses revealed negative association in boys only, specifically on the Gross Motor score of the MABC-II ((β (95% CI) = -1.09 (-2.15; -0.13), $p = 0.044$) (Table 4).

Weighted quantile sum model

The results of the WQS model are presented in Table 5. No correlation was found between the WQS indexes and either the scores of the clinical examination or the MABC-II in the whole population. After stratification by sex, significant negative association was observed with the Gross Motor score of the MABC-II, but only in boys (β (95% CI) = -2.36 (-3.42; -0.62), $p = 0.023$). Among the six chemicals included, PFOA, PFNA and PCB-180 were the primary contributors to the negative effect, collectively accounting for more 50% of the observed association with the motor outcomes (Table 6).

Table 5 Adjusted associations (β coefficient and 95% confidence intervals (CI)) between WQS index and scores of the clinical examination and the MABC-II test performed in preschool children. Statistically significant results ($p < 0.05$) are reported in bold

	Clinical Examination				MABC-II					
	Total Score		Motor specific clinical score		Total Score		Fine Motor		Gross Motor	
	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
WQS	-7.77	(-25.86 ; 11.35)	2.01	(-4.25 ; 8.82)	-0.47	(-1.48 ; 0.57)	0.25	(-0.58 ; 1.11)	-1.14	(-2.45 ; 0.28)
Girls	9.31	(-13.32 ; 21.52)	6.19	(-2.02 ; 14.20)	0.41	(-1.20 ; 2.01)	0.51	(-0.31 ; 1.91)	1.70	(-0.70 ; 2.52)
Boys	-11.74	(-29.41 ; 7.65)	-0.97	(-6.28 ; 7.99)	-1.17	(-2.41 ; 0.08)	-0.27	(-1.43 ; 0.84)	**-2.36**	**(-3.42 ; -0.62)**

Table 6 Weights from weighted quantile sum regression for pollutant index and risk of lower Gross Motor score of the MABC-II test in boys. Weights above 0.167 are in bold

Increased risk of developing a lower Global Motor score in Boys	
Chemical	*Weight*
PFOA	**0.38**
PFNA	**0.25**
PCB 180	**0.18**
PFHxS	0.09
PFOS	0.08
PCB 153	0.02

Discussion

We assessed cord blood concentrations of six EDCs and investigated their combined effects on child neuromotor development at 6 years of age.

PCA revealed a negative association between the second component (Comp2) and the Total score of the clinical examination in the whole population. Comp2 was characterized by high loading factors for PCB-153 and – 180.

Sex-specific analysis showed a negative association between exposure to a mixture of EDCs and the Gross Motor score of the MABC-II in boys, as identified by both PCA and WQS. PCA highlighted PFASs and PCB-180 as significant loading factors, while WQS identified PFOA, PFNA, and PCB-180 as the chemicals with the greatest impact.

Impact of EDC mixtures on motor skills in children

Effects of antenatal exposure to PCBs or PFASs on the development of motor function are inconsistently reported in literature (Appendix A and B).

Prenatal PCB exposure has been shown to be associated with altered neonatal motor performance and reflexes [59–62] in some studies but not others [63–67]. In toddlers, associations between antenatal exposure to some PCB and more minor neurological dysfunctions were reported [29, 68–70]. However, no or positive correlations [29, 66, 71–73] were found in other similar studies.

Using developmental assessment instruments, mostly the psychomotor index of the BSID, some studies demonstrated a negative association [74–78]. However, 13 other studies, overall more recent and carried out on a smaller population, did not confirm this findings [27, 30, 66, 79–88]. Higher levels of organochlorine pollutants were, however, linked to significant motor delay in one of them [30]. Most studies using quantitative motor or visuo-motor tests, such as the Motor domain area of the McCarthy Scales of Children's Ability test, failed to identify specific impairment [69, 73, 89–97].

Interestingly, scores worsened at 7 years of age when parental and home characteristics were less optimal [98]. More recently, Forns et al. reported poorer fine motor skills associated with greater prenatal exposure to PCB-153, but not to other PCBs such as -118, -138, or -180, at 4 years of age [94]. Additionally, one single Dutch study identified detrimental influence of antenatal exposure to PCB-183 on ball skills in 14-year-olds assessed with the MABC test [99]. No other article has examined motor function in adolescents.

Only one study analysed the impact of prenatal exposure to PFASs on clinical examination using the Neonatal Network Neurobehavioral Scale. This study found no association with any of the 11 outcomes [100], although a 10-fold increase in prenatal PFOA exposure increased the odds of hypotonia. Among studies evaluating motor development in infants, seven of them showed negative correlations [31, 32, 48, 101–104] while three reported no association [105–107]. In older children, specific motor tests or questionnaires did not reveal negative impacts on fine or global motor functioning [95, 102, 108]. However, a positive correlation was found between antenatal PFOA exposition and the Wide Range Assessment of Visual Motor Abilities (WRA-VMA) which assesses visual-motor (drawing subtest), fine motor (pegboard subtest) and visuospatial (matching subtest) skills [49].

The effects of PCBs and PFASs had already studied together in large cohort studies including the Sapporo/Hokkaido Study [33, 83, 84, 106], the INMA Project [78, 94, 102], and the INUENDO cohort [95]. However, in these prospectives studies, each chemical was analysed individually. Considering the interaction of various exposures, single-pollutant models were less interpretable when studying correlated chemical pollutants. Studies analyzing the effect of prenatal exposure to PFAS mixtures demonstrated negative associations with motor development in children aged 1 to 3 years [32, 48, 101]. However, these combined effects were not investigated in

older children. Evidence regarding the negative impact of PFASs on motor development in older children remained inconclusive to date [95, 102, 108]. To our knowledge, no prior study had analyzed the combined effects of PCBs and PFASs on motor development.

Our results for the whole population were consistent with studies reporting negative effects of antenatal PCBs exposure on neuromotor development. Furthermore, consistent with previous research, PFASs did not appear to have significant negative effect on motor function in preschool children when boys and girls were analyzed together. Interestingly, the negative correlation observed in our clinical examination data, which does not seem to be fully explained by motor deficit, leads us to suspect other cognitive impairments. Indeed, this test aims to briefly evaluate the basic skills predictive of learning disabilities in primary school. It not only includes clinical assessment of motor acquisitions, but also other prerequisites for learnings such as attentional or language, all of which would deserve a more detailed analysis.

Sex impact

In sex-specific analyses, the negative association between Comp2 and the Total clinical examination score was not significant. However, we showed a negative association between antenatal exposure to a mixture of EDCs and the Gross Motor score of the MABC-II, as observed in both the PCA and WQS models. In both approaches, a mixture of PCB-180 and PFASs was implicated.

Although our results had to be interpreted with caution due to the small sample size, they were consistent with the existing literature. Indeed, most studies investigating sex-specific associations between prenatal PCBs or PFASs exposure and child's neurodevelopment also suggested that boys were more vulnerable to environmental chemicals than girls. Regarding psychomotor development at six months, Kishi et al. reported that higher exposure to five PCB congeners was associated with a lower developmental score in boys, compared with two PCB congeners in girls [33]. Similarly, Berghuis et al. found that higher exposure to PCBs was associated with more optimal scores in girls [29]. The adverse effects of antenatal PFAS exposure on motor development were also found to be larger in boys than in girls [31, 32, 101]. In the Flemish Environment and Health Study, prenatal exposure to higher organochlorine pollutants, including PCBs, were associated with a significant motor delay, an effects more pronounced in boys than in girls [30]. However, some studies did not identify any sex-specific correlations when boys and girls were analysed separately [48, 49, 102, 106]. Finally, better motor skills at 4 years in boys more exposed to PFOA *in utero* were reported in only one study, which assessed motor function using a simple questionnaire [107].

Although the exact mechanisms are unknown, some hypotheses underlying the sex-specific effects of EDCs on motor development have been put forward. First of all, pharmacokinetic modelling in animal studies has shown longer half-lives and a greater tissue accumulation of some EDCs in male than in female rats [109–111]. Chemical exposure during gestation may alter foetal thyroid and sex hormone levels, which can adversely affect cognitive functions in later life, in a sexually dimorphic manner [5, 112]. Furthermore, EDCs can have a direct deleterious effect on specific neurons. For example, Nguon et al., who examined sex effects of a certain mixture of PCBs on cerebellar development and motor functions in rat neonates, found a reduced cerebellar mass in pups, more pronounced in male than female pups [113]. The cerebellum plays an essential role not only in motor control (including balance and coordination) but also in motor learning and cognition. The development of the cerebellum takes place from the early embryonic period until the first years of life making this brain area particularly vulnerable to environmental insults [114]. Another explanation for sex-specific effects can be the differences in interference with the expression of genes, particularly those coding for hormonal receptors [115]. All these data are consistent with our findings that prenatal EDCs mixture exposure interferes with motor outcome mainly in boys. However, more studies should be conducted to elucidate the sex differences of EDCs effect on neurodevelopment.

Strengths and limitations

Strengths of this study include the prospective design and the use of complementary clinical methods to assess different components of neuromotor development. The selected instruments were adapted for preschool-age children and more sensitive than traditional questionnaires for measuring pre-clinical alterations in motor functions. All children were seen by the same examiner to minimize the risk for bias due to interobserver variation. Moreover, the main EDCs of three families of EDCs were collected at birth in blood cord. The long half-life of these compounds in humans indicates a steady exposure condition during pregnancy. As such, a single cord blood measure of EDCs levels has been suggested as a good indicator of foetal exposure [116]. Moreover, the ante- and perinatal periods constitute critical moments for the development of the central nervous system. Finally, two validated statistical approaches were used to evaluate the impact of a mixture of EDCs on neuromotor function, with analyses adjusted for covariates collected prospectively.

However, some potential limitations of the current study should be mentioned. The main limitation of this study includes the relatively small number of

participants. There was considerable loss to follow-up for neurodevelopmental assessment during the study period, which increased the risk of selection bias. However, the characteristics of subjects in the original cohort were similar to those in the final sample [35]. Other toxicants such as lead, which adverse effects on the developing brain have long been studied [117], could have been added to the analyses. A choice had to be made taking into account the limited volume of the blood sample. Additionally, the relationship between EDCs and developmental measures may have been confounded by postnatal environmental influences that were not evaluated in the present study. For example, environmental encouragement has been found to correlate with the pace of motor skills development [118], but this kind of stimulation is difficult to calibrate. Moreover, as mentioned by Torres-Sanchez et al. [119], children who were most exposed to chemicals in utero seems to be those who are also exposed to less stimulating developmental environment. In our population, the motor performance of participating children was rather poor. This is in line with previous studies showing secular declines in physical activity in children [120]. Moreover, our results of clinical examination and movement performance showed a trend towards improvement with increasing age, as previous studies have shown improvement in manual dexterity [121], aiming and catching [122] and balance [123] with age. Children around the age of 6 normally spend their time performing fine and gross motor activities and the time spent practicing positively influence the mastery of specific prehension skills [124]. Concerning the clinical significance of the neuromotor developmental level observed in this cohort of preschool-aged children, it is difficult to predict later motor development or school functioning. Subtle neuromotor deficits are likely to interfere with different skills depending on the motor function, such as the acquisition of writing skills. Also, it remains to be determined whether and how the subtle motor deficits observed here persists and have an impact on the acquisition of subsequent motor skills during development. Finally, comparisons of results between different studies must be made carefully. Even on a same toxicants family, compounds might exert opposite effects, and their actions can also vary depending on factors such as the level of exposure, sex, or the presence of other pollutant(s) [18].

Conclusion

There is growing concern that exposure to some endocrine-disrupting chemicals during critical periods of human development could increase the risk of neurodevelopmental disorders, including motors disabilities.

This study aimed to assess the neuromotor function of preschool children exposed in utero to a mixture of PCBs and PFASs using two validated statistical approaches. Our findings strengthen existing evidence that environmental toxicants adversely affect the neuromotor development of young children, with boys appearing to be particularly vulnerable.

Further longitudinal research is needed to elucidate the long-term impacts of prenatal exposure to chemical mixtures on motor development and related developmental disorders.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01156-9.

Supplementary Material 1

Author contributions

C.B. designed the work, performed analysis and interpretation of the results, and wrote the main manuscript textP.D., C. P., C.C. and F.B. made some analysis and revised the workA-S.P. and L.R. designed the work, performed interpretation of data and revised the workAll of the authors have read and approved the paper. This article has not been published previously and is not considered by any other peer-reviewed journal.The authors have no competing interests to declareFunding sources supporting this work are provided by the Léon Fredericq Foundation of Liege. This study was approved by collegial decision from the university hospital-faculty medical Ethics Committee of Liege (Nr 2019 / 67).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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