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# Association of exposure to mixture of chemicals during pregnancy with cognitive abilities and fine motor function of children

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ABSTRACT

Chemical exposures often occur in mixtures and exposures during pregnancy may lead to adverse effects on the fetal brain, potentially reducing lower cognitive abilities and fine motor function of the child. We investigated the association of motheŕs exposure to a mixture of chemicals during pregnancy (i.e., organochlorine compounds, per- and polyfluoroalkyl substances, phenols, phthalates, organophosphate pesticides) with cognitive abilties and fine motor function in their children. We studied 1097 mother–child pairs from five European cohorts participating in the Human Early Life Exposome study (HELIX). Measurement of 26 biomarkers of exposure to chemicals was performed on urine or blood samples of pregnant women (mean age 31 years). Cognitive abilities and fine motor function were assessed in their children (mean age 8 years) with a battery of computerized tests administered in person (Raveńs Coloured Progressive Matrices, Attention Network Test, N-back Test, Trail Making Test, Finger Tapping Test). We estimated the joint effect of prenatal exposure to chemicals on cognitive abilities and fine motor function using the quantile-based g-computation method, adjusting for sociodemographic characteristics. A quartile increase in all the chemicals in the overall mixture was associated with worse fine motor function, specifically lower scores in the Finger Tapping Test [-8.5 points, 95 % confidence interval (CI) −13.6 to −3.4; −14.5 points, 95 % CI –22.4 to −6.6, and −18.0 points, 95 % CI −28.6 to −7.4) for the second, third and fourth quartile of the overal mixture, respectively, when compared to the first quartile]. Organochlorine compounds, phthalates, and per- and polyfluoroalkyl substances contributed most to this association. We did not find a relationship with cognitive abilities. We conclude that exposure to chemical mixtures during pregnancy may influence neurodevelopment, impacting fine motor function of the offspring.

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## 1. Introduction

Cognitive abilities, such as general intelligence, memory, attention, or cognitive flexibility, are among the strongest predictors of healthy and successful lives (Lövdén et al., 2020, Mashburn et al., 2023). An increasing number of findings suggest that cognitive abilities are grounded in sensorimotor experiences and that cognitive development is strongly related to fine motor function (Martzog et al., 2019), which is a strong predictor of mental and physical functioning during the life-course (Austin et al., 2011). As the developing fetus is particularly susceptible to environmental toxins, there is a growing concern to protect future children from such toxins (Lanphear et al., 2005). Humans can be exposed to thousands of chemicals, which are currently being produced (Landrigan et al., 2018, Landrigan and Goldman, 2011, Grandjean and Landrigan, 2006) and many of them cross the placenta (Mose et al., 2007, Porpora et al., 2013) and can adversely affect development of the fetal brain (Zoeller et al., 2012).

It is well known that prenatal exposure to organochlorine (OC) compounds, per – and polyfluoroalkyl substances (PFAS), phenols, phthalates, and organophosphate (OP) pesticides may be associated with altered infant brain development, which could manifest as lower cognitive abilities and worse fine motor function (Braun, 2017, Vrijheid et al., 2016). These chemicals are widely present as legacy chemicals in nature or currently used in households, food and many consumer products. Many studies have evaluated health effects of single chemicals or small groups of chemicals, despite the fact that humans are exposed to mixtures of chemicals simultaneously (Zoeller et al., 2012). The effects of multiple simultaneous exposures during early life on cognitive abilities and fine motor function in childhood have been investigated using approaches that simply correct for multiple testing or identify the best predictors through variable selection (Julvez et al., 2021). However, new methods have been developed to investigate mixtures that aim to account for the joint effect of combinations of chemicals (Lazarevic et al., 2019). The simultaneous exposure to mixtures of chemicals may elicit effects that would otherwise be ignored in an analysis using a single-pollutant approach, such as additive or synergistic effects, and can lower the threshold for the harmful effects of individual exposures (Zoeller et al., 2012, Kortenkamp, 2014).

Some recent publications that assessed the exposure to a mixture of chemicals using these novel approaches on offspring's cognitive abilities (Tanner et al., 2020, Loftus et al., 2021, van den Dries et al., 2021, Luo et al., 2022, Lee et al., 2021, Yim et al., 2022) and fine motor function (Daniel et al., 2020, Luo et al., 2022) provided mixed results. Some found strong associations, others only with some outcomes, in some population subgroups or no associations at all. However, the previous studies mainly focused on a selected group of chemicals, such as phthalates (Daniel et al., 2020, Loftus et al., 2021, Day et al., 2021, Li et al., 2020), phenols and phthalates (Guilbert et al., 2021), PFAS (Luo et al., 2022, Skogheim et al., 2021), persistent organic pollutants (Yim et al., 2022), and nonpersistent chemicals (van den Dries et al., 2021), while assessment of a mixture to a wider range of chemical groups is scarce (Tanner et al., 2020). However, in the real world, for example commonly in households, one is often exposed to a broad group of chemicals at the same time. All of the previous studies were based only on a cohort from one country, which limits their generalizability. Capitalizing on an exposome cohort covering various regions of Europe, our objective was to study the association of mother's exposure to a mixture of chemicals during pregnancy (OC compounds, PFAS, phenols, phthalates, and OP pesticides) with cognitive abilities and fine motor function in children.

## 2. Material and methods

### 2.1. Participants

We utilized data from the Human Early Life Exposome (HELIX) study (Maitre et al., 2018), a collaborative project across six established longitudinal population-based birth cohorts in six European countries: the Born in Bradford (BiB) study in the UK (Wright et al., 2013), the Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant (EDEN) study in France (Heude et al., 2016), the INfancia y Medio Ambiente (INMA) Project in Spain (Guxens et al., 2012), the Kaunus cohort (KANC) in Lithuania, the Norwegian Mother, Father and Child Cohort Study (MoBa) (Magnus et al., 2016) and the RHEA Mother Child Cohort study in Crete, Greece (Chatzi et al., 2017). As KANC had missing data on most of the chemicals in the prenatal samples analyzed in this study, we did not include it.

A subcohort of 1097 mother–child pairs were recruited for a detailed investigation including neuropsychological assessment at 6–12 years old. They were selected from the entire cohorts so that there were approximately the same number of mother–child pairs from each cohort (specifically 205 in BiB, 198 in EDEN, 272 in MoBa, 199 in RHEA and 223 in INMA). Inclusion and exclusion criteria varied between cohorts and are described elsewhere (Maitre et al., 2018).

### 2.2. Exposure to chemicals

Maternal samples for the assessment of exposure to chemicals were collected in the first and third trimester for INMA, first trimester for RHEA, during the first and the second trimester for EDEN and MoBa, and during the second and the third trimester for BiB. In the present study, we analyzed 26 biomarkers of exposure to chemicals, which were assessed in all five cohorts: 5 OC compounds, 4 PFAS, 5 phenols, 7 phthalates, and 5 OP pesticides. These chemicals were selected as they belong to groups, within which individual members share biological properties and are often repleacable for one another. Complete methodology including specific values of limit of quantification and limit of detection are available elsewhere (Haug et al., 2018, Tamayo-Uria et al., 2019). Briefly, measurements of most chemicals were performed at the Department of Food Safety at the Norwegian Institute of Public Health (NIPH) in Norway. Some INMA samples were analyzed at the Laboratory of Public Health in Guipuzcoa in Spain (OC compounds) (Goñi et al., 2007), Institute for Occupational Medicine in Aachen in Germany (PFAS) (Manzano-Salgado et al., 2015), and Hospital del Mar Medical Research Institute in Barcelona in Spain (phthalates) (Valvi et al., 2015). Some RHEA samples were assessed at the National Institute for Health and Welfare in Kuopio, Finland (OC compounds) (Koponen et al., 2013) and some EDEN samples at the Center for Disease Control and Prevention in the US (phenols) (Philippat et al., 2012). For all assessments at the NIPH or their contract laboratories, concentrations were also reported below limit of quantification whenever a signal was observable. For samples where the concentrations were below limit of detection, singly imputed values were obtained using a quantile regression approach.

The concentration of OC compounds was determined in serum or plasma in most cases using methods reported by Caspersen (Caspersen et al., 2016), but another method was used in INMA (Goñi et al., 2007). The concentrations of OC compounds were adjusted for lipids (ng/g of lipids), which were determined in the Fürst Medical Analysis Laboratory in Norway in serum or plasma using the FS kit from DiaSys (phospholipids) or the ADVIA® Chemistry XPT System (other lipids). In INMA and RHEA, total cholesterol and triglycerides were determined with the Cobas Mira self-analyzer and phospholipids were calculated based on a formula (Covaci et al., 2006). Total fat percentage was calculated according to Grimvall (Grimvall et al., 1997).

Concentration of PFAS was determined in serum or plasma using the method by Haug (Haug et al., 2009). In INMA maternal plasma samples, concentrations of PFAS were determined according to Manzano-Salgado (Manzano-Salgado et al., 2015). Assessment of the comparability between labs has been previously described (Haug et al., 2018).

In urine, analysis of phenols (Sakhi et al., 2018), OP pesticides (Cequier et al., 2016) and phthalates (Sabaredzovic et al., 2015) was

performed. In the majority of INMA maternal samples, phthalates were determined according to Valvi (Valvi et al., 2015). The urinary concentrations of these three chemical groups were adjusted for creatinine (μg/g of creatinine). Measurements of concentration of creatinine in urine in most samples were performed on an AU680 Chemistry System form Beckman Coulter using DRI® Creatinine-Detect® Test at Fürst Medisinsk Laboratorium, Norway. Creatinine in maternal samples of INMA was determined by the Jaffé method - Beckman Coulter© AU5400, while an enzymatic reaction using a Roche Hitachi 912 chemistry analyzer was utilized in EDEN.

### 2.3. Cognitive abilities and fine motor function

Cognitive abilities and fine motor function were assessed at the average age of 8 years old (range 6–12 years) with a battery of standardised, non-linguistic, and culturally blind computerized tests. In the present study, we investigated six individual outcomes: general non-verbal intelligence, sustained attention, working memory, cognitive flexibility (task switching and task shifting), and fine motor speed.

General non-verbal intelligence was assessed by Raven's Coloured Progressive Matrices (Raven and Raven, 1998). Participants had to apply logical reasoning and detect an organizing principle in visual materials, requiring participants to recognize spatial, design, and numerical relationships. The outcome was the total number of correct responses, where higher values indicated higher non-verbal intelligence.

Sustained attention was assessed with the Attention Network Test (Rueda et al., 2004). It consisted of the presentation of a row of five fish appearing either above or below a fixation point and participants had to indicate the direction, in which the central fish was pointing, ignoring distractions. The outcome that we used was standard error of the hit reaction time, where higher values indicate inattentiveness.

Working memory was assessed with the N-back Test (Vuontela et al., 2003). Participants were required to monitor a series of stimuli (colours and numbers) presented in the centre of the screen and had to respond whenever a given stimulus was the same as the one presented in previous trials (1-, 2-, and 3-back). We selected 3-back results since they require higher working memory demands. The outcome used was d prime, a measure derived from signal detection theory, with higher levels indicating better working memory (Forns et al., 2014).

The Trail Making Test (Lezak et al., 2004) was used to assess task switching and task shifting, which both indicate cognitive flexibility. In part A, participants had to draw lines connecting encircled numbers in a numerical order, and in part B, they had to draw lines alternating between numbers and letters in an ascending sequence. The outcomes were task switching (unconscious shift in attention) and task shifting (conscious shift in attention), with higher values indicating lower cognitive flexibility. Task switching was the time to complete part B. Task shifting was calculated as follows: (time to complete part A minus time to complete part B) divided by time to complete part A.

Fine motor function was assessed with fine motor speed, which was measured by the Finger Tapping Test (Lezak et al., 2004). Participants had to tap a key for 15 s, twice with their preferred hand and twice with their non-preferred hand. The average value of the sums of taps for the preferred hand and the non-preferred hand was used as the outcome, with higher values indicating higher fine motor speed.

### 2.4. Confounders

We selected confounding variables based on a directed acyclic graph (DAG) as factors that are antecedent of the exposure and have an effect on the outcome (Supplement, Figure S1). Data was obtained from questionnaires administered during pregnancy, which included mother's age at the time of exposure assessment, mother's education (low / middle / high), father's education (low / middle / high), mother's country of origin (born in the country of the cohort / not born in the country of the cohort), mother's pre-pregnancy body mass index (calculated from self-reported weight and measured height, $kg/m^2$; underweight or normal weight / overweight / obesity), mother's parity (no previous child / one previous child / two or more previous children) and mother's active smoking during pregnancy (yes / no).

In addition, we adjusted for offspring's sex (male / female), which was obtained from hospital records, offspring's age at the time of outcome assessment, which was calculated based on the visit date. Both these variables are strong determinants of the outcomes, as cognitive abilities and fine motor function differ for boys and girls and increase with age. Moreover, as there were differences in characteristics of participants between individual subcohorts (Supplement, Table S1 and S2) and there could be also batch effects, we also adjusted for subcohort (BiB / EDEN / INMA / MoBa / RHEA).

### 2.5. Statistical analysis

Prior to the analysis, we used the expectation–maximization algorithm to impute the missing data on confounders (7.7 % for father's education, <5% for other confounders), using the package *Amelia* in R. To estimate the joint effect of all chemicals on cognitive abilities and fine motor function of the offspring, we used the quantile-based g-computation method in R, which has been previously described in detail (Keil et al., 2020). The quantile g-computation estimates the effect on an outcome by simultaneously increasing all chemicals within the mixture by a quartile. It decreases type one error and deals with co-pollutant confounding, as it allows assessment of the joint effect of the overall mixture as well as a specific chemical group (e.g. phthalates), while adjusting for confounding by other chemical groups. We adjusted all models for confounders detailed above.

We first investigated the overall mixture effects (all chemicals in the model) on each of the outcomes, fitting a linear model. Further, we explored non-linearity the following way: For each outcome, we repeatedly fit the full model, adding one by one each individual chemical squared, and tested if this model has a better fit than the full linear model, using Akaike information criterion (AIC). If the AIC was lower for the non-linear model than for the linear one, we compared their fit, utilizing likelihood ratio (LR) test. In case the p value from LR test was below 0.05, we considered this as evidence of non-linearity for the specific chemical tested. If more chemicals individually showed a better fit with a quadratic term for a specific outcome, we combined these quadratic terms into one final model, with the rest of chemicals as linear. We then assessed with the LR test, if the final model reached a better fit than the fully linear one. If the p value from the LR test was $< 0.05$, we chose the final model with the combined quadratic terms.

The models with the outcomes non-verbal intelligence and sustained attention had a better fit as linear for all chemicals. The model with the outcome working memory included hexachlorbenzene (HCB) with a quadratic term. The models with the three remaining outcomes fit better when quadratic terms for more chemicals were included. For all of them, the final models with the combined quadratic terms had a better fit than the fully linear one. The model with the outcome task switching had the best fit with quadratic terms for perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), and mono-2-ethyl-5-oxohexyl phthalate (MEOHP). The model with the outcome task shifting included quadratic terms for PFHxS, PFOS, mono-n-butyl phthalate (MnBP), and dimethyl phosphate (DMP). For the outcome fine motor speed, the model included quadratic terms for perfluorooctanoate (PFOA), HCB, and oxybenzone (OXBE). As we tested six outcomes, we applied Bonferroni correction and accepted results as statistically significant if the p value was $< 0.008$.

When we identified an association between the overall mixture and a specific outcome, we investigated the exposure effect within each chemical group on the identified outcome, while adjusting for the other chemical groups (one summary variable for each group). In addition, we estimated which chemicals within the mixture were contributing the most to the overall mixture effect for the model. In line with a previous

study (van den Dries et al., 2021), we assumed linearity in this model and did not include the quadratic terms. This analysis generates percentage of positive or negative weight corresponding to the extent, to which each chemical contributes to the association. Data analysis was performed using R statistical programming language, version 4.0.5 (Team, 2021).

## 3. Results

We studied 1097 mother–child pairs (see Tables 1 and 2 and Supplement, Figures S2 and S3 for their descriptive characteristics). Mothers were on average 31 years old during pregnancy. Half of the cohort were mothers with university education, 12 % of them were obese before pregnancy, and 17 % of them smoked when pregnant.

Fig. 1 presents differences in estimated outcomes for each exposure quartile compared to the lowest quartile in all chemicals within all chemical groups. The overall mixture of all chemicals was associated only with lower fine motor speed for the second, third, and fourth quartile (-8.5 points, 95 % confidence interval (CI) −13.6 to −3.4; −14.5 points, 95 % CI −22.4 to −6.6; and −18.0 points, 95 % CI −28.6 to −7.4) of the overall mixture, respectively, when compared to the first quartile (p value for the overall model 0.003). When Bonferroni correction was applied, no associations were observed between the overall mixture and general non-verbal intelligence, sustained attention, working memory, task shifting, or task switching (Supplement, Table S3).

Further analyses on the exposure effect within each group of chemicals, while adjusting for the other chemical groups, were ran for fine motor speed (Fig. 2 and Supplement, Table S4). A quartile increase in the OC compounds mixture was associated with lower scores in fine motor speed (-4.4 points, 95 % CI −7.3 to −1.5 for the second quartile; −6.7 points, 95 % CI −10.9 to −2.4 for the third quartile; and −6.7 points, 95 % CI −12.4 to −1.1 for the fourth quartile, when compared to the first quartile). Similarly, a quartile increase in the phthalates mixture was associated with lower fine motor speed as well (-3.1 points, 95 % CI −4.9 to −1.2 for the second quartile; −6.2 points, 95 % CI −9.9 to −2.5 for the third quartile; and −9.3 points, −14.8 to −3.7 for the fourth quartile, when compared to the first quartile). To a smaller extent, we observed an association between the PFAS mixture and fine motor speed, however, the pattern of the association did not show a dose–response relation and only the second and third quartile were significantly different from the first quartile (-3.2 points, 95 % CI −5.5 to −1.0 for the second quartile; −4.0 points, 95 % CI −7.2 to −0.7 for the third quartile; when compared to the first quartile). Mixtures of phenols and OP pesticides were not associated with fine motor speed.

Table 3 presents the contributed weight for each chemical included in the overall mixture on fine motor speed. Overall, the total contribution of chemical concentration in the negative direction (−19.2 points of lower fine motor speed) was greater than for the positive direction (+9.0 points of higher fine motor speed). Considering each group of chemicals, OC compounds, PFAS, and phthalates had a major negative weight (36 %, 34 %, and 24 %, respectively). Concerning individual chemicals, PFOA, HCB, and MEOHP had the greatest negative weight (28 %, 20 %, and 12 %, respectively). Other chemicals had a negative weight lower than 10 %.

**Table 1**
Characteristics of participants (n = 1097).

| | Distribution |
|---|---|
| Offspring's age at outcome assessment, years | 8.2 ± 1.6 |
| Offspring's sex (female *vs.* male) | 497 (45.3) |
| Mother's age at exposure assessment, years | 31.1 ± 4.8 |
| Mother's educational level | |
| Low | 161 (15.2) |
| Middle | 362 (34.2) |
| High | 535 (50.6) |
| Father's educational level | |
| Low | 192 (19.0) |
| Middle | 374 (36.9) |
| High | 447 (44.1) |
| Mother's prepregnancy body mass index | |
| Underweight or normal weight | 719 (66.7) |
| Overweight | 229 (21.2) |
| Obesity | 130 (12.1) |
| Mother's country of birth (country of the cohort *vs.* others) | 910 (84.0) |
| Mother's parity | |
| No child | 497 (46.4) |
| One child | 401 (37.4) |
| Two or more children | 173 (16.2) |
| Mother's smoking during pregnancy (yes *vs.* no) | 178 (16.8) |
| Cognitive abilities and fine motor function in offspring | |
| Non-verbal intelligence | 26.9 ± 6.4 |
| Sustained attention | 0.3 ± 0.1 |
| Working memory | 1.2 ± 1.1 |
| Task switching (minutes) | 1.5 ± 0.9 |
| Task shifting | 0.1 ± 0.4 |
| Fine motor function | 126.5 ± 23.2 |

Note: Values are frequency numbers and percentages for categorical variables, mean and standard deviation for continuous variables. Missing data on covariates were not imputed.

**Table 2**
Distribution of prenatal exposures to chemicals.

| | Median (Q1; Q3) | Mean ± SD |
|---|---|---|
| **Organochlorine compounds**, ng/g lipids | | |
| Dichlorodiphenyldichloroethylene (DDE) | 104.7 (51.8; 222.1) | 203.1 ± 307.1 |
| Hexachlorbenzene (HCB) | 16.3 (11.2; 26.0) | 25.6 ± 32.0 |
| Polychlorinated biphenyl (PCB) −138 | 18.2 (11.1; 32.3) | 25.2 ± 25.2 |
| Polychlorinated biphenyl (PCB) − 153 | 35.3 (20.8; 61.2) | 49.3 ± 58.9 |
| Polychlorinated biphenyl (PCB) − 180 | 20.8 (11.6; 37.2) | 33.1 ± 47.6 |
| **Per- and polyfluoroalkyl substances**, μg/l | | |
| Perfluorooctanoate (PFOA) | 2.6 (1.7; 3.5) | 2.8 ± 1.8 |
| Perfluorononanoate (PFNA) | 0.7 (0.4; 1.1) | 0.8 ± 0.6 |
| Perfluorohexane sulfonate (PFHxS) | 0.6 (0.4; 1.0) | 0.8 ± 1.1 |
| Perfluorooctane sulfonate (PFOS) | 7.1 (4.6; 10.7) | 8.6 ± 6.2 |
| **Phenols**, μg/g creatinine | | |
| Propyl paraben (PRPA) | 44.2 (8.9; 134.2) | 193.1 ± 778.1 |
| Bisphenol A (BPA) | 2.8 (1.6; 6.6) | 7.2 ± 12.9 |
| B-butyl paraben (BUPA) | 3.4 (0.4; 14.4) | 13.1 ± 26.6 |
| Oxybenzone (OXBE) | 4.9 (1.5; 27.5) | 146.2 ± 701.4 |
| Triclosan (TRCS) | 6.3 (1.5; 79.9) | 101.8 ± 215.5 |
| **Phthalates**, μg/g creatinine | | |
| Monoethyl phthalate (MEP) | 178.9 (72.0; 468.5) | 447.9 ± 964.6 |
| Mono-*iso*-butyl phthalate (MiBP) | 38.7 (23.3; 60.7) | 54.5 ± 61.6 |
| Mono-n-butyl phthalate (MnBP) | 29.6 (18.3; 47.3) | 57.7 ± 236.7 |
| Mono benzyl phthalate (MBzP) | 7.3 (3.6; 15.3) | 17.8 ± 48.2 |
| Mono-2-ethylhexyl (MEHP) | 8.7 (4.4; 15.3) | 13.9 ± 22.2 |
| Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) | 18.2 (10.5; 31.2) | 31.3 ± 61.1 |
| Mono-2-ethyl-5-oxohexyl phthalate (MEOHP) | 14.1 (8.3; 23.7) | 23.0 ± 43.6 |
| **Organophosphate pesticides**, μg/g creatinine | | |
| Dimethyl phosphate (DMP) | 8.4 (4.1; 16.4) | 14.2 ± 20.8 |
| Dimethyl thiophosphate (DMTP) | 5.0 (2.1; 12.4) | 12.1 ± 22.3 |
| Dimethyl dithiophosphate (DMDTP) | 0.6 (0.2; 4.6) | 6.3 ± 21.1 |
| Diethyl phosphate (DEP) | 3.3 (1.9; 6.4) | 5.6 ± 9.5 |
| Diethyl thiophosphate (DETP) | 0.6 (0.1; 2.6) | 2.6 ± 5.1 |

Note: Q1, first quartile; Q3, third quartile; SD, standard deviation.

## 4. DISCUSSION

In the present study, capitalizing on more than 1000 mother–child pairs from 5 European countries, we found that prenatal exposure to a mixture of 26 chemicals, in particular OC compounds, phthalates, and PFAS, was associated with lower fine motor function, as assessed by fine motor speed, in 8 year old children. We did not find any association of

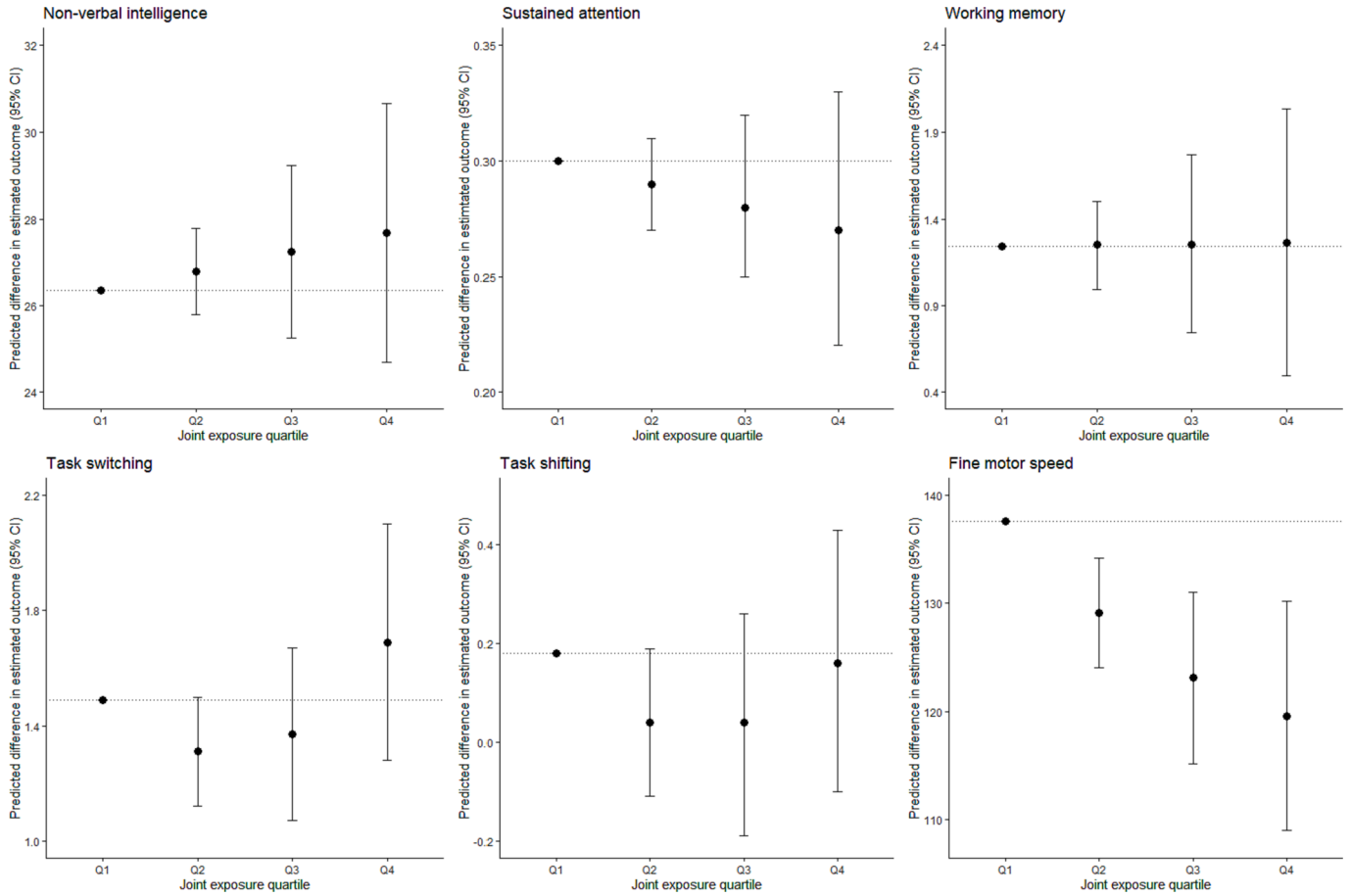


**Fig. 1. Predicted differences in estimated outcomes for each exposure quartile compared to the lowest quartile in all biomarkers of exposure within all chemical groups** *Models adjusted for cohort, offspring's sex, offspring's age at the time of outcome assessment, mother's age at the time of exposure assessment, mother's educational level, father's educational level, mother's country of birth, mother's pre-pregnancy body mass index, mother's parity, and mother's smoking during pregnancy. Higher values indicate better performance in non-verbal intelligence, working memory and fine motor speed, while worse performance in sustained attention, task switching, and task shifting. The models with the outcomes non-verbal intelligence and sustained attention are linear. The model with the outcome working memory includes a quadratic term for hexachlorbenzene. The model with the outcome task switching includes quadratic terms for perfluorohexane sulfonate, perfluorooctane sulfonate, and mono-2-ethyl-5-oxohexyl phthalate. The model with the outcome task shifting includes quadratic terms for perfluorohexane sulfonate, perfluorooctane sulfonate, mono-n-butyl phthalate, and dimethyl phosphate. The model with the outcome fine motor speed includes quadratic terms for perfluorooctanoate, hexachlorbenzene, and oxybenzone.*

prenatal exposure to this mixture of chemicals with cognitive abilities (i.e., general non-verbal intelligence, sustained attention, working memory, and cognitive flexibility).

Previous literature, which did not take into account chemical mixtures, indicates that prenatal exposure to OC compounds may be related to lower early motor development (Forns et al., 2012). To the best of our knowledge, no study assessed the association of the mixture of OC compounds with fine motor function. Our finding that exposure to a mixtures of phthalates may influence fine motor function in children is in accordance with some (Kim et al., 2011, Daniel et al., 2020, Polanska et al., 2014), but not all (Gascon et al., 2015) previous studies; others found an association only in females and not males (Balalian et al., 2019, Doherty et al., 2017). Daniel et al. assessed the exposure to the mixtures of seven phthalate metabolites in more than 200 mother–child pairs residing in New York (Daniel et al., 2020). They utilized Weighted Quantile Sum (WQS) to estimate the association of the mixtures with fine motor function in 11 years old children and found a significant association with worse fine motor function only among females (Daniel et al., 2020). Luo et al. investigated the effects of a mixture of 10 PFAS in two year old children based on more than 2000 mother–child pairs from Shanghai, using a measure of motor development, which also included assessment of fine motor function. Utilizing quantile g-computation, they found that the mixture of PFAS was associated with worse motor function, when the outcome was dichotomized. However, the association was not present when the score was utilized as a continuous outcome. Their findings are not directly comparable to our study as they included largely different compounds within the PFAS mixture (Luo et al., 2022).

The potential negative effects of prenatal exposure to chemical mixtures on fine motor function in children is of concern. Fine motor function, which can be defined as small muscle movements requiring close eye-hand coordination, requires a complex communication between the premotor and motor cortex, cerebellum, basal ganglia, corticospinal tracts, and peripheral nerves, not to mention visuospatial, sensory, and executive function processing (Burr and Choudhury, 2020). Previous studies showed that better fine motor function in children is predictive of greater reading as well as mathematical skills and general academic success (Fischer et al., 2020). Other results indicated that fine motor function but not gross motor skills in childhood predicted reasoning in adolescence and that this association mediated the relationship between early fine motor function and later reading and math ability (Cortes et al., 2022). As imaging studies on effects of chemicals on the structure and function of the brain are scarce, the neural mechanisms underlying the detected association with fine motor function are not known. As brain regions underlying the development of fine motor function and cognitive abilities differ and have different critical windows, it is possible that the timing of the exposures is crucial in influencing the impact on the cognitive or motor domain.

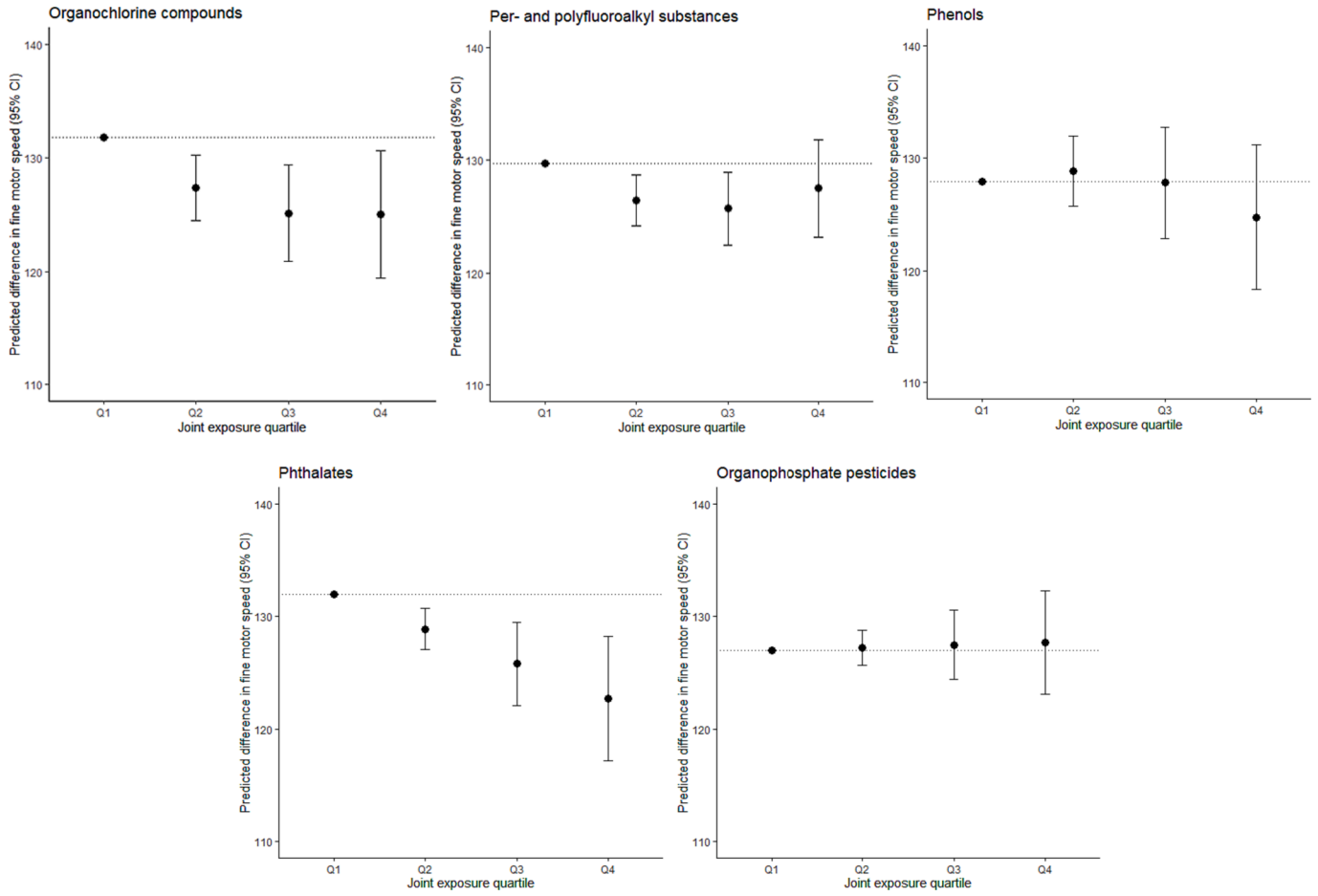


**Fig. 2. Predicted differences in fine motor function for each exposure quartile compared to the lowest quartile in biomarkers of exposure within individual chemical groups** *Models adjusted for cohort, offspring's sex, offspring's age at the time of outcome assessment, mother's age at the time of exposure assessment, mother's educational level, father's educational level, mother's country of birth, mother's pre-pregnancy body mass index, mother's parity, mother's smoking during pregnancy, and all the other chemical groups. The models include quadratic terms for perfluorooctanoate, hexachlorbenzene, and oxybenzone.*

As opposed to less frequently investigated fine motor function, more epidemiological studies were perfomed with the outcome of cognitive abilities (Martínez-Martínez et al., 2021). Our findings on cognitive abilities were null, which is not in line with several previous studies (Luo et al., 2022, Tanner et al., 2020, van den Dries et al., 2021), although comparison is difficult because of the use of different approaches to investigate mixture effects and different chemical mixture combinations. Using quantile g-computation, in the aforementioned study by Luo et al., the authors found that a mixtures of PFAS was associated with decreased cognitive and language skills in two years old children (Luo et al., 2022). Studying more than 700 mother–child pairs residing in Sweden, Tanner et al. utilized WQS and found that prenatal exposure to a mixture of 26 potential endocrine-disrupting chemicals was related to lower cognitive abilities among 7-year old boys, and the effect was mostly driven by bisphenol compounds (Tanner et al., 2020). Utilizing quantile g-computation on more than 700 mother–child pairs from Rotterdam, Van den Dries et al. discovered that prenatal exposure to the mixture of phthalates, OP pesticides, and bisphenol was associated with lower non-verbal IQ in children; the association was driven mainly by phthalates (van den Dries et al., 2021). On the contrary, two other mixture studies did not provide evidence of effects on cognitive abilities. Yim et al. assessed the exposure to a mixture of persistent organic pollutants using more than 500 mother–child pairs from a Japanese birth cohort (Yim et al., 2022). Utilizing Bayesian kernel machine regression as well as quantile g-computation, they did not find effects on psychomotor and mental development in 6 months old children (Yim et al., 2022). Loftus et al. used multivariable WQS regression to estimate the prenatal exposure to the mixture of 22 phthalate metabolites on more than 1000 mother–child pairs from an American cohort and they observed predominantly null associations between mixtures of prenatal phthalates and language skills and IQ at 3 to 6 years old (Loftus et al., 2021).

The heterogeneous results across studies could be partially atributted to differences in the exposure levels of the studied chemicals due to varying policies, industries, and behaviors in individual countries. When compared to our pooled cohort, the exposure levels of phthalates in the Columbia Center for Children's Environmental Health birth cohort (Daniel et al., 2020) were highly variable. For example, the median exposure level was five times lower for mono-*iso*-butyl phthalate (MiBP) and slightly lower for monoethyl phthalate (MEP), but almost twice higher for mono benzyl phthalate (MBzP), slightly higher for MEOHP, and similar for mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) (Balalian et al., 2019). In the Shanghai birth cohort study, participants were prenatally exposed to greater levels of PFAS (the median exposure levels were almost five times higher for PFOA, twice for perfluorononanoate (PFNA), and slightly higher for PFOS), except for PFHxS, where the exposure was similar to our cohort (Luo et al., 2022). In the Dutch Generation R Study, the median exposure level to bisphenol A was half the amount in our pooled cohort. Participants from the Generation R Study were also exposed to a smaller extent to phthalates (the median levels were approximately three times lower for MiBP, and twice for MnBP, MBzP, MEHHP, MEOHP, and MEP). However, they were exposed to a greater extent to OC pesticides (median levels three times higher for dimethyl thiophosphate (DMTP), twice for DMP,

**Table 3**
Adjusted effect contribution for each chemical included in the overal mixture model on fine motor function.

| Biomarker of exposure | Negative effect contribution B (95 % CI) | Weight (%) | Positive effect contribution B (95 % CI) | Weight (%) |
|---|---|---|---|---|
| **Organochlorine compounds** | | | | |
| DDE | −0.2 (-1.6; 1.2) | 1 | | |
| HCB | −3.8 (-7.6; 0.9) | 20 | | |
| PCB-138 | | | 1.8 (-1.2; 4.8) | 20 |
| PCB-153 | −1.5 (-5.0; 2.0) | 8 | | |
| PCB-180 | −1.3 (-4.1; 1.4) | 7 | | |
| *Total* | | *36* | | *20* |
| **Per- and polyfluoroalkyl substances** | | | | |
| PFOA | −5.3 (-9.0; −1.6) | 28 | | |
| PFNA | −0.9 (-2.7; 0.9) | 5 | | |
| PFHxS | | | 0.7 (-0.9; 2.2) | 7 |
| PFOS | −0.2 (-1.8; 1.5) | 1 | | |
| *Total* | | *34* | | *7* |
| **Phenols** | | | | |
| PRPA | −0.1 (-1.1; 1.0) | 0 | | |
| BPA | −0.3 (-1.4; 0.9) | 1 | | |
| BUPA | −0.3 (-1.5; 0.8) | 2 | | |
| OXBE | | | 4.1 (0.7; 7.5) | 46 |
| TRCS | | | 0.1 (-1.0; 1.1) | 1 |
| *Total* | | *3* | | *47* |
| **Phthalates** | | | | |
| MEP | −0.8 (-1.8; 0.2) | 4 | | |
| MiBP | −0.3 (-1.4; 0.9) | 1 | | |
| MnBP | | | 0.0 (-1.2; 1.3) | 0 |
| MBzP | −1.4 (-2.7; −0.1) | 7 | | |
| MEHP | −0.1 (-1.6; 1.4) | 0 | | |
| MEHHP | | | 1.7 (-0.8; 4.2) | 19 |
| MEOHP | −2.3 (-4.7; 0.1) | 12 | | |
| *Total* | | *24* | | *19* |
| **Organophosphate pesticides** | | | | |
| DMP | −0.1 (-1.5; 1.3) | 0 | | |
| DMTP | −0.3 (-1.8; 1.2) | 2 | | |
| DMDTP | | | 0.6 (-0.6; 1.8) | 7 |
| DEP | −0.1 (-1.3; 1.0) | 1 | | |
| DETP | −0.3 (-1.2; 1.1) | 0 | | |
| *Total* | | *3* | | *7* |

Note: BPA = Bisphenol A; BUPA = B-butyl paraben; DDE = Dichlorodiphenyldichloroethylene; DEP = Diethyl phosphate; DETP = Diethyl thiophosphate; DMDTP = Dimethyl dithiophosphate; DMP = Dimethyl phosphate; DMTP = Dimethyl thiophosphate; HCB = Hexachlorbenzene; MBzP = Mono benzyl phthalate; MEHHP = Mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP = Mono-2-ethylhexyl; MEOHP = Mono-2-ethyl-5-oxohexyl phthalate; MEP = Monoethyl phtalate; MiBP = Mono-iso-butyl phthalate; MnBP = Mono-n-butyl phthalate; OXBE = Oxybenzone; PCB = Polychlorinated biphenyl; PFHxS = Perfluorohexane sulfonate; PFOA = Perfluorooctanoate; PFNA = Perfluorononanoate; PFOS = Perfluorooctane sulfonate; PRPA = Propyl paraben; TRCS = Triclosan.

diethyl thiophosphate (DETP), and diethyl phosphate (DEP)), except for dimethyl dithiophosphate (DMDTP), where the median level of exposure was 1.5 times lower than in our cohort (van den Dries et al., 2021).

Our study is strenghtened by a large sample size of mother–child pairs residing in five different European countries. We used the quantile g computation, which allowed us to investigate non-linear, complex combinations of chemicals, which approximates real world exposures. However, several limitations need to be mentioned. The cohorts included in our analysis differed in the pregnancy period when data on exposure to chemicals was assessed. Specifically, exposure was assessed in INMA in the first and the third trimester, in RHEA in the first trimester, in EDEN and MoBa in the first or the second trimester and BiB in the second or the third trimester. Previous studies suggest unique periods of susceptibility to chemical exposure and the consequent adverse effects during brain development, given that the developmental periods and neurodevelopmental processes vary between trimesters (Zhu et al., 2020). However, the relatively small sample sizes of participant in individual cohorts in our study did not allow us to determine trimester-specific associations to reveal effects of the sample collection timing. Next, the exposure to chemicals was measured only at one time point, which may result in imprecise estimates, in particular for the compounds with short elimination half-lives. Furthermore, as older and more educated mothers tend to be overrepresented in our sample, we cannot fully generalize our findings. In addition, residual confounding may be present. Specifically, our adjustment for parental education and country of birth might not have reduced all confounding effects of socioeconomic status. Furthermore, other confounding factors may be present, such as mother's cognitive ability, mental health, prenatal stress or quality of the home environment.

Even though the quantile-based g-computation method has many strengths, some weaknesses should be mentioned. The mixture under consideration only includes a subset of the measured exposures while controlling for other measured exposures. Such conditional mixture effects may be of interest in some settings where exposure sources influence the levels of some, but not all components of the mixture. Quantile g-computation forces to specify a parametric non-linear model, rather than assuming non-linearity. It estimates the parameters of a joint marginal structural model, which quantify the average effects of modifying all exposures simultaneously, with the limitation that the underlying model is not smooth and may not adequately capture the dose–response function. When the non-linearities are known, quantile g-computation is unbiased, however, whether this holds in realistic settings when non-linearities are unknown is currently unclear. In the end, the utility of quantized exposures depends on the context, it may suffer from difficulty in extrapolating results to other populations and reduced power when a linear model fits the data well.

To conclude, our study shows that prenatal exposure to a mixture of chemicals, mainly driven by OC compounds, phthalates, and PFAS, is related to worse fine motor function in children but not cognitive abilities. This suggests that these chemicals may affect motor abilities through mechanisms that are distinct from effects on cognition. Future studies need to reproduce our findings and further investigations should clarify the mediating role of structural and functional brain alterations to understand the neural pathways that may be influenced. Longer, prospective studies are necessary to reveal if the association to worse fine motor function remains until adulthood and how it impacts global functioning of affected individuals.

## CRediT authorship contribution statement

**Pavla Brennan Kearns:** Data curation, Formal analysis, Writing – original draft, Conceptualization. **Michiel A. van den Dries:** Methodology, Software, Writing – review & editing. **Jordi Julvez:** Writing – review & editing. **Mariza Kampouri:** Writing – review & editing. **Mónica López-Vicente:** Writing – review & editing. **Lea Maitre:** Writing – review & editing. **Claire Philippat:** Writing – review &

editing. **Line Småstuen Haug:** Writing – review & editing. **Marina Vafeiadi:** Writing – review & editing. **Cathrine Thomsen:** Writing – review & editing. **Tiffany C Yang:** Writing – review & editing. **Martine Vrijheid:** Funding acquisition, Resources, Writing – review & editing. **Henning Tiemeier:** Writing – review & editing. **Mònica Guxens:** Conceptualization, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108490.

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