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Prenatal exposure to organophosphorus pesticides and childhood neurodevelopmental phenotypes

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Abstract

Prenatal exposure to organophosphorus pesticides (OPs) has been associated with different neurodevelopmental outcomes across different cohorts. A phenotypic approach may address some of these differences by incorporating information across scales and accounting for the complex correlational structure of neurodevelopmental outcomes. Additionally, Bayesian hierarchical modeling can account for confounding by collinear co-exposures. We use this framework to examine associations between prenatal exposure to OPs and behavior, executive functioning, and IQ assessed at age 6–9 years in a cohort of 404 mother/infant pairs recruited during pregnancy. We derived phenotypes of neurodevelopment with a factor analysis, and estimated associations between OP metabolites and these phenotypes in Bayesian hierarchical models for exposure mixtures. We report seven factors: 1) Impulsivity and Externalizing, 2) Executive Functioning, 3) Internalizing, 4) Perceptual Reasoning, 5) Adaptability, 6) Processing Speed, and 7) Verbal Intelligence. These, along with the Working Memory Index, were standardized and scaled so that positive values reflected positive attributes and negative values represented adverse outcomes. Standardized dimethylphosphate metabolites were negatively associated with Internalizing factor scores ($\hat{\beta} - 0.13$, 95% CI − 0.26, 0.00) but positively associated with Executive Functioning

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factor scores ($\hat{\beta}\,0.18$, 95% CI 0.04, 0.31). Standardized diethylphosphate metabolites were negatively associated with the Working Memory Index ($\hat{\beta}\,-0.17$, 95% CI − 0.33, − 0.03). Associations with factor scores were generally stronger and more precise than associations with individual instrument-specific items. Factor analysis of outcomes may provide some advantages in etiological studies of childhood neurodevelopment by incorporating information across scales to reduce dimensionality and improve precision.

1. Introduction

Prenatal exposure to organophosphorus pesticides (OPs) has been associated with impaired neurodevelopment in both urban (Engel et al., 2016, 2011; Rauh et al., 2006) and agricultural populations (Eskenazi et al., 2007). Specifically, prenatal OP exposure has been associated with measures of cognition, including lower IQ scores and lower scores on the Bayley Scales of Infant Development Mental Development Index (Engel et al., 2016; Eskenazi et al., 2007; Rauh et al., 2006); developmental delay (Liu et al., 2015, 2016); as well as various measures of behavior, including impaired social responsiveness (Furlong et al., 2014); indicators of Pervasive Developmental Disorder (Eskenazi et al., 2007); and inattention (Marks et al., 2010).

Although the literature linking prenatal OP exposure to neurodevelopment is robust, the exact nature of the neurodevelopmental deficit imparted by OPs is difficult to determine based on the existing evidence. Typically, studies have considered only a single component of neurodevelopment at a time, such as IQ or behavior. However, there are major conceptual advantages in jointly modeling domains of neurobehavioral development (Rauh and Margolis, 2016; Robinson, 2012). Accounting for the interrelations between developmental domains is more clinically relevant because neurological functions are mutually dependent. For example, higher-level inhibitory control – typically considered to be a component of executive functioning – relies on more basic processing speed capability, which is typically measured in intelligence tests (Ridderinkhof and van der Molen, 1997). By jointly considering behavior, cognition, and executive functioning, we may also better characterize patterns of deficits in neurodevelopment (Castellanos et al., 2006; Mattison and Mayes, 2012; Sinzig et al., 2008) that result from OP exposure, which may ultimately provide insights into etiological pathways. Disruptions to an underlying process may have cascading effects upon other biological processes, which could result in the clustering of behaviors into phenotypes. For instance, OPs can negatively influence serotoninergic and dopaminergic processing (Aldridge et al., 2005a, 2005b, 2004; Slotkin and Seidler, 2008; Venerosi et al., 2010). Serotonin, in turn, can influence aggression, other problematic social behaviors, depression, and Attention Deficit Hyperactivity Disorder (Cadoret et al., 2003; Eley et al., 2004; Zoroğlu et al., 2002). Animal and human studies do support that OPs may be associated with these outcomes (Bouchard et al., 2010; Eskenazi et al., 2007; Furlong et al., 2014; Middlemore-Risher et al., 2010; Ricceri et al., 2003, 2006). Other biological mechanisms, such as oxidative stress (Soltaninejad and Abdollahi, 2009), DNA damage (Mehta et al., 2008), and long lasting impacts on the dopaminergic systems (Aldridge et al., 2005b), may have downstream effects on a variety of outcomes that could coalesce into a phenotypic presentation of traits.

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Just as neurodevelopment is complex and multifaceted, so is human exposure to environmental chemicals (Stingone et al., 2017). Previous studies of OPs and neurodevelopment have generally not considered multiple chemical co-exposures, which may, if correlated, confound or alter the OP-neurodevelopment relationship (reviewed in (Bellinger, 2013)). Chemicals may be correlated with each other due to similar sources, such as plasticizers in consumer products, insecticides for pest control, or multiple compounds found in food due to production, delivery practices, or common dietary patterns (Engel and Wolff, 2013). In the Mount Sinai Children's Environmental Health Center, prenatal exposure to several potential neurotoxicants was measured, including OP pesticides, as well as pyrethroids, phthalates and environmental phenols (Barr et al., 2005; Berkowitz et al., 2003; Engel et al., 2011; Wolff et al., 2008). Exposure to these chemicals was widespread in this population due to the approved use of OP pesticides for residential pest control during this period, a city-wide pesticide spraying program to control West Nile Virus in the late 1990s and early 2000s (Gyure, 2009; Thier, 2001), and placement of phthalates and phenols in consumer products commonly used by reproductive aged women (Buckley et al., 2012).

In order to explore the impact of multi-dimensionality in both exposures and outcomes, we evaluate associations between OPs and neurodevelopmental phenotypes, while accounting for chemical co-exposures (specifically, phthalates, phenols, and pyrethroid pesticides). Since prior studies of OPs and neurodevelopment report subgroup heterogeneity (Engel et al., 2011; Furlong et al., 2014), we also consider possible sources of heterogeneity in associations due to race/ethnicity, child sex, and genetic variants in *PON1*, a gene which is involved in the detoxification of OPs.

2. Methods

2.1. Study Recruitment and Population

The Mount Sinai Children's Environmental Health Center is a prospective cohort study of 404 mother infant-pairs from New York City. We recruited women during prenatal visits at either the Mount Sinai Diagnostic and Treatment Center, which serves a predominantly East Harlem population, or one of two private practices on the Upper East Side of Manhattan. Eligible mothers were primiparous with singleton pregnancies, and delivered at the Mount Sinai Hospital between May 1998 and July 2001 (Berkowitz et al., 2003, 2004). Exclusions have been detailed elsewhere (Berkowitz et al., 2003; Engel et al., 2007). Mothers completed questionnaires during their third trimester that assessed a variety of sociodemographic, behavioral, and medical history characteristics. We also obtained maternal spot urine samples between 25 and 40 weeks of gestation (mean = 31.2 weeks).

We invited participants to return for follow-up visits with their child at ages 1, 2, 4–5, 6, and 7–9 years. At follow-up visits, mothers completed questionnaires describing sociodemographic features and developmental milestones. The Home Observation for Measurement of the Environment (HOME scale) (Bradley et al., 1989) was administered in the office at the 1 and 2 year follow-up visits. The HOME subscales include Involvement, Learning Materials, Organization, Acceptance, Responsivity, and Variety (descriptions provided in Appendix A).

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2.2. Exposure biomarker measurements and PON1

Six dialkylphosphate metabolites, including three dimethylphosphate (DMP) and three diethylphosphate (DEP) metabolites, were analyzed in two batches between 2002 and 2003 at the Centers for Disease Control and Prevention (CDC). Quality control and laboratory methods have been published previously (Barr et al., 2005; Bravo et al., 2004).

Samples were also analyzed for 9 phthalate, 3 pyrethroid, and 5 phenol metabolites, using laboratory and quality control methods that have been described previously (Barr et al., 2010; Kato et al., 2005; Ye et al., 2005). Briefly, phthalates in urine were measured using automated sample preparation and an on-line solid-phase extraction method in conjunction with isotope dilution high-performance liquid chromatography/tandem mass spectrometry (SPE-HPLC-MS) (Kato et al., 2005). Urinary phenols were also measured using SPE-HPLC-MS (Ye et al., 2005). For the pyrethroids, an internal standard mixture of isotopically labeled 3-phenoyxbenzoic acid (3-PBA) and *trans*-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*t*-DCCA) was used to spike 2 mL of urine, which was then incubated with Beta-glucuronidase/sulfarase to liberate the conjugated metabolites. Hydrolysates were extracted with OASIS HLB mixed-mode solid-phase extraction cartridges, which were then washed with 5% methanol in a 0.1% acetic acid solution. Metabolites were eluted with methanol. HPLC/MS was used to analyze the extracts. *t*-DCCA was quantified with isotope dilution calibration, while 3-PBA and *c*-DCCA were quantified using the labeled 3-PBA and labeled *c*-DCCA as internal standards (Barr et al., 2010).

Maternal *PON1* polymorphisms were measured using clamp-dependent and linking emulsion allele-specific polymerase chain reaction (Chen et al., 2005).

2.3. Child behavior, executive functioning, psychometric intelligence testing

We measured children's executive functioning and behavior at the 4, 6, and 7–9 year visits using parent report measures, and IQ at the 6 and 7–9 year visits using performance-based measures.

The Behavior Rating Inventory of Executive Functioning (BRIEF) is a parent-report assessment of children's problems with executive functioning over the past 6 months (Bodnar et al., 2007). Parents reported whether each behavior had been a problem on a 3-point scale (never, sometimes, and often). Validity studies report good reliability with high test-retest reliability (mean r_S = 0.81 for parents across scales) and internal consistency (Cronbach's alphas range from 0.80 to 0.98 across scales) (Gioia et al., 2000). Indices include the Behavioral Regulation Index and the Metacognition Index, both of which are age normed and combined to form the overall Global Executive Composite. Detailed descriptions of the indices and subscales are included in Appendix B.

The Behavior Assessment System for Children (BASC) is a parent-report assessment of children's adaptive and problem behaviors in the home and community setting (Sandoval and Echandia, 1995). Internal consistency reliability of this instrument is good (Cronbach's alphas average 0.80 across scales and ages), and test-retest reliabilities are also high (mean r_S = 0.85 for preschool, mean r_S = 0.87 for children ages 6–11) (Sandoval and Echandia, 1994,

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1995). Composite indices include Externalizing Behaviors, Internalizing Behaviors, Adaptive Skills, and the Behavioral Symptoms Index. Parents rate the occurrence of a behavior on a 4-point scale (Never, Sometimes, Often, Almost always). Scores are age-normed and reported as T-scores. Detailed descriptions of the composites and subscales are included in Appendix B. The BASC and BRIEF were both completed at the 4–5, 6, and 7–9 year visits. We used the mean T-scores across all visits.

We administered the Wechsler Preschool and Primary Scales of Intelligence-III (WPPSI-III) at age 6 (mean age = 6.2, SD = 0.2), and the Wechsler Intelligence Scales-IV (WISC-IV) between the ages of 7–9 years (mean age = 7.8, SD = 0.8). WISC-IV composite scores include the Verbal Comprehension score, the Perceptual Reasoning score, the Working Memory Index, and Processing Speed. Similarly, the WPPSI-III composites are corollaries of the WISC-IV composites and include Verbal Intelligence, Performance IQ (similar to Perceptual Reasoning), and Processing Speed, but not Working Memory. The WISC-IV and WPPSI-III are highly correlated (Full Scale IQ r_S = 0.84 in our population); thus, if a child returned for both visits we used the WISC-IV scores for all subtests.

2.4. Neurodevelopmental factor analysis and outcomes

We assessed neurodevelopmental factors by performing dimension reduction on the BRIEF, BASC, and WPPSI-III/WISC-IV instruments with a principal components analysis. We included composites and subscales in the factor analysis if they were measured at both the 6 and 7–9 year visits. This allowed us to include participants who had a measure at either time point. If the participant had measures at both visits, we averaged the score. To stabilize the factor analysis, we included all participants with available neurodevelopmental follow-up data, which included children who were enrolled after delivery and were thus missing biomarker data. In sensitivity analyses we examined the factor structure while restricting to the population who were enrolled at birth and included in the etiologic analyses. We used an orthogonal varimax rotation to ensure neurodevelopmental outcome factors were uncorrelated. We also scaled factors so that positive/adverse characteristics go in the same direction across factors in regression analyses, with positive scores indicating better outcomes and negative scores indicating more adverse outcomes. To determine the number of factors, we examined solutions using parallel analysis and using the Kaiser Criterion, which indicates that factors with eigenvalues greater than one should be retained. To select a solution, we considered both statistical fit and consistency with prior factor analyses in the literature. Factor analysis was performed in SAS v9.3.

Additionally, since the WISC-IV Working Memory Index provides unique information on a performance-based metric of executive functioning, and could not be included in the factor analysis because it is a component of the WISC-IV but not the WPPSI-III (and thus would have resulted in a decreased sample size for the factor analysis), we also included this index as an outcome in models that were restricted to participants with WISC-IV measures.

In order to assess the utility of the factor analysis approach over a more traditional approach, we also conducted analyses of associations between the OPs and the individual items from the factors that displayed associations with the OPs.

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2.5. Co-exposures

We included biomarkers of phthalates, phenols, and pyrethroid pesticides as co-exposures in our analysis. Four phthalate biomarkers are metabolites of the same parent compound, Di(2-ethylhexyl) phthalate (DEHP) and were thus included as a micromolar sum of those metabolites [mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)]. Other phthalate metabolites were individually included: monoethyl phthalate [MEP, a metabolite of diethyl phthalate], mono-n-butyl phthalate (MnBP, a metabolite of di-n-butyl phthalate [DnBP]), monoiso- butyl phthalate (MiBP, a metabolite of di-isobutyl pthalate), mono(3-carboxypropyl) phthalate (MCPP, a nonspecific metabolite of several high molecular weight phthalates and a minor metabolite of DnBP), and monobenzyl phthalate (MBzP, a metabolite of benzylbutyl phthalate). The pyrethroid metabolites 3-phenoxybenzoic acid (3-PBA) and *cis*- and *trans*-(2,2-dichlorovinyl)−2,2-dimethylcyclopropane-1-carboxylic acid (*c*-DCCA and *t*-DCCA) displayed a low frequency of detection and were dichotomized to indicate concentrations above or below the limit of detection (LOD). The DCCA isomers and 3-PBA were highly collinear; only five participants with detectable levels of *c*-DCCA or *t*-DCCA did not have detectable levels of 3-PBA, so the DCCA metabolites were excluded from the analysis. Phenols included metabolites for bisphenol A (BPA), benzophenone-3 (BP3), triclosan, 2,4-dichlorophenol (2,4-DCP) and 2,5-dichlorophenol (2,5–DCP). We excluded the phenol 2,4-DCP because it is a marker of the same parent compound as 2,5-DCP, but had a lower detection frequency. All continuous co-exposures, outcomes, and covariates were standardized to have a mean of 0 and standard deviation of 1. A beta coefficient of one can then be interpreted as an increase in one standard deviation of the factor score per one standard deviation increase in the exposure.

2.6. Statistical methods

We examined demographic characteristics of participants at enrollment by follow-up status. We used frequentist chi-square goodness-of-fit tests and alpha of 0.05 to assess if participants from the original birth cohort with OP biomarker data who did not return for follow-up differed from participants who had OP biomarker data and returned for a complete neurodevelopmental evaluation.

2.7. Bayesian hierarchical exposure analyses

In order to address potential issues of collinearity among metabolites and to stabilize models with large numbers of co-exposures and interactions, we used a Bayesian hierarchical modeling framework. We employed hierarchical shrinkage techniques and specified priors for means and variances of beta coefficients for all variables. We assigned independent normal prior distributions with a mean of zero and a variance of $1/\tau^2$ (MacLehose et al., 2007), where τ equals 1 for all exposures and covariates (priors with mean of 0 and standard deviation of 1). 10,000 burn-in samples were discarded and we used 50,000 iterations to arrive at the posterior estimates. We visually inspected trace plots and autocorrelation plots to assess convergence.

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We imputed values below the limit of detection (< LOD) at each iteration of the Markov chain Monte Carlo algorithm from a truncated normal distribution with parameters defined as the mean and standard deviation of the underlying distribution, a lower bound of 0, and an upper bound equal to the LOD (WinBUGS package djl.trunc.norm) (Carmichael et al., 2010; Uh et al., 2008). If an OP metabolite was missing due to analytic interference in the lab, the missing value within a class was imputed based on the other non-missing values within that class, as has been described previously (Engel et al., 2007). Diethyl- and dimethyl-phosphate metabolites were then summed on a molar basis at each iteration of the Markov chain Monte Carlo (MCMC) algorithm to obtain total diethylphosphate (ΣDEPs) and total dimethylphosphate (ΣDMPs) biomarker concentrations.

Phthalate and phenol metabolite concentrations that were below the LOD were imputed as described above. Missing covariate data were imputed at each iteration of the MCMC algorithm under the assumption that covariates were missing at random. Covariates with missing data included HOME subscale scores, alcohol consumption during pregnancy, and maternal IQ (enrollment characteristics presented in Table 1). For imputation, the HOME subscale scores were modeled as normally distributed random variables conditional on race, education, child sex, maternal IQ, smoking during pregnancy, canned fish consumption during pregnancy, the factor scores, marital status, and maternal age at enrollment. We modeled alcohol consumption during pregnancy using a logistic model conditional on race, education, canned fish consumption, smoking, the factor scores, marital status, maternal age at enrollment, maternal IQ, and HOME scores. Maternal IQ was modeled as a normally distributed random variable conditional on race, education, smoking during pregnancy, canned fish consumption, marital status, age at enrollment, HOME scores, and the factor scores. Models were fit using WinBUGS1.4.

2.8. Covariate Selection

We constructed directed acyclic graphs (DAGs) for each factor, and considered the following variables for inclusion in the DAGs: maternal education at follow-up (high school or less, some college, or bachelor's degree), race/ethnicity (non-Hispanic white, Hispanic, black), maternal marital status at follow-up (single, living with a partner, married), maternal age, HOME environment (overall scores included as continuous, subscales included as ordinal categorical tertile variables due to their limited range), smoking during pregnancy (ever/never), alcohol use during pregnancy (none, light drinking < 3 drinks on average per week during any trimester, moderate to heavy drinking of ≥ 3 drinks on average per week during any trimester), child sex, canned fish consumption during pregnancy (< 1 time per week vs ≥ 1 time per week during pregnancy), Spanish language spoken in home, OP analysis batch, creatinine, and an indicator variable for examiner for the WISC-IV/WPPSI-III. We used the DAGs to identify and adjust for the minimally sufficient set for each factor. These minimally sufficient adjustment sets by definition exclude variables that could be intermediates between exposure and neurodevelopmental factors, such as adverse pregnancy outcomes and/or mode of delivery. We also included creatinine and a binary variable for OP analysis batch in all models. Final adjustment sets for each factor are included in Appendix C. In sensitivity analyses, we assessed self-reported environmental tobacco smoke as a potential confounder for all models.

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2.9. Interaction analyses

Prior toxicological and human literature has reported modification by sex, and race/ethnicity may represent different sources of exposure and outcome ranges in our sample. *PON1* produces enzymes that detoxify OPs. Thus, we assessed modification by race/ethnicity, sex, and maternal *PON1* genotype status (*PON1* Q192R and *PON1* −108C > T polymorphisms). The *PON1* polymorphisms of −108C > T and Q192R were dichotomized (−108: CC vs CT or TT; Q192R: QQ vs QR or RR). We considered interactions to be present if the 95% credible interval for the interaction term did not cross the null. Interactions between OPs and possible modifiers were assessed one at a time; i.e., we assessed interactions between ΣDMPs and race/ethnicity separately from interactions between ΣDEPs and race/ethnicity.

3. Results

Of the 404 mother/child pairs that participated in the original birth cohort, 162 returned for at least one complete neurodevelopmental follow-up visit when their child was between 6 and 9 years old. Of the participants with complete neurodevelopmental data and OP biomarker data, 141 had complete co-exposure data and were included in the analysis. Participants included in this analysis were generally young (64% under 25 at enrollment) and non-white (82%). Most participants reported no alcohol consumption (83%) and no smoking during pregnancy (84%), and most had an educational attainment of high school or less at enrollment (73%) (Table 1). Single marital status at enrollment was the only predictor of returning for follow-up ($p = 0.03$), and the distributions of education at enrollment, maternal age at delivery, race, alcohol, and smoking were generally similar for those included in this analysis compared to those who were not.

Individual OP metabolites varied in their frequency of detection, with dimethylthiophosphate (DMTP) displaying the highest frequency at 90.1% detects and diethyldithiophosphate (DEDP) displaying the lowest frequency at 10.6% detects (Table 2). Results were similar when including all 158 participants with OP biomarker data. Detection frequencies for the phthalates were high, ranging from 99.3% to 100% for the individual metabolites. Among the phenols, BP3 and 2,5-DCP were detected in every sample, while BPA was detected in 85.8% of samples and triclosan was detected in 78.0% of samples. The pyrethroid metabolite 3-PBA had a much lower detection frequency and was only detected in 23.4% of samples.

3.1. Bayesian exposure mixture analysis of neurodevelopmental factors

210 children with available neurodevelopmental outcome data were included in the factor structure, 48 of whom were enrolled after birth. We examined several criteria for factorability of the neurodevelopmental outcome data. Kaiser's measure of sampling adequacy was 0.71, above the standard of 0.60 (Field et al., 2012), and Bartlett's test of sphericity was significant ($\chi 2\ (666) = 13{,}875$, $p < 0.01$). Parallel analysis indicated six factors had eigenvalues greater than those generated from random data, while seven factors had eigenvalues greater than one. After examining the two solutions, we determined that the seven factor solution was almost equivalent to the six factor solution, with the seven factor solution including a separate factor for verbal intelligence. In the six factor solution, the

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items for verbal intelligence loaded with perceptual reasoning items. We selected the seven factor solution because perceptual reasoning and verbal intelligence capture different aspects of intelligence (Johnson and Bouchard, 2005), and it had both good statistical fit based on the eigenvalues and was in line with previous literature on neurodevelopment. All neurodevelopmental scales loaded on at least one factor at > 0.30, and all had sufficiently high communalities (all scales had communalities > 0.50, and the average communality was 0.79), thus all scales were retained. Factor structures were similar for varimax and promax rotation. In order, the seven factors explained 37.92%, 13.71%, 7.86%, 6.33%, 5.10%, 4.25%, and 3.05% of the variance in the data, for a total of 78.22%. In order of variance explained, these seven factors are herein described as: 1) Impulsivity/Externalizing, 2) Executive Functioning, 3) Internalizing, 4) Perceptual Reasoning, 5) Adaptability, 6) Processing Speed, and 7) Verbal Intelligence (Table 3).

In sensitivity analyses we examined consistency of the factor structure by race, and after restricting to the 141 participants who are included in these etiologic analyses (data not shown). Factor structures were similar in all cases.

We examined studentized residuals and leverages and identified and excluded one outlier from both frequentist and Bayesian models with the highest residuals in several factor models. This participant had extremely low behavioral factor scores and non-detectable OP metabolite levels, and exclusion of this observation changed effect estimates by more than 20%.

Bayesian autocorrelation, trace, and density plots indicated adequate mixing and model convergence.

After adjustment for covariates and co-exposures, ΣDMPs were associated with better posterior mean scores on the Executive Functioning factor ($\hat{\beta}\,0.18$, 95% CI 0.04, 0.31), which was supported by a positive association with the Working Memory Index ($\hat{\beta}\,0.12$, 95% CI − 0.02, 0.25) (Table 4). Conversely, ΣDMPs were associated with more adverse Internalizing factor scores ($\hat{\beta} - 0.13$, 95% CI − 0.26, 0.00). ΣDEPs were associated with more adverse scores on the Working Memory Index ($\hat{\beta} - 0.17$, 95% CI − 0.33, − 0.03), with no other notable associations among the individual factor scores. The magnitude of each of these associations is relatively small, representing less than a quarter of a standard-deviation change in the outcome per one standard deviation increase in exposure.

Associations of ΣDMPs with the higher-loading individual item scores within the Executive Functioning factor were generally similar, while associations were null for the lower-loading items. In contrast, the association between ΣDMPs and items within the Internalizing factor was restricted to the BASC's Anxiety scale ($\hat{\beta} - 0.14$, 95% CI − 0.28, − 0.01), with no other associations among items in that factor (Table 5).

In sensitivity analyses, we explored the potential for residual confounding by environmental tobacco smoke and found that it did not materially change estimates in any model.

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3.2. Heterogeneity in associations by modifying factors

There were no interactions between sex, race/ethnicity, or *PON1* and the ΣDMPs or ΣDEPs, for any factor. However, there was an interaction between race and ΣDMPs for the WISC-IV's Working Memory Index. The positive association between ΣDMPs and the Working Memory Index was present only among black children ($\hat{\beta}\,0.34$, 95% CI 0.15, 0.53), but not among Hispanic ($\hat{\beta}\,-\,0.09$, 95% CI − 0.27, 0.08) or white children ($\hat{\beta}\,0.16$, 95% CI − 0.16, 0.49).

4. Discussion

Using a Bayesian hierarchical approach, we report associations between ΣDMPs and more adverse Internalizing factor scores. Among the items that comprise the Internalizing factor, the inverse associations with ΣDMPs appeared to be largely restricted to anxiety. Associations between DMP parent pesticides and internalizing characteristics have been previously reported in murine models and one human study. Malathion induces anxiety and/or depressive behaviors in adult rats when administered in adulthood or in utero (Assini et al., 2005; Brocardo et al., 2007; Hashjin et al., 2013). In humans, occupational exposure to malathion has also been associated with depression in adult farmers (Beard et al., 2014). Although there are no previously published findings of exposure to OPs in utero and internalizing, anxiety, or depressive symptoms in childhood, one study has reported an association between prenatal exposure to ΣDMPs and Pervasive Developmental Disorder (PDD) at 24 months as measured by the Child Behavior Checklist (CBCL) (Eskenazi et al., 2007). The PDD designation in the CBCL includes some behaviors that are indicative of general internalizing psychopathology, such as avoiding eye contact and being unresponsive to affection.

We also report a negative association between ΣDEPs and the Working Memory Index, which is consistent with other analyses within this cohort (Engel et al., 2011), although our analytic approach enabled estimation with more precision. Several previous studies report associations between OPs and deficits in different domains of IQ, including the Working Memory Index, (Bouchard et al., 2011; Engel et al., 2011; Rauh et al., 2011, 2006), although we report inverse associations only for ΣDEPs and the Working Memory Index.

Finally, we report an unexpected positive association between ΣDMPs and the Executive Functioning factor. This was supported by an elevated, but non-significant, association with the Working Memory Index, which is typically considered to be a component of executive functioning. This association between ΣDMPs and the Working Memory Index differed by race/ethnicity, with a positive association among blacks and no associations among whites or Hispanics. This positive association between ΣDMPs and executive functioning among blacks, but not Hispanics or whites, was unexpected and may reflect residual confounding by race-specific factors. It also may be a chance finding since this population is quite small and the confidence intervals were wide.

In contrast to our findings, several previous studies have reported adverse associations between OPs and various measures of executive functioning, including attention, ADHD, and working memory (Bouchard et al., 2010, 2011; Eskenazi et al., 2014; Marks et al., 2010;

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Rauh et al., 2011, 2006; Yu et al., 2016), although studies examining prenatal exposure originate from only two other cohorts (Bouchard et al., 2011; Marks et al., 2010; Rauh et al., 2011). In the CHAMACOS cohort, Marks et al. (Marks et al., 2010) reported associations between ΣDMPs and ΣDEPs and parent-report measures of attention problems at 3.5 but not 5 years, and also associations with a performance-based measure of attention, the Kiddie Connors Performance Test (K-CPT). ΣDEPs, but not ΣDMPs, were additionally associated with a psychometrician rating of ADHD symptoms in the same cohort of 5 year olds (Marks et al., 2010). Also in CHAMACOS, Bouchard et al. reported strong associations between increasing prenatal levels of ΣDMPs (but not DEPs) and worse performance on the Working Memory Index at seven years of age, along with other dimensions of IQ (Bouchard et al., 2011). In the Columbia Center for Children's Environmental Health, Rauh et al. report associations between prenatal chlorpyrifos exposure, which devolves into DEPs, and parent-report measures of ADHD problems and attention problems, at 3 years (Rauh et al., 2006). In the same cohort, Rauh et al. reported associations between prenatal exposure to chlorpyrifos and more adverse performance on the Working Memory Index (Rauh et al., 2011). Therefore, the existing literature on associations with specific cognitive domains is limited and somewhat mixed. Our findings of an adverse association between prenatal DEP exposure and the Working Memory Index is supported by the studies from the Columbia Center for Children's Environmental Health, which are based on a population of women residing in New York City that were enrolled at the same time as our cohort. However, we also report a positive association between ΣDMPs and the Executive Functioning factor, which seemingly contradicts the associations reported in the CHAMACOS cohort.

These inconsistencies may be attributed in part to the limitations of the DAP biomarkers as estimates of exposure to organophosphorus pesticides. DAP biomarkers are non-specific, with the same metabolite produced by multiple parent compounds which may vary in their toxicities. The CHAMACOS cohort was recruited in an agricultural region of California and over 80% of households had a farmworker that lived in the household during pregnancy. Thus the CHAMACOS cohort participants were likely exposed to a different constellation of pesticides than the urban Mount Sinai or Columbia populations. In a recent pooled analysis of these cohorts, significant heterogeneity was found in associations between ΣDMPs and the Bayley Mental Development Index (MDI) by cohort. Associations between ΣDMPs and the MDI in CHAMACOS were substantially more deleterious than the three other included cohorts, and the authors argued that a specific agricultural pesticide used in the Salinas Valley that devolves into DMPs (possibly oxydemeton-methyl, which is only used in agricultural applications and not in urban settings), may partly explain this pattern (Engel et al., 2016). Although the exact sources of OP exposure in our population are unknown, during the majority of our study period, chlorpyrifos and diazinon were approved for residential pesticide applications (EPA, 2000). In addition, New York City implemented a city-wide pesticide spraying program to control West Nile Virus in the late 1990s and early 2000s, which consisted of malathion and pyrethroids, depending on the year. Thus we assume that pesticide exposure in our population came from a combination of diet, personal and household pesticide use, and outdoor exposures to areas with mosquito and pest control programs (e.g., parks). These sources of exposure likely resulted in different constellations of pesticide exposures than in the agricultural population of CHAMACOS. The exposure

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profile of our cohort is likely much more similar to the Columbia cohort, and thus their findings of an adverse association between chlorpyrifos and Working Memory are highly relevant. We are unable to compare our findings of improved executive functioning with increasing DMP exposure with any cohorts other than CHAMACOS, since the Columbia cohort measured only a chlorpyrifos-specific biomarker. We did not find inverse associations between ΣDEPs and the Executive Functioning factor, which was somewhat surprising since working memory is a component of executive functioning. However, the parent-report measure of the BRIEF (from which the majority of the Executive Functioning factor is derived) displays almost no correlation with the performance-based measures of executive functioning (the Working Memory Index) in our data ($r_s = 0.09$). This lack of correlation is consistently reported in the executive functioning measurement literature (reviewed in (Toplak et al., 2013)). In previous studies, parent-report and performance-based measures of executive functioning load on different factors, suggesting they measure different underlying features of executive functioning (Bodnar et al., 2007; McAuley et al., 2010). Our Executive Functioning factor, which is comprised entirely of parent-report features, may reflect a broad capacity to self-regulate and execute goal-directed behaviors in a home or community environment while coping with typical environmental distractions. In contrast, the Working Memory Index is measured by an external examiner whose goal is to direct and keep a child on task in an environment that is relatively controlled and free of external distraction. Thus, the Working Memory Index may reflect a child's working memory capacity only in this very specific context (Toplak et al., 2013). Future studies of OPs and neurodevelopment should consider incorporating broader performance-based measures of behavior and executive functioning.

4.1. Strengths and limitations of study

Primary strengths of this study include the incorporation of hierarchical modeling techniques for the exposures, the use of dimension reduction across multiple scales and subscales of behavior, executive functioning, and intelligence, the longitudinal nature of the study, and the diverse multiethnic makeup of the cohort. Epidemiological investigations of exposure mixtures are still in their infancy, and have typically focused on confounding by co-exposures within a class of compounds (e.g. within phthalates), rather than across classes of compounds. Bayesian hierarchical models allowed the stable estimation of effects in the presence of collinearity and a high number of covariates relative to sample size, through the use of prior assignment (Dunson et al., 2008; Herring, 2010). The use of factor scores resulted in reduced dimensionality of the outcomes and enabled comparison of risk estimates across a wide range of outcomes in an easily interpretable format. Factor scores may also capture information over and above individual item scores, since this method incorporates additional information contained in the correlation matrix of a variety of items, and may have reduced variance. The diversity of the cohort additionally allowed us to estimate race-specific associations and establish the consistency of the adverse findings for whites, blacks, and Hispanics, which represent unique demographic groups in New York City.

Primary limitations that have not already been discussed include loss to follow-up and the use of a single spot urine sample to characterize exposures. The intra class correlation

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coefficients of DAP biomarker measures across pregnancy are low (Spaan et al., 2015). Thus, this analysis likely does not capture all of the critical windows of exposure for OPs and neurodevelopment. Approximately 60% of the original cohort did not return for follow-up or were missing at least one of the neurodevelopmental instruments included in the factor analysis. If this missingness was systematically related to childhood neurodevelopment (e.g., mothers with lower executive functioning or IQ may have been less likely to complete the full panel of parent-report instruments), then our results might underrepresent these lower-functioning individuals. However, the only known and testable characteristic that differed between those who did and did not return was marital status, which was included as a covariate in several models. Still, if other unknown covariates predicted follow-up, these could bias associations. Finally, the reproducibility of the dimension reduction technique may be limited across cohorts, since substantial variability is explained by instrument rather than underlying domain (Bodnar et al., 2007), and instrument selection is highly variable across cohorts. However, in cohorts that collected the BASC, the BRIEF, and IQ measures, we expect that a factor analysis should reveal similar underlying patterns. We reported similar structures across SES groups, and the factor structure of our behavioral factors was similar to the structure from a prior factor analysis of the BASC and the BRIEF (without IQ) (Reynolds and Kamphaus, 1998), which supports the existence of a common underlying structure across populations.

Finally, there is the possibility that other environmental exposures, such as flame retardants, organochlorine pesticides or PCBs, air pollution, lead, heavy metals, as well as others, may confound our associations. We did not measure flame retardants, air pollution, and non-lead heavy metals in this population, and organochlorines, PCBs, and lead were only measured on a subset of the population. Including them would have eliminated approximately a third of our population and destabilized the analysis. Future studies with a wider array of environmental biomarkers may be warranted.

5. Conclusions

In this prospective study of in utero exposure to OP pesticides, we report adverse associations between ΣDMPs and Internalizing Factor scores, and between ΣDEPs and the Working Memory Index. We also report an unexpected positive association between ΣDMPs and the Executive Functioning factor that appeared to be mostly driven by a strong positive association among black participants. Dimension reduction across multiple scales of neurodevelopment allowed assessment of broad phenotypes of development, eased presentation of associations, and incorporated information across multiple scales to enhance precision of estimates.

Acknowledgments

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Appendix A. Descriptions of HOME observation for the environment subscales

The HOME subscales include 1) Involvement, which measures how an adult interacts physically with the child (sample items include: parent keeps child within visual range, talks to child while doing work); 2) Learning Materials, which measures whether a child has appropriate play materials at home and elsewhere (sample items include: child has one or more large muscle activity toys); 3) Organization, which measures how a child's time is organized outside the house and what the child's personal space looks like (sample items include: safe play environment, regular caregivers); 4) Acceptance, which measures how the adult disciplines the child (sample items include: parent does not shout at child during the visit, parent not overly restrictive of the child's movements), 5) Responsivity, which measures the emotional and verbal sensitivity and responsivity of parent to the child (sample items include: mother caresses or kisses child at least once during visit), and 6) Variety, which measures opportunities for variety in daily stimulation (sample items include: father provides some caregiving every day, family visits or receives visits from relatives approximately once a month).

Appendix B. Instruments included in factor analysis of behavior, executive functioning, and IQ

Instrument	Scales	Age Assessed, N children
Wechsler Preschool and Primary Scales of Intelligence (WPPSI-III)	Verbal IQ (subtest: Vocabulary), Performance IQ (subtests: Block Design, Matrix Reasoning, Picture Concepts) Processing Speed Index (subtests: Symbol Search, Coding) Full Scale IQ	6 years (n = 162)
Wechsler Intelligence Scale for Children (WISC-IV)	Verbal IQ (subtests: Vocabulary), Perceptual Reasoning (subtests: Block Design, Matrix Reasoning, Picture Concepts) Processing Speed Index (subtests: Symbol Search, Coding) Full Scale IQ	7–9 years (n = 161)
Behavior Rating Inventory of Executive Functioning (BRIEF)	Behavioral Regulation Index (subtests: Inhibit, Shift, Emotional Control) Metacognition Index (Initiate, Working Memory, Plan/ Organize, Organization of Materials, Monitor) Global Executive Composite	4–9 years (N = 242)
Behavioral Assessment Scale for Children (BASC)	Externalizing Problems (Aggression, Hyperactivity, Conduct Problems) Internalizing Problems (Anxiety, Depression, Somatization,) Adaptive Skills composite (Adaptability, Leadership, Social Skills) Other Problems (Atypicality, Withdrawal) Behavioral Symptoms Index (Aggression, Hyperactivity, Anxiety, Depression, Attention, Conduct Problems, Atypicality)	4–9 years (N = 238)

210 participants had the BASC, the BRIEF, and either the WPPSI-III or the WISC-IV

BRIEF items and descriptions:

The Behavioral Regulation Index includes these clinical scales:

- Inhibit (the ability to control impulses),

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- Shift (the ability to switch between activities and tolerate change),
- Emotional Control (the ability to regulate emotional responses appropriately).

The Metacognition Index includes these clinical scales:

- Initiate (the ability to begin activities and generate problem-solving strategies),
- Working Memory (the ability to hold information when completing a task),
- Plan/Organize (the ability to set goals, develop steps, and anticipate events),
- Organization of Materials (the ability to put work, play, and storage spaces in order), and
- Monitor (the ability to check one's own work and performance).

Appendix C. List of covariates included in each model

Creatinine and OP analysis batch included in all models

Impulsivity and Externalizing Factor:

HOME scores, smoking during pregnancy, race/ethnicity, child sex, marital status, Spanish speaker

Executive Functioning Factor:

HOME scores, smoking during pregnancy, race/ethnicity, child sex, maternal education, maternal age, maternal IQ

Internalizing Factor:

HOME scores, race/ethnicity, maternal education

Perceptual Reasoning Factor, Verbal Intelligence Factor, and Working Memory Index:

HOME scores, race/ethnicity, maternal education, marital status, maternal age, maternal IQ, alcohol consumption during pregnancy, Spanish speaker, IQ examiner ID, canned fish consumption

Adaptability Factor:

HOME scores, maternal age, child sex, marital status, maternal education, canned fish consumption

Processing Speed Factor:

HOME scores, maternal education, Spanish speaker, IQ examiner ID, child sex

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Table 1

Characteristics of mount sinai children's environmental health center study population by follow up status.

	Original Birth cohort N = 404	Did not return for Follow-up N = 263	Follow-up Population N (%) N = 141
Maternal marital status at enrollment[a]			
Married	117 (29)	83 (32)	34 (24)
Living with partner	98 (24)	68 (26)	30 (21)
Single/Divorced/Widowed	189 (47)	112 (43)	77 (55)
Missing (n)	0	0	0
Maternal education at enrollment			
High school or less	288 (72)	186 (71)	102 (73)
Some college or higher	113 (28)	75 (29)	38 (27)
Missing (n)	3	2	1
Maternal age at enrollment			
< 20	142 (35)	101 (38)	41 (29)
20–25	132 (33)	83 (32)	49 (35)
> 25	130 (32)	79 (30)	51 (36)
Missing (n)	0	0	0
Maternal race			
Black or other race	118 (29)	76 (29)	42 (30)
White	86 (21)	60 (23)	26 (18)
Hispanic	200 (50)	127 (48)	73 (52)
Missing (n)	0	0	0
Any smoking during pregnancy			
None	337 (83)	218 (83)	119 (84)
Any	67 (17)	45 (17)	22 (16)
Missing (n)	0	0	0
Alcohol use during pregnancy			
None	337 (85)	222 (86)	115 (83)
Light	49 (12)	30 (12)	19 (14)
Moderate	10 (3)	6 (2)	4 (3)
Missing (n)	8	5	3
Canned fish consumption during pregnancy			
< 1 times per week	341 (84)	218 (83)	123 (87)
1 or more times per week	63 (16)	45 (17)	18 (13)
Missing (n)	0	0	0
Child sex			
Male	220 (54)	148 (56)	72 (51)
Female	184 (46)	115 (44)	69 (49)
Missing (n)	0	0	0

Follow-up population restricted to those with a complete panel of biomarkers. Follow-up population includes those with complete biomarker data and a complete neurodevelopmental follow-up visit. Comparison population includes those without biomarker data or those who did not return for a complete follow-up visit.

[a]Maternal marital status at enrollment differed for those with biomarker data who returned for follow-up vs those who didn't (p = 0.03). No other enrollment characteristics differed by follow-up status.

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Table 2

Distributions of organophosphorus pesticide metabolites and co-exposures in study population (n=141).

	N	Values > LOD (% of total)	Median (Geometric SD)	25, 75 percentile	Min, Max
Organophosphorus Pesticides (nm/L)					
DEPs					
Diethylthiophosphate (DETP)	141	113 (80.1)	9.9 (3.5)	4.9, 16.4	0.8, 122.3
Diethyldithiophosphate (DEDP)	141	15 (10.6)	0.1 (3.9)	0.1, 0.1	0.1, 59.9
Diethylphosphate (DEP)	141	62 (44.0)	0.2 (14.0)	0.2, 24.8	0.2, 219.7
ΣDEP	141	124 (87.9)[a]	16.6 (4.0)	7.6, 41.7	1.0, 344.0
DMPs					
Dimethylthiophosphate (DMTP)	141	127 (90.1)	23.5 (6.0)	8.0, 70.5	0.6, 4754.3
Dimethyldithiophosphate (DMDP)	141	35 (24.8)	0.3 (5.9)	0.3, 0.3	0.3, 275.1
Dimethylphosphate (DMP)	141	87 (61.7)	12.6 (9.0)	0.6, 46.6	0.6, 1173.0
ΣDMP	141	133 (94.3)[a]	37.1 (5.2)	12.7, 147.8	1.5, 4903.6
Phthalates (ng/mL)					
ΣDEHP (μm/L) [a]	141	141 (100.0)[a]	0.3 (3.4)	0.1, 0.5	0.0, 8.8
Low- MWP*(μm/L) [a]	141	141 (100.0)[a]	2.4 (4.0)	1.0, 5.7	0.1, 313.8
Monoethyl phthalate (MEP)	141	141 (100.0)	192.9 (4.2)	79.7, 482.7	6.5, 29528.4
Mono-n-butyl phthalate (MBP)	141	141 (100.0)	31.9 (3.4)	14.1, 75.2	1.1, 4042.5
Monoisobutyl phthalate (MIBP)	141	139 (99.3)	6.2 (3.0)	2.9, 13.7	0.2, 63.0
Mono(3-carboxypropyl) phthalate (MCPP)	141	139 (99.3)	2.7 (3.0)	1.6, 6.0	0.1, 129.3
Monobenzyl phthalate (MBZP)	141	141 (100.0)	14.8 (3.7)	6.3, 33.3	0.6, 481.2
Phenols (ng/mL)					
Biphenyl-A (BPA)	141	121 (85.8)	1.2 (2.8)	0.6, 2.2	0.3, 35.2
Benzophenone-3 (BP3)	141	141 (100.0)	6.8 (7.4)	2.9, 22.1	0.2, 9290.0
2,5-Dichlorphenol (2,5-DCP)	141	141 (100.0)	54.4 (5.5)	22.4, 174.0	2.8, 8510.0
Triclosan	141	110 (78.0)	21.1 (5.2)	7.9, 86.5	2.3, 1790.0
Pyrethroids (binary for above or below the LOD)					
3-PBA	141	33 (23.4)			

Low molecular weight phthalates include MEP, MBP, MIBP Distributional values were computed after imputing values below the LOD from a normal distribution truncated at the LOD.

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[a]Values > LOD for sum values indicate number of observations where at least one metabolite in the sum is above the LOD

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Table 3

Varimax rotated factor pattern structure and item loadings of childhood neurodevelopmental scales (n = 210).

Factor 1 **Impulsivity & Externalizing**		**Factor 2** **Executive Functioning**		**Factor 3** **Internalizing**		**Factor 4** **Perceptual Reasoning**		**Factor 5** **Adaptability**		**Factor 6** **Processing Speed**		**Factor 7** **Verbal Intelligence**	
Scale	**Loading**	**Scale**	**Loading**	**Scale**	**Loading**	**Scale**	**Loading**	**Scale**	**Loading**	**Scale**	**Loading**	**Scale**	**Loading**
Externalizing Problems[a]	0.90	Metacognition Index[b]	0.89	Internalizing[a]	0.88	Perceptual Reasoning IQ[c]	0.97	Adaptive Skills Index[a]	0.89	Processing Speed Index[c]	0.96	Vocabulary[c]	0.85
Aggression[a]	0.78	Planning[b]	0.83	Anxiety[a]	0.77	Matrix Reasoning[c]	0.76	Social Skills[a]	0.85	Coding[c]	0.88	Verbal IQ[c]	0.83
Conduct[a]	0.76	Global Exec Composite[b]	0.79	Somatization[a]	0.67	Block Design[c]	0.72	Leadership[a]	0.85	Symbol Search[c]	0.71	Full Scale IQ[c]	0.57
Hyperactivity[a]	0.74	Working Memory[b]	0.78	Withdrawal[a]	0.67	Picture Concepts[c]	0.71	Adaptability[a]	0.56	Full Scale IQ[c]	0.36	Organization[b]	0.38
Behavioral Reg Index[b]	0.69	Monitor[b]	0.77	Depression[a]	0.64	Full Scale IQ[c]	0.70	Attention[a]	− 0.36			Symbol Search[c]	0.31
Behavioral Symp Index[a]	0.68	Initiate[b]	0.77	Atypicality[a]	0.58	Verbal IQ[c]	0.39	Initiate[a]	− 0.30				
Inhibit[b]	0.66	Organization[b]	0.62	Behavioral Symp Index[a]	0.53	Vocabulary[c]	0.31						
Emotional Control[b]	0.63	Attention[a]	0.57	Shift[b]	0.50								
Adaptability[a]	− 0.59	Inhibit[b]	0.56	Emotional Control[b]	0.44								
Shift[b]	0.51	Behavioral Reg Index[b]	0.50	Behavioral Reg Index[b]	0.38								
Global Exec Composite[b]	0.49	Behavioral Symp Index[a]	0.42	Global Exec Composite[b]	0.31								
Depression[a]	0.46	Shift[b]	0.42										
Attention[a]	0.45	Hyperactivity[a]	0.37										
Monitor[b]	0.41	Emotional Control[b]	0.35										
Organization[b]	0.35	Atypicality[a]	0.30										
Adaptive Skills[a]	− 0.33												
Atypicality[a]	0.30												
Internalizing[a]	0.30												
Working Memory	0.3												
Factor Structure													
% Variance accounted for	37.92		13.71		7.86		6.33		5.10		4.25		3.05
Eigenvalue	14.03		5.07		2.91		2.34		1.89		1.57		1.13

Factor structure was similar when restricting to the 141 participants included in regression analyses.

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[a] BASC scales.

[b] BRIEF scales.

[c] WISC-IV or the WPPSI-III scales. Only items with loadings with absolute values > 0.30 are shown here. Loadings are from a factor analysis with orthogonal varimax rotation (factors are uncorrelated). Positive loadings for items from the BRIEF and BASC all indicate more problems with those items, except for the BASC's Adaptive Skills, Social Skills, Leadership, and Adaptability.

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Table 4

Overall associations between OPs and neurodevelopmental factor scores (n = 141).

	ΣDMPs $\hat{\beta}$ (95% CI)[a]	ΣDEPs $\hat{\beta}$ (95% CI)[a]
Impulsivity & Externalizing Factor	− 0.02 (− 0.16, 0.11)	0.08 (− 0.06, 0.22)
Executive Functioning Factor	0.18 (0.04, 0.31)	− 0.05 (− 0.21, 0.11)
Internalizing Factor	− 0.13 (− 0.26, 0.00)	− 0.03 (− 0.16, 0.11)
Perceptual Reasoning Factor	0.00 (− 0.14, 0.13)	− 0.02 (−0.17, 0.14)
Adaptability Factor	− 0.02 (− 0.14, 0.12)	− 0.08 (−0.23, 0.07)
Processing Speed Factor	− 0.01 (− 0.14, 0.13)	0.03 (− 0.12, 0.19)
Verbal Intelligence Factor	0.07 (− 0.04, 0.19)	− 0.03 (− 0.17, 0.09)
Working Memory Index (n = 119)	0.12 (− 0.02, 0.25)	− 0.17 (− 0.33, − 0.03)

In Tables 4 and 5, scores have been scaled so that positive scores indicate more positive outcomes and negative scores indicate more adverse outcomes.

Creatinine, OP analysis batch, HOME scores, maternal IQ, maternal education at follow-up, maternal marital status at follow-up, maternal age, maternal race/ethnicity, Spanish language spoken at home, IQ examiner ID, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, maternal canned fish consumption during pregnancy, child sex, and alcohol were included in a DAG used to derive minimally sufficient sets for each factor. See Appendix C for full list of covariates for each factor.

[a]These Bayesian posterior means and 95% credible intervals are from models that include both ΣDAP measures (ΣDEPs and ΣDMPs), the molar sum of DEHP and the individual phthalate congeners of MEP, MIBP, MBP, MCPP, MBZP, as well as the individual phenol biomarkers BPA, BP3, 2,5-DCP, and triclosan, and the pyrethroid metabolite 3-PBA.

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Table 5

Associations between DMPs and individual factor items from executive functioning and internalizing factors (n = 141).

Rank of Item Loading	Items from Executive Functioning Factor	Associations with ΣDMPs $\hat{\beta}$ (95% CI)¥	Items from Internalizing factor	Associations with ΣDMPs $\hat{\beta}$ (95% CI)
1	BRIEF Metacognition Index	0.13 (− 0.01, 0.28)	BASC Internalizing Composite	−0.07 (− 0.20, 0.06)
2	BRIEF Planning	0.16 (0.02, 0.30)	BASC Anxiety	− 0.14 (− 0.28, − 0.01)
3	BRIEF Global Executive Composite	0.11 (− 0.04, 0.25)	BASC Somatization	0.01 (− 0.12, 0.14)
4	BRIEF Working Memory	0.14 (− 0.01, 0.28)	BASC Withdrawal	− 0.12 (− 0.27, 0.03)
5	BRIEF Monitor	0.14 (0.00, 0.28)	BASC Depression	− 0.03 (− 0.17, 0.11)
6	BRIEF Initiate	0.10 (− 0.05, 0.25)	BASC Atypicality	0.05 (−0.07, 0.17)
7	BRIEF Organization	0.00 (− 0.13, 0.14)	BASC Behavioral Symptoms Index	− 0.00 (− 0.14, 0.14)
8	BASC Attention	0.13 (− 0.01, 0.26)	BRIEF Shift	0.00 (− 0.13, 0.14)
9	BRIEF Inhibit	0.13 (− 0.01, 0.28)	BRIEF Emotional Control	− 0.03 (− 0.18, 0.12)
10	BRIEF Behavioral Regulation Index	0.05 (− 0.10, 0.19)	BRIEF Behavioral Regulation Index	0.05 (− 0.10, 0.19)
11	BASC Behavioral Symptom Index	− 0.00 (− 0.14, 0.14)	BRIEF Global Executive Composite	0.11 (− 0.04, 0.25)
12	BRIEF Shift	0.00 (− 0.13, 0.14)		
13	BASC Hyperactivity	0.02 (− 0.12, 0.15)		
14	BRIEF Emotional Control	− 0.03 (− 0.18, 0.12)		
15	BASC Atypicality	0.06 (− 0.06, 0.18)		

¥These Bayesian posterior means and 95% credible intervals are from models that include both ΣDAP measures (ΣDEPs and ΣDMPs), the molar sum of DEHP and the individual phthalate congeners of MEP, MIBP, MBP, MCPP, MBZP, as well as the individual phenol metabolites BPA, BP3, DCP25, and triclosan, and the pyrethroid metabolite 3-PBA.

In Tables 4, 5, scores have been scaled so that positive scores indicate more positive outcomes and negative scores indicate more adverse outcomes.

Creatinine, OP analysis batch, HOME scores, maternal IQ, maternal education at follow-up, maternal marital status at follow-up, maternal age, maternal race/ethnicity, Spanish language spoken at home, IQ examiner ID, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, maternal canned fish consumption during pregnancy, child sex, and alcohol were included in a DAG used to derive minimally sufficient sets for each factor. Covariates for the executive functioning items were the same as those for the executive functioning factor (detailed in Appendix C), while covariates for the internalizing items were the same as those for the internalizing factor.