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Prenatal Exposure to Nonpersistent Chemical Mixtures and Offspring IQ and Emotional and Behavioral Problems

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c04455.

Ten tables: Table S1 and S2 present the descriptive statistics of biomarker concentrations included and excluded in the analyses by weeks of gestation. Table S3 presents the characteristics of study sample and those excluded from the Generation R cohort. The distributions of the averaged chemical biomarker concentrations (ug/g creatinine) across pregnancy can be found in Table S4 and correlations between averaged exposure biomarkers are presented in Table S5. Table S6 shows the descriptive statistics of nonverbal IQ, internalizing problems, attention problems, aggressive behavior, and autistic traits. Table S7 presents the Adjusted estimates for associations between mixtures of pregnancy averaged biomarker concentrations (ug/g creatinine) and nonverbal IQ, and emotional and behavioral symptoms. Table S8 shows the associations with externalizing problems, Table S9 presents the same models as in Table S7 with additional adjustment for birth year, and Table S10 presents the sex stratified results (PDF)

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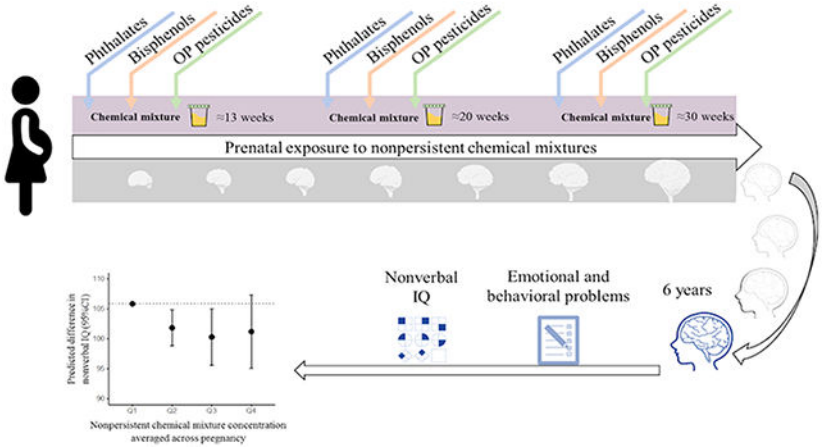
Abstract

Prenatal exposure to nonpersistent chemicals such as phthalates, bisphenols, and organophosphate (OP) pesticides is ubiquitous and occurs in mixtures. So far, epidemiological studies investigating neurodevelopmental consequences of these exposures have mainly been restricted to single-pollutant models. Thus, we studied the association between prenatal exposure to nonpersistent chemical mixtures and child IQ and emotional and behavioral problems. Data came from 782 mother–child pairs. Eleven phthalate, one bisphenol, and five OP pesticide urinary exposure biomarkers were measured three times during pregnancy and averaged. Nonverbal IQ, internalizing and attention problems, aggressive behavior, and autistic traits were assessed at child age 6 years. We used quantile g-computation to estimate the change in each outcome per quartile increase in all chemicals within the mixture. Higher exposure to the mixture was associated with lower nonverbal IQ(−4.0 points (95%CI = −7.0, −1.0), −5.5 points (95%CI = −10.2, −0.9), and −4.6 points (95%CI = −10.8, 1.5) for the second, third, and fourth quartile,

respectively, compared to the first quartile). These results were mainly driven by the phthalate mixture. No association was observed with emotional and behavioral problems. Prenatal exposure to nonpersistent chemical mixtures was associated with lower nonverbal IQ in children. Exposure to chemical mixtures during gestation is universal and may impact neurodevelopment.

Graphical Abstract



Keywords

prenatal exposures; vulnerable population; nonpersistent chemicals; endocrine disruptor chemicals; chemical mixtures; neurodevelopment

INTRODUCTION

Since the start of the industrial revolution, a plethora of chemicals have been introduced in the global environment. Of those, more than 5000 chemicals are currently being produced on a large scale.[1-3] Many chemicals end up directly in the environment.[4,5] In addition, numerous chemicals reach the general population via consumer and food products.[6,7] This extensive usage of chemicals has led to a widespread exposure of the general population. Results from biomonitoring studies have shown that three main chemical groups to which humans are continuously exposed are phthalates, bisphenols, and organophosphate (OP) pesticides.[8] Phthalates and bisphenols are chemicals typically used as solvents and plasticizers to improve plastic product characteristics and therefore are present in products such as food packaging materials, cosmetics, and flooring materials.[9-16] OP pesticides are insecticides, in particular used to protect crops in agricultural settings, which are present in, for example, fruit and vegetables.[17-19] Although exposure sources and routes vary between these three chemical groups, diet is an important source of exposure to OP pesticides, phthalates, and bisphenols. These compounds are nonpersistent and, consequently after exposure, rapidly metabolized and excreted.[20-22]

Studies have shown that these chemicals can reach the fetus when pregnant women are exposed since they are able to cross the placental barrier and the fetal blood brain barrier.[23-29] During gestation, the brain is particularly susceptible to chemical insults

because many vital biological processes take place to ensure normal brain growth.[30] Animal studies have provided ample support for a relation between low-dose exposure to phthalates, bisphenols, and OP pesticides and impaired neurodevelopment and behavior in offspring.[31-33] However, epidemiological studies investigating associations between prenatal exposure to these nonpersistent chemicals and neurodevelopmental outcomes, including IQ and emotional and behavioral problems have not been consistent.[34-37]

In real world situations, fetal exposure to these nonpersistent chemicals co-occurs in exposure combinations. Except for a small number of studies,[38-42] the majority of studies investigating the association between prenatal exposure to these chemicals and neurodevelopment in children, including our previous work,[43-45] have applied single exposure models, which have important limitations.[46] For example, co-occurring chemical exposures may join additively to produce larger effects which cannot be investigated.[47-49] Further, single exposure analyses may be biased if potential cochemical confounding exists. Finally, the rate of type I errors may inflate when correlated chemical exposures are modeled separately.[50] Examining the overall mixture effect by looking at joint exposures may overcome such limitations and provide effect estimates that more closely resemble real-world exposures.[50] Further, adverse effects on neurodevelopment during childhood may affect health later in life. For example, higher IQ in children is predictive of healthy behavior, higher educational achievement, and better employment later in life.[51,52] Moreover, children with behavior problems are more likely to have a depression in adulthood.[53,54] Therefore, the aim of this study is to expand our previous work by investigating whether prenatal exposure to the overall additive mixture effect of phthalates, bisphenols, and OP pesticides is associated with offspring nonverbal IQ and emotional and behavioral problems.

METHODS

Study Population.

The Generation R Study is a prospective population-based birth cohort designed to investigate early environmental and genetic determinants of development. All pregnant women who lived in the study area, Rotterdam, The Netherlands, were eligible. In total 8879 pregnant women were enrolled between 2002 and 2006.[55] Between February 2004 and January 2006, women provided three spot urine samples during ultrasound visits at <18 weeks, 18–25 weeks, and >25 weeks of gestation. In total, 2083 women provided a complete set of three urine samples. At child age 6 years, the mother-child pairs were invited to the clinic to engage in a follow-up study and to collect data including neurobehavioral data. Of the 2083 mothers that provided three urine samples prenatally, 1405 mother-child pairs provided data at the follow-up visit. Of those, 782 mothers had complete data on prenatal exposure biomarkers and neurodevelopment at the child age of 6 years. Mothers provided written informed consent for themselves and for their children. The study protocol underwent human subjects review at Erasmus Medical Center, Rotterdam, The Netherlands (MEC 198.782.2001.31, MEC-2007-413).

Exposure Biomarker Measures.

Specific information regarding urine specimen collection and the process for urine analyses of phthalate metabolites, bisphenols, and OP pesticide metabolites can be found elsewhere.[56-58] In short, concentrations of 18 phthalate metabolites were determined by utilizing a solid-phase extraction method followed by enzymatic deconjugation of the glucuronidated phthalate monoesters coupled with high performance liquid chromatography electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS).[59] Regarding bisphenols, eight biomarkers were quantified using a liquid–liquid extraction method followed by enzymatic deconjugation of the glucuronidated bisphenols coupled with HPLC-ESI-MS/MS.[59] The limits of detection (LOD) for phthalate and bisphenol biomarkers ranged between 0.008–1.11 μg/L. Next, six nonspecific dialkylphosphate (DAP) metabolites of OP pesticides were measured using gas chromatography coupled with tandem mass spectrometry (GC–MS/MS). As a result, three dimethyl (DM) metabolites and three diethyl (DE) metabolites were detected with LODs in the range of 0.06–0.50 μg/L. Finally, creatinine concentrations were also measured to account for urine dilution.[60]

Supporting Information (SI) Table S1 presents the descriptive statistics of biomarker concentrations included in the analyses by weeks of gestation. We included a total of 17 exposure biomarkers with more than 50% detection rate in the analysis (11 phthalate metabolites, one bisphenol, and five OP pesticides metabolites) including phthalic acid (PA, an end metabolite of all phthalates used as a proxy for unmeasured phthalate metabolites). SI Table S2 presents the descriptive statistics of biomarker concentrations excluded in the analyses by weeks of gestation. Among the 17 exposure biomarkers included in the study, the concentrations below the LOD for the 11 phthalate metabolites and bisphenol A were not estimated by the lab and were therefore imputed by LOD divided by the square root of 2.[61] For the five DAP metabolites, the concentrations below the LOD were estimated by the lab and were therefore used.[62]

Nonverbal IQ.

The nonverbal IQ score was measured at the age of 6 years using the reliable and validated Snijders-Oomen Nonverbal Intelligence Test–Revised (SON-R).[63-65] The SON-R test correlates well with the Wechsler Preschool and Primary Scale of Intelligence with a reliability score of 0.9.[63-65] The SON-R test was chosen because of the multiethnic composition of the Generation R Study. Spoken or written language is not required for this test and instructions can also be given nonverbally. The SON-R contains six language-independent subtests: Patterns, Mosaics, Puzzels, Situations, Categories, and Analogies. These subtests are classified into two empirical groups: Performance tests (Patterns, Mosaics, Puzzles) and Reasoning tests (Situations, Categories, Analogies). Because of time constraints, one performance subtest, that is, Mosaics, and one reasoning subtest, that is, Categories, was selected to have at least one subtest of each empirical group. These two subtests cover spatial insight (Mosaics) and abstract reasoning abilities (Categories). Subtest raw scores were transformed into a single age-standardized nonverbal IQ score using age-specific reference scores provided in the manual (mean = 100, SD = 15). The correlation between the IQ score based on these two subtests and the full SON-R IQ battery was high (r = 0.86).[66]

Child Emotional and Behavioral Problems.

Emotional and behavioral problems in children were measured using the primary care giver (mostly mothers)-reported Child Behavior Checklist (CBCL) 1.5–5[67] at child age 6 years and Social Responsiveness Scale (SRS)[68] at child age 7 years. The CBCL is a globally validated and reliable instrument that quantifies emotional and behavioral problems of the preceding 2 months on a continuous scale using 99 items.[67] Each item is scored on a 3-point rating scale 0 = “not true”, 1 = “somewhat or sometimes true”, and 2 = “very true or often true”. Emotional problems were assessed using the internalizing problems syndrome scale, which consisted of the summed raw scores of Emotionally Reactive (nine items), Anxious/Depressed (eight items), Somatic Complaints (11 items), and Withdrawn (eight items) syndrome scales, generating a score ranging from 0 to 72 points. Behavioral problems were assessed using the attention problems and the aggressive behavior syndrome scales. The attention problems syndrome scale (five items) generates a score ranging from 0 to 10 points. The aggressive behavior syndrome scale (19 items) generates a score ranging from 0 to 38 points. Syndrome scales are generalizable across 23 countries, including The Netherlands.[69]

Autistic traits were assessed using a SRS short form.[68] The SRS is a valid quantitative measure of subclinical and clinical autistic traits and determines several dimensions of inter-personal behavior, communication and repetitive/stereotypic behavior characteristic of autism.[70] The SRS is reported by the mother based on her observation of the child’s social behavior during the previous 6 months. The SRS has excellent correspondence to autism classification according to the Developmental, Dimensional, and Diagnostic interview (3Di) and the Autism Diagnostic Observation Schedule (ADOS).[71] In this study, a modified version of the SRS tool, consisted of 18 items, was used to lower the participant burden.[72] Each item is scored on a 4-point rating scale 0 = “never true” to 3 = “almost always true”, generating a score ranging from 0 to 72 points. The SRS and the modified version of the SRS have shown to be highly correlated ($r > 0.90$) among test scores.[73]

Potential Confounders.

Information on maternal age (year in continuous), maternal prepregnancy body mass index (BMI) (kg/m^2 in continuous), maternal education level (low: < 3 years of high school; intermediate: 3+ years of secondary education; and, high: university degree or higher vocational training), maternal ethnicity (Dutch national origin, other-Western, and non-Western), household income (<1200 euro/month, 1200–2000 euro/month, >2000 euro/month), marital status (married/partner, single), parity (0, 1, or 2+), maternal smoking (no smoking, smoked until pregnancy recognized, and continued smoking during pregnancy), maternal alcohol use (no alcohol consumption, alcohol consumption until pregnancy recognized, continued occasionally (<1 glass/week for at least two trimesters), and continued frequently (≥1 glass/week for at least two trimesters)), and maternal psychological dysfunction (score in continuous), using the Brief Symptom Inventory (BSI),[74] was collected during pregnancy. Maternal IQ was determined using the computerized Ravens Advanced Progressive Matrices Test, set I[75,76] when mother-child pairs visited the 6-year examination (score in continuous). Data on child sex (female, male) was collected at

birth and child age at assessment (years in continuous) was reported during the 6-year examination.

Statistical Analyses.

Prior to the main analyses, we used the Multivariate Imputation by Chained Equations (MICE) method in R[77,78] to impute 10 times the few biomarker concentrations that were missing due to insufficient volume or machine errors (<2.6% for DETP, and <1% for other biomarkers) and missing confounder data (<13%). The 10th imputed data set was used for the main analyses.

We expressed the biomarker concentrations on a creatinine basis (ug/g creatinine) to correct for urine dilution. We then log10 transformed and averaged the concentrations across pregnancy. Nonpersistent chemicals such as phthalates, bisphenols, and OP pesticides are rapidly metabolized and excreted in urine.[79,80] The individual exposure biomarker concentrations may therefore fluctuate over short periods of time as a consequence of contact with varying exposure sources (e.g., different diet). Therefore, the mean of the three concentrations is a better measure of exposure across pregnancy. Next, internalizing problems, attention problems, aggressive behavior, and autistic traits scores were square root transformed to improve normality of the residuals.

In order to estimate the joint effect of phthalate metabolites, bisphenol, and OP pesticide metabolite concentrations on offspring nonverbal IQ and emotional and behavioral problems, we used the quantile-based g-computation method in R.[81] Quantile g-computation estimates the effect estimate of simultaneously increasing all exposures within the mixture by a single quantile.[81] This approach also permits one to investigate the joint effect of a specific chemical group within the overall mixture (e.g., OP pesticide metabolites) while adjusting for potential confounding by other chemicals in the mixture (e.g., phthalate metabolites and bisphenols). By investigating the joint effect of the mixture, the quantile g-computation decreases multiple testing (i.e., type one error) and deals with copollutant confounding. Further, quantile g-computation allows for the identification of additive and synergistic effects of the mixture and has the ability to model nonlinearity.[81]

We first investigated the mixture effect of all chemical biomarkers combined (i.e., overall mixture effect) on offspring nonverbal IQ and emotional and behavioral problems. We estimated the change in the outcome (effect estimate) of simultaneously increasing all exposures within the mixture by a single quartile. We explored whether the associations between each biomarker and each outcome were nonlinear by including the squared exposure biomarker concentrations in the models and testing if the model improved using Akaike information criteria. We found that adding a quadratic term for monomethyl phthalate (MMP) in the nonverbal IQ models, for diethylthiophosphate (DETP) in the internalizing problems models, for mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) in the attention problems models, and for mono(3-carboxypropyl) phthalate (MCPP) in the aggressive behavior models the model fit significantly improved ($P < 0.05$). When one or more quadratic terms are present in the final model, the joint mixture association with a given outcome calculated by the quantile g-computation is determined by a quadratic term estimate and the estimate for the lower-order joint mixture effect, similar to a linear

regression. Further, we predicted differences between each quartile and the first quartile based on the estimated outcome (Y) score for each quartile Q,

$$Y_{Q_q} = B_0 + [B_1 \times (q)] + [B_2 \times (q)^2]$$

in which q is the integer value assigned to each quartile ($q = 0, 1, 2, 3$), B_0 is the intercept, B_1 is the mixture estimate, and B_2 is the quadratic term estimate (if included). Coefficients for each quartile Q_q compared to the lowest (reference) quartile Q_0 were calculated by the difference between the predicted$Y$ for each quartile, $Y_{Q_q} - Y_{Q0}$. Second, we investigated the combined exposure effect of chemical biomarkers within each chemical group on offspring nonverbal IQ and emotional and behavioral problems while adjusting for the other chemical groups. All models were adjusted for fetal sex, maternal age, maternal BMI, maternal education level, maternal ethnicity, household income, marital status, parity, maternal smoking, maternal alcohol use, maternal IQ, and child age at assessment. Models for internalizing problems, attention problems, aggressive behavior, and autistic traits were additionally adjusted for maternal psychopathology.

As a secondary analysis, we investigated which chemical biomarker concentrations within the mixture were contributing the most to the overall mixture effect for the chemical exposure-outcome models where we observed an association. Since this question does not have straightforward answers in nonlinear models, we performed this investigation excluding product terms and quadratic terms, thereby assuming linearity. Further, instead of investigating the mixture association with attention problems and aggression behavior separately, one could also investigate the effect on externalizing problems which combines the two scales. We therefore carried out a sensitivity analyses in which we investigated whether prenatal exposure to the mixture is associated with externalizing problems. Next, birth year might predict exposure concentrations of nonpersistent chemical because of the strong temporal patterns of these exposures and because birth year might be a marker of other direct pathways between other unmeasured exposures and neurodevelopment. We therefore carried out a sensitivity analysis in which we additionally adjusted the main models for birth year. Finally, several studies have suggested that sex may be a potential effect estimate modifier in the association of prenatal exposure to phthalates, bisphenols, and OP pesticides and neurodevelopmental outcomes, including mixture studies.[38,41,82-84] We therefore explored potential effect modification by sex via stratification.

RESULTS

The median age of pregnant women at enrollment was 31 years (Table 1). The majority of the women were Dutch (58%), were nulliparous (62%), were nonsmokers (77%), had obtained a high level of education (55%), and had a high household income (71%). SI Table S3 compares the sociodemographic and lifestyle characteristics of the study sample with the characteristics of the excluded participants of the Generation R cohort. Mothers of children included in the analysis were more likely to have a Dutch national origin, to be older, and have a higher socioeconomic status compared to mothers excluded from the analyses.

The biomarker concentration distributions are presented in SI Table S4. Pearson and Spearman rank correlations are presented in SI Table S5, and a graphical representation of the correlations can be found in Figure 1. Correlations were generally high within phthalate metabolites and OP pesticide metabolites (e.g., Pearson correlation between (mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) metabolites = 0.76 and between dimethylphosphate (DMP) and diethylphosphate (DEP) metabolites = 0.60) (Figure 1). However, chemical groups had low to moderate correlation between them (e.g., Pearson correlation between bisphenol A and MECPP = 0.25). The distribution of nonverbal IQ and the emotional and behavioral outcomes without square root transformation can be found in SI Table S6.

Higher exposure to the overall mixture was associated with lower nonverbal IQ (−4.0 points (95% CI −7.0, −1.0), −5.5 points (95% CI −10.2, −0.9), and −4.6 points (95% CI −10.8, 1.5) for the second, third, and fourth quartile of the overall mixture, respectively, compared to the first quartile) (Figure 2A and SI Table S7). No association was observed between the overall mixture and internalizing problems, attention problems, aggressive behavior, and autistic traits (Figure 2B-E and SI Table S7). Further, when we explored the associations between prenatal exposure to the mixture of each individual chemical group while adjusted for other chemicals, we observed a similar pattern for the association between the phthalate metabolite mixture and nonverbal IQ compared to the association of the overall chemical mixture (Figure 2A and SI Table S7).

Higher exposure to the phthalate metabolite mixture was associated with lower nonverbal IQ (−3.4 points (95% CI −6.3, −0.6), −4.4 points (95% CI −8.8, −0.1), and −2.9 points (95% CI −8.4, 2.6) for the second, third, and fourth quartile of the phthalate mixture, respectively, compared to first quartile). No associations were observed between the bisphenol mixture and the OP pesticide mixture with nonverbal IQ (SI Figure A2 and SI Table S7). No association was observed for each of the individual chemical groups with internalizing problems, attention problems, aggressive behavior, and autistic traits (Figure 2B-E and SI Table S7). Table 2 presents the adjusted effect contribution for each averaged chemical biomarker concentration included in the overall mixture effect on nonverbal IQ. The partial effects provide information on the contributed weight on the overall effect of each chemical biomarker concentration. Overall, the total contribution of chemical exposure biomarkers in the negative direction (−5.4 points of lower nonverbal IQ) was greater than the total contribution of chemical exposure biomarkers in the positive direction (+3.8 points of higher nonverbal IQ). When looking into each chemical group, phthalate metabolites had the highest negative contribution (72.8%) followed by OP pesticide metabolites (27.2%), while bisphenol A did not contribute to the negative association. Among these, MECPP (26.5%) was the metabolite that contributed the most to the negative association.

Next, prenatal exposure to the mixture was not associated with externalizing problems (SI Table S8). Further, results additionally adjusting for birth year were similar to the main models (SI Table S9). Finally, sex stratified analyses for the association between the joint mixture effect and nonverbal IQ showed similar effect estimates for boys and girls as compared to the main analyses (SI Table S10). Further, regarding aggressive behavior we observed no association for the overall joint effect among boys. However, girls in the

second (B = 0.34, 95%CI = 0.01, 0.67), third (B = 0.48, 95%CI = −0.06, 1.02), and fourth exposure quartile (B = 0.43, 95%CI = −0.31, 1.17) had more aggressive behavior problems as compared to girls in first quartile of the exposure.

DISCUSSION

We observed that exposure to higher concentrations of a mixture of phthalates, bisphenol, and OP pesticides during pregnancy was associated with lower nonverbal IQ in children aged 6 years, and mainly phthalates were driving the association. Also, this association had a nonlinear dose–response relationship with the second, third, and fourth quartiles having very similar differences in nonverbal IQ when compared to the first quartile. No associations were observed between prenatal exposure to the mixture of phthalates, bisphenol, and OP pesticides and emotional and behavioral problems.

The majority of epidemiological studies examining prenatal exposure to nonpersistent chemicals in relation to offspring neurodevelopment have investigated single exposures.[85] Although some of these studies have been suggestive of an association, systematic reviews have revealed that the evidence for a relation is inconclusive.[34-37] The practice of exploring associations with neurodevelopmental outcomes using separate exposure models has important limitations. First, it increases the chance of false positive associations as an artifact of increasing the number of tests performed and ignores potential cochemical confounding.[50,85,86] Moreover, chemicals have the potential to produce additive health effects and this cannot be explored with single exposure models.[86,87]

To the best of our knowledge, only two previous studies have investigated the effect of chemical mixtures on IQ. All previous studies investigated the overall effect of the mixture using a different method, weighted-quantile sum (WQS) regression, and none have jointly estimated the effect of phthalates, bisphenols, and OP pesticides, but only focused on phthalates or on a different combination of chemicals. Loftus et al. (2021) investigated the overall mixture effect of third trimester phthalate exposure on child IQ. Thirteen phthalate metabolites were measured in pregnant women and cognitive outcomes including full-scale IQ were measured at child age 4–6 years. Contrary to our observation, this study found no evidence for an association. Next, Tanner et al. (2020) explored whether early pregnancy exposure to a mixture of 26 persistent and nonpersistent endocrine-disrupting chemicals (EDCs) was associated with IQ in children aged 7 years. This study found higher exposure to the EDC mixture to be associated with a lower IQ, only in boys. Among a wide variety of EDCs, this study incorporated several phthalate metabolites and bisphenols and found bisphenol F to be the strongest contributor to the mixture effect. Additionally, monoethyl phthalate (MEP) and monobenzyl phthalate (MBzP) metabolites and bisphenol A were also identified as having a substantial contribution to the overall mixture effect. In contrast, we observed that prenatal exposure to a mixture was associated with nonverbal IQ and found no differences in sex specific results when compared to the main result. Further, we found that MEP had only a weak contribution to the negative effect in nonverbal IQ whereas MBzP and bisphenol A had a nonsignificant contribution toward the positive effect. The strongest contributors to the overall negative mixture association on nonverbal IQ were MECPP, MCPP, monoisobutyl phthalate (MiBP), and dimethylthiophosphate (DMTP). In a previous

work where we used the same population to investigate phthalate metabolites exposure in association with nonverbal IQ using separate regression analyses, we showed that the averaged concentrations of MCPP and PA across pregnancy had the largest association with nonverbal IQ with larger effect estimates as compared to the estimates observed in this study.[45] These different findings indicate that by modeling co-occurring chemical exposures, exposure biomarkers combinations playing a substantial role in the association with a certain outcome might be identified, that are missed in single regression models that do not adjust for or take into account coexposure effects. This observation is consistent with a primary concern of estimating effects of individual exposures, coexposure confounding.

Regarding emotional and behavioral problems, one study investigated the effect of averaged exposure to phthalates across two measurements during pregnancy (16 and 26 weeks of gestation).[42] This study assessed children's emotional and behavioral problems at ages 2, 3, 4, 5, and 8 years using the Behavioral Assessment System for Children-2. Similar to our findings, they did not find an association between prenatal exposure to a mixture of nine phthalate metabolites and emotional and behavioral problems in children.[42] Also, Day et al. (2021) investigated whether prenatal exposure to a mixture of nine phthalate metabolites measured in early and late pregnancy was associated with autistic traits and behavior problems in children aged 4–5 years. They found that higher early pregnancy phthalate mixture concentrations were associated with more autistic traits in children and identified MCPP, MBzP, and MEP as the main contributors to the overall effect.[41] Although the sample size was relatively small for stratified analyses, this study also observed that higher late pregnancy exposure to a mixture of phthalates was associated with increased externalizing problems only in boys (n = 243), with MCPP and MBzP as the main contributors to the overall effect.[41] In contrast, we observed that higher pregnancy exposure to the mixture was associated with more aggressive behavior in girls. However, our sex specific results should be interpreted with caution since the sample sizes were small, not formally tested using an interaction, and not adjusted for multiple testing.

Comparability between studies should be done carefully. Nonpersistent chemicals have short half-lives. Concentrations measured in a single spot urine sample may therefore not be accurate in estimating pregnancy exposure because biomarker concentrations may vary from day to day within each subject resulting in high (within-subject) temporal variability.[79,80,88] We averaged the levels measured across the three trimesters of pregnancy to obtain a more precise estimate of exposure across pregnancy. Studies based on a single spot urine measurement might be more prone to measurement error resulting in imprecise effect estimates. Also, the different exposure biomarkers incorporated in the mixture of each study (e.g., only phthalates versus a mixture of different chemical groups), and the potential differences in exposure patterns across different populations could complicate comparisons. Further, different statistical approaches to study exposure mixtures and health outcomes can yield to different results. In our study we used the quantile g-computation method, whereas all other previous studies used the WQS regression to estimate the joint exposure effect. Similar to the quantile g-computation method, the WQS regression estimates the effect by increasing all exposures by a single quantile. Both methods share the simplicity of inference (effect as a whole) and can easily include multiple exposures that co-occur to estimate the additive effects. In regards to the direction and the shape of the dose–response

relationship, the WQS regression approach is limited by the assumptions of linearity of the exposure effects and directional homogeneity (i.e., effects of all exposures are zero or in the same direction)[81,85] whereas the quantile g-computation is able to incorporate nonlinear effects of individual exposures and the mixture as a whole and does not assume directional homogeneity.[81] This allowed us to identify a nonlinear effect in the association between the overall mixture and nonverbal IQ in our study. Several studies exploring chemical exposure effects in both humans and animals indicate that the exposure–disease associations may not be linear.[89] For example, Vandenberg et al. (2012) stated in their review that low-dose exposure to EDCs (including phthalates and bisphenols) and nonmonotonic dose–response curves are frequently observed.[90,91] Further, in the WQS regression, the direction of the effect estimate associated with the exposures should be specified a priori and should be the same for all, either negative or positive[38,40-42] enforced by the assumption of directional homogeneity.[81] In contrast, quantile g-computation estimates the health effect in relation to all exposures in the condition that all increase by a single quantile, but without specifying a priori the direction of the associations and allowing them to go into different directions. Therefore, some estimated associations within the overall mixture can be reflected as a weight in the unexpected direction, regardless of statistical significance. For example, in our study we observed that the overall mixture was associated with lower nonverbal IQ, while some exposure biomarkers within the mixture contributed nonsignificantly toward a higher nonverbal IQ (i.e., positive weight). While we would not expect, a priori, for any exposures related to the biomarkers to lead to improved health outcomes, our findings may reflect unknown mechanisms or residual confounding. Therefore, replication studies in populations with different exposure patterns and different confounding structures are warranted to better understand these counterintuitive findings. Next, it is important that the independent effects from these models are interpreted with caution, because the observed association with nonverbal IQ is for the joint exposure of all biomarkers combined. Furthermore, the independent effect estimates come from a model in which we assume linearity whereas the observed association was nonlinear. Finally, none of the independent effects were statistically significant, which shows that the combined effect may be more important. Another innovative method that is able to estimate the additive health effects of exposure to mixtures is the Bayesian kernel machine regression (BKMR). BKMR has many benefits such as the ability to concurrently estimate the effect of chemical classes with high within class correlations next to the calculation of the association of separate chemicals within a chemical class on a health outcome.[92] However, the quantile g-computation method and the WQS only provide one or two parameters for a dose response estimation whereas the dose response parameters of the BKMR are not easily interpretable.

The phthalate and bisphenol A concentration levels observed in this study sample were similar as compared to several other studies investigating prenatal exposures. For instance, the median concentrations for MBzP (2–6 ng/mL), MCPP (1–2 ng/mL), MEOHP (6–9 ng/mL), and bisphenol A (2 ng/mL) are somewhat of the same magnitude to concentrations measured in Israel (1, 1, 6, and 2 ng/mL, respectively)[93] or Canada (5, 1, 9, and 1 ng/mL, respectively).[94] However, in the United States concentrations were slightly higher (e.g., MBzP = 7 ng/mL, MCPP = 2, MEOHP 11 ng/mL.[95] DAP metabolite concentrations in this study were higher than most other studies in pregnant women.[96-99] Variation in exposure

concentration across studies may be due to variation in diet, protocols and timing of urine collection, the use of products, and metabolic rate. Next, correlations were generally high within phthalate metabolites and OP pesticide metabolites. However, chemical groups had low to moderate correlation across groups. Similarly, higher within chemical group correlations as compared to between group correlations have been noted previously in the Human Early-Life Exposome (HELIX) project.[100] In this project, correlations for 87 environmental exposures during pregnancy (19 exposure groups) were assessed in six European birth cohorts. The implication of lower correlations between groups as compared to within group may suggest that studies investigating the joint mixture effect of a single chemical group are not greatly affected by copollutant confounding from exposures coming from other chemical groups.[100,101] As shown by biomonitoring studies and concentrations observed in this study, exposures to nonpersistent chemicals co-occur. Real life exposure mixtures are complex and may have both similar and mixed modes of action which can result in additive or nonadditive effects, even when correlations between chemical groups are low.

There are some limitations to our study that needs to be considered. First, our study used three spot urine samples during pregnancy to measure the exposure which is most probably a better indicator of exposure across gestation. Nevertheless, measurement error might still have occurred and resulted in imprecise effect estimates.[80] Second, the timing of the urine collection varies between 8 am and 8 pm and most likely consist of a combination of first morning and random urine spot samples. This may be of concern given the fact that fluid intake and the time of day may affect concentrations of chemicals, urine volume, and excretion rate.[102-104] However, concentrations were adjusted for creatinine and it is unlikely that the timing of urine collection could be a confounder in these associations. Third, mothers of children included in the analysis were more likely to have a Dutch national origin, to be older, and have a higher socioeconomic status as compared to children excluded from the full generation R cohort. Therefore, potential selection bias might have occurred in our study and influenced our results. Unfortunately, at the moment the quantile-g computation method does not allow to include analytical strategies to correct for potential selection bias such as inverse probability censoring weighting. Next, during the data collection wave, the CBCL/1.5–5 was used to measure emotional and behavior problems because it was expected that most children that would participate in the follow up study, would be younger than 6 years. At the end of the assessment 6208 children had sufficient data on CBCL/1.5–5. Of those, 58% were younger than 6 years. As per recommendation of the Achenbach System of Empirically Based Assessment (ASEBA) manual we used the version for younger children if a group comprises children below and above the cutoff. This ensures that the assessment in one examination is uniform. This may have influenced the results since the CBCL 6–18 would be more appropriate to assess emotional and behavioral problems in children of 6 years or older although many items are not appropriate in children at the lower end of the range, for example, “My child smokes, chews, or sniffs tobacco”. However, Cronbach’s alpha values for all scales were the same in children younger and older than 6 years. Therefore, in children older than 6 years, emotional and behavioral problems were also reliably measured.[105] Further, by using a single imputed data set we assumed that the imputed value was a true observation in our

analyses and did not correct (by pooling) for the uncertainty about the prediction of the missing values. This may have resulted in less precision. However, only few covariates were missing (<13%). Another limitation might be that our study only relied on questionnaires completed by the primary care giver (mostly mothers). This measure can therefore be less accurate as compared to multiple informant measures (both parents, teacher and/or caregivers in preschool or daycare centers report). Next, we used the SRS to measure autistic traits on a continuous spectrum which increases power and reduces the impact of outcome misclassification (e.g., children with symptoms just below the clinical cutoff will be defined as free of having Autism Spectrum Disorder).[106] However, the SRS might measure a trait (e.g., affected social cognition) which is shared by another emotional or behavioral problem (e.g., Attention Deficit Hyperactivity Disorder), indicating measurement error or that comorbidity of such behavior problems does exist at these ages.[106] Finally, in this study nonadditivity of chemicals in the association was not investigated. Therefore, we may have overlooked potential synergistic effects. However, when exposure biomarkers have a high correlation, the inclusion of a nonlinear term (e.g., a quadratic term) can comprise nonadditive effects in the joint mixture association.[107] In this study, in which biomarker correlations vary between low, moderate, and high, it is likely that we (partly) miss nonadditive effects in the joint effect. Nevertheless, the study of Belzak and Bauer (2019) revealsrevealed that it is of importance to bear in mind that nonlinearity in the joint mixture exposure estimates may also comprise nonadditivity, even when interactions between biomarkers are not formally included in the statistical model.

This study has also several strengths, such as the large sample size, three repeated exposure measures of the three chemical groups to asses pregnancy exposure, and in-depth neurodevelopmental data on the children. Further this study is strengthened by the use of a mixture analytical method, the quantile-g computation, which allows for modeling of complex exposure combination corresponding to real world exposure situations, is able to deal with additive and synergistic effects of the exposures, and reduces the number of tests substantially.

In conclusion, higher prenatal exposure to a mixture of phthalates, bisphenol, and OP pesticides was associated with lower nonverbal IQ and phthalates were driving the association. No association was observed between prenatal exposure to the nonpersistent chemical mixture and emotional and behavioral problems in children. Gestational exposure to a combination of chemicals is universal and may be related to neurodevelopment. Future studies are needed to confirm our results, extend these by including more chemicals that share similar exposure sources, and investigating other mixture combinations of chemical groups that may co-occur. The quantile-g computation method might be a valuable tool to investigate these mixture combinations and estimate more closely the real-world neurodevelopmental consequences of co-occurring chemical exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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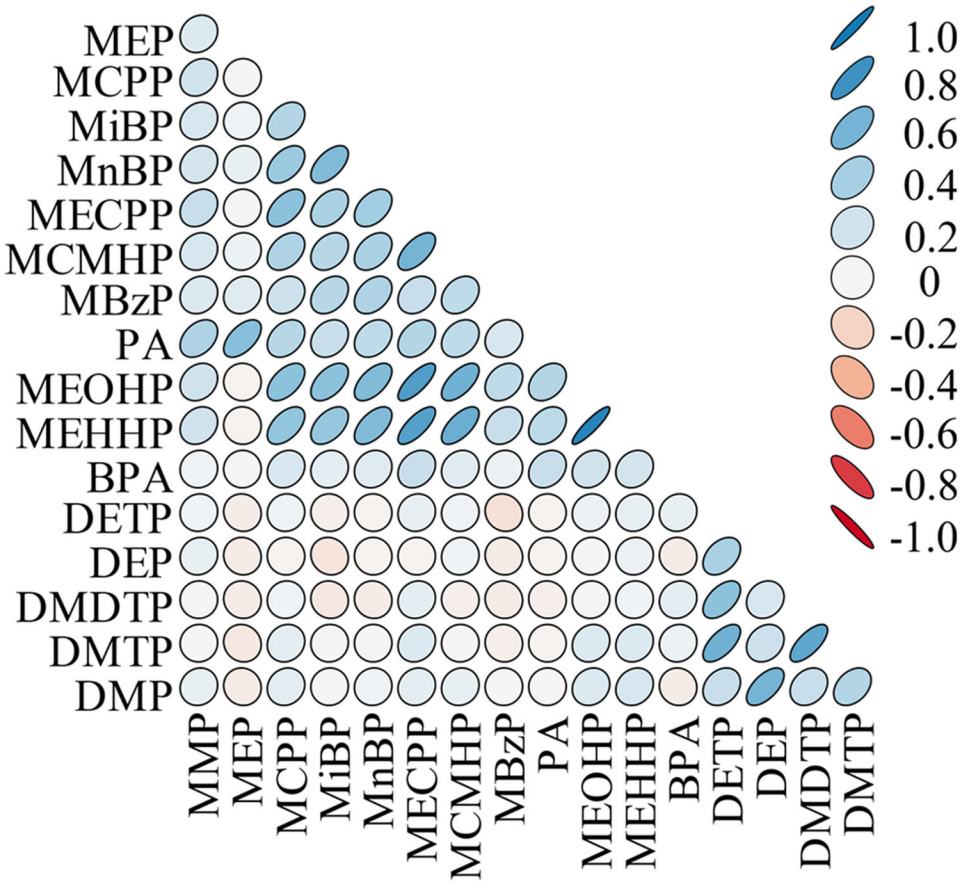

Figure 1.

Pearson correlation matrix for pregnancy averaged exposure biomarker concentrations. Corresponding data and Spearman rank correlations can be found in SI Table S5. Abbreviations: MMP = monomethyl phthalate, MEP = monoethyl phthalate, MCPP = mono(3-carboxypropyl) phthalate, MiBP = monoisobutyl phthalate, MnBP = mono-*n*-butyl phthalate, MECPP = mono-(2-ethyl-5-carboxypentyl) phthalate, MCMHP = mono-[(2-carboxymethyl) hexyl] phthalate, MBzP = monobenzyl phthalate, PA = phthalic acid, MEOHP = mono-(2-ethyl-5-oxohexyl) phthalate, MEHHP = mono-(2-ethyl-5-hydroxyhexyl) phthalate, BPA = bisphenol A, DMDTP= dimethyldithiophosphate, DMTP = dimethylthiophosphate, DMP = dimethylphosphate, DETP = diethylthiophosphate, and DEP = diethylphosphate.

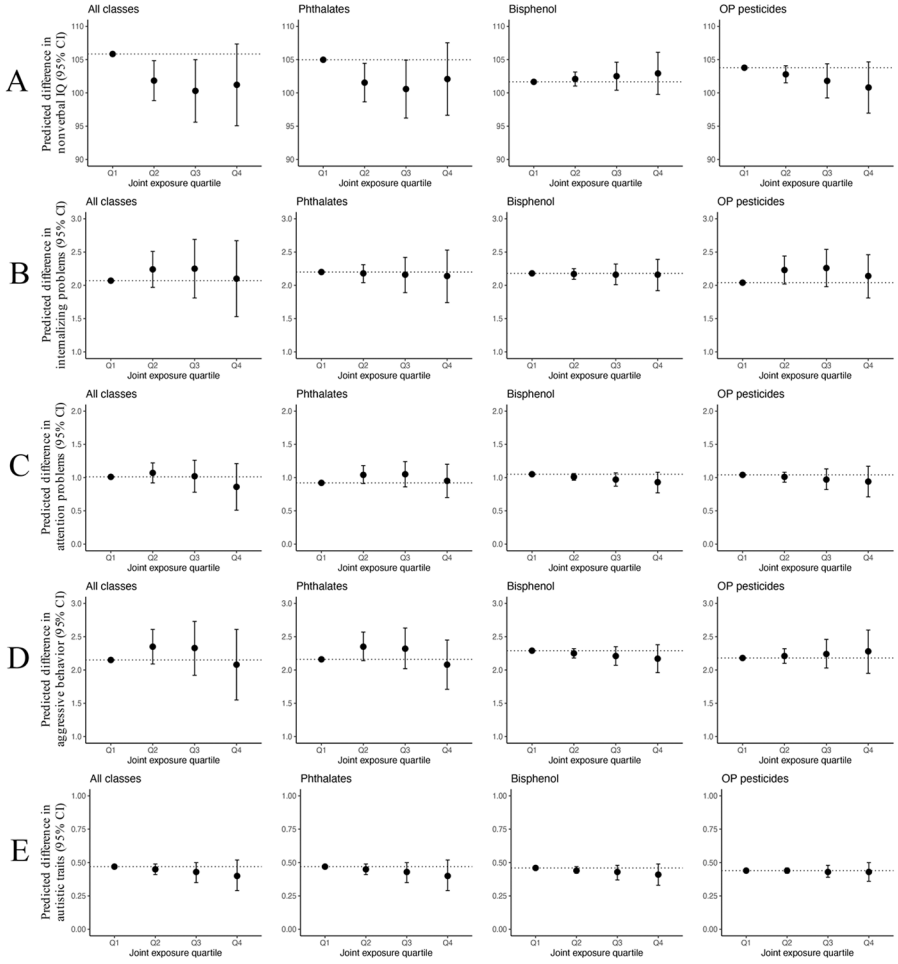

Figure 2.

Adjusted difference (95% confidence interval) in estimated outcome for each exposure quartile (Q2–Q4) compared to the lowest quartile (Q1) in all chemicals measured and within each chemical class. Corresponding numeric data are reported in SI Table S7. Each row corresponds to a different mixture model with a different outcome (A: Nonverbal IQ. B: Internalizing problems, C: Attention problems. D: Aggressive behavior. E: Autistic traits). Adjusted for fetal sex, maternal age, maternal prepregnancy bmi, maternal education level, maternal ethnicity, household income, marital status, parity, maternal smoking, maternal alcohol use, maternal IQ, and child age at assessment. Models for internalizing problems, attention problems, aggressive behavior, and autistic traits are additionally adjusted for maternal psychopathology. Models of the phthalate metabolite mixture additionally adjusted for log 10-transformed pregnancy-averaged concentrations of bisphenol A and the OP pesticide metabolites. Models of bisphenol (bisphenol A) additionally adjusted for log 10-transformed pregnancy-averaged concentrations of phthalate and OP pesticide metabolites. Models of the OP pesticide metabolite mixture additionally adjusted for log 10-transformed pregnancy-averaged concentrations of phthalate metabolites and bisphenol A.

Table 1.

Characteristics of Study Participants (n = 782)

		distribution[a]
maternal age (years)		31 (28, 34)
maternal ethnicity		
	Dutch	57.7
	other western	12.7
	nonwestern	29.6
maternal IQ		100 (90, 107)
	missing, n	19
maternal education		
	low	14.8
	intermediate	30.2
	high	55.0
	missing, n	24
household income		
	<1200€/month	12.6
	1200–2000€/month	16.5
	>2000€/month	70.9
	missing, n	101
maternal psychopathology		0.13 (0.08, 0.33)
	missing, n	94
maternal body mass index (kg/m^2)		22 (21, 25)
	missing, n	97
maternal parity		
	0	62.3
	1	26.6
	≥2	11.1
	missing, n	4
maternal marital status		
	married/living with partner	89.8
	no partner	10.2
	missing, n	29
maternal smoking during pregnancy		
	no smoking during pregnancy	77.2
	until pregnancy recognized	8.9
	continued during pregnancy	13.9
	missing, n	63
maternal alcohol consumption during pregnancy		
	no consumption during pregnancy	36.7
	until pregnancy recognized	17.5
	continued occasionally	39.3

		distribution[a]
	continued frequently	6.5
	missing, *n*	40
child age at assessment		5.9 (5.8, 6.0)
child sex (female)		49.1

[a]Median (25th percentile, 75th percentile) for continuous variables and percentage for categorical variables.

Table 2.

Adjusted Effect Contribution for Each Averaged Chemical Biomarker Concentration Included in the Overall Mixture Effect on Nonverbal IQ ($n = 708$)[a]

	negative effect contribution		weight	positive effect contribution		weight
biomarker	**B**	**95%CI**	**%**	**B**	**95%CI**	**%**
Phthalate Metabolites						
MMP	−0.29	−1.36, 0.78	5.3			
MEP	−0.21	−1.39, 0.98	3.8			
MCPP	−0.84	−2.07, 0.38	15.5			
MiBP	−0.77	−2.08, 0.55	14.1			
MnBP				0.46	−0.88, 1.81	12.2
MECPP	−1.44	−2.95, 0.07	26.5			
MCMHP				0.68	−0.58, 1.93	17.9
MBzP				0.41	−0.68, 1.50	10.8
PA	−0.41	−1.70, 0.88	7.6			
MEOHP				0.94	−1.31, 3.18	24.6
MEHHP				0.38	−1.70, 2.46	10.0
total	−3.96		72.8	2.87		75.5
Bisphenol					-	-
BPA				0.41	−0.61, 1.43	10.9
total				0.41		10.9
OP Pesticide Metabolites						
DMDTP	−0.08	−1.42, 1.27	1.4			
DMTP	−0.79	−2.35, 0.76	14.6			
DMP	−0.61	−1.92, 0.70	11.2			
DETP				0.26	−1.01, 1.53	6.8
DEP				0.26	−1.05, 1.56	6.8
total	−1.48		27.2	0.52		13.6
Total Mixture						
total	−5.44		100%	3.80		100%

[a]Models adjusted for fetal sex, maternal age, maternal prepregnancy bmi, maternal education level, maternal ethnicity, household income, marital status, parity, maternal smoking, maternal alcohol use, maternal IQ, and child age at assessment. Abbreviations: MEP = monoethyl phthalate, MMP = monomethyl phthalate, MiBP = monoisobutyl phthalate, MnBP = mono-n-butyl phthalate, MECPP = mono-(2-ethyl-5-carboxypentyl) phthalate, MCMHP = mono-[(2-carboxymethyl) hexyl] phthalate, MEOHP = mono-(2-ethyl-5-oxohexyl) phthalate, MEHHP = mono-(2-ethyl-5-hydroxyhexyl) phthalate,

MCPP = mono(3-carboxypropyl) phthalate, mBzP = monobenzyl phthalate, PA = phthalic acid, BPA= bisphenol A, DMDTP = dimethyldithiophosphate, DMTP = dimethylthiophosphate, DMP = dimethylphosphate, DETP = diethylthiophosphate, and DEP = diethylphosphate.