HHS Public Access

Author manuscript

Neurotoxicol Teratol. Author manuscript; available in PMC 2022 January 05.

Published in final edited form as:

Neurotoxicol Teratol. 2021 ; 83: 106947. doi:10.1016/j.ntt.2021.106947.

Prenatal phthalate exposures and Autism Spectrum Disorder symptoms in low-risk children

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Abstract

Background: Prenatal exposure to environmental chemicals has been associated with Autism Spectrum Disorder (ASD) symptoms in some, but not all, studies, but most research has not accounted for other childhood behavior problems.

Objectives: To evaluate the specific associations of prenatal phthalate exposures with ASD symptoms in children (ages 3–6) accounting for other behavior problems, and to assess sex differences in these associations.

Methods: We measured phthalate metabolites in prenatal urine samples. Mothers completed the Social Responsiveness Scale-2nd edition (SRS-2) to assess child ASD symptoms and the Child Behavior Checklist (CBCL) to assess general behavior problems. We assessed associations of the sum of di-(2-ethylhexyl) phthalate metabolites, monobutyl phthalate, mono-isobutyl phthalate, and

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Research data for this article

Researchers interested in accessing ARCH data can apply through the Child Health Advances from Research with Mothers website: http://www.epi.msu.edu/charmstudy/researchers

Conflict of Interests: None of the authors have a financial or personal conflict of interest in this study.

monoethyl phthalate (mEP) with ASD symptoms, adjusting for other behavior problems, using linear regression models (n=77).

Results: Most associations were null, and the sample size limited power to detect associations, particularly in the stratified analyses. After adjusting for internalizing and externalizing problems from the CBCL, ASD symptoms increased for each doubling of prenatal mEP concentration among boys only.

Conclusions: Further investigation of maternal prenatal urinary phthalate metabolite concentrations and ASD symptoms while adjusting for other behavioral problems is warranted.

Keywords

Autism Spectrum Disorder; Broad Autism Phenotype; Child Behavior Checklist; endocrine disruptors; phthalates; Social Responsiveness Scale–2nd edition

1. Introduction

Phthalates are ubiquitous, non-persistent chemicals that disrupt endocrine processes (1). Fetuses are particularly sensitive to hormonal disruption because neurodevelopment begins as early as embryogenesis (2). Experimental studies have linked prenatal phthalate exposures to offspring neurodevelopmental toxicities (3, 4). While prenatal phthalate exposures have been associated with neurobehavioral deficits in humans(5–7), associations with Autism Spectrum Disorder (ASD) symptoms in humans are inconsistent, in part due to the operationalization of ASD symptoms and modification of associations by child sex and by other behaviors. Some studies have found no associations of prenatal phthalate exposures with ASD symptoms (8), whereas others have noted low-molecular weight phthalates were positively associated with ASD-like social deficits (7). Additionally, studies have found that child sex modifies associations of prenatal phthalate exposures and ASD diagnosis (5) and other behavior problems (6).

The Social Responsiveness Scale (SRS) (9) is a measure frequently used in research to assess severity of ASD symptoms (7, 8), but the SRS's discrimination of ASD symptoms from those of other childhood behavior problems may be limited when used alone, which may contribute to the mixed associations of prenatal phthalate exposure and ASD outcomes (5, 7, 8, 10, 11). Administering the SRS in combination with other behavior problem measures, such as the Child Behavior Checklist (CBCL) (12), may improve SRS ASD symptom discrimination from symptoms of co-occurring childhood behavior problems (13) by allowing researchers to statistically adjust models for other child behavior problems (14). Therefore, our objectives were to 1) determine if prenatal phthalate exposures were associated with ASD symptoms using a series of models that addressed variation from co-occurring internalizing and externalizing behavior problems and 2) to determine if the associations were modified by sex.

1. Methods

2.1 Subjects

We used data from a sub-study of the Archives for Research on Child Health (ARCH) cohort study, the ARCH Child Development Cohort (ARCH-CDC, n= 132). ARCH and ARCH-CDC have been described previously (14). Briefly, to be eligible for ARCH, women had to be 18 years of age or older and be able to communicate in English. Enrolled women were interviewed, and maternal blood and urine were collected in the first and second trimester. A third urine sample was collected in the third trimester. All subjects gave their informed consent prior to participation and the Institutional Review Boards of Michigan State University and the Michigan Department of Health and Human Services approved the study.

Mother-child dyads were included in this study if the mother had prenatal urinary phthalate metabolite concentrations measured, the pregnancy was a singleton pregnancy, the child was born at 37 weeks of gestation or later, and they had complete data for the outcome measure. A total of 77 dyads were eligible.

2.2 Urine Collection and Analysis

This analysis used urinary phthalate metabolite concentrations measured in the first prenatal visit urine sample, generally obtained between 10 – 14 weeks of gestation. Spot-urine samples were collected by clean catch method and poured off into a second sterile polypropylene container prior to routine clinical testing. Urine was stored in the clinic at 4°C and was transported to the lab for processing within 24 hours of collection. Urine was aliquoted and stored at −80°C until sent for analysis.

Creatinine (μg/mL) and the following metabolites (ng/mL) were analyzed using methods previously described (15): 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), monobutyl phthalate (mBP), monoisobutyl phthalate (miBP), and monoethyl phthalate (mEP). Following enzymatic deconjugation and solid phase extraction, high performance liquid chromatography - electrospray ionization with tandem triple quadrupole mass spectrometer measured urinary phthalate metabolite and creatinine concentrations (Shimadzu LC-30AD Series HPLC system, Shimadzu Corporation, Kyoto, Japan/Sciex 5500, ESI-MS/MS; Applied Biosystems, Foster City, CA). Internal Quality Control for the analytical run included method blank, a spiked blank, and a pair of matrix-spiked sample duplicates. Samples with concentrations lower than the LOD were imputed using LOD/√2. We corrected urinary phthalate metabolites for creatinine to account for urine dilution (μg/g creatinine), and summed creatinine-corrected molar concentrations of mEHP, mEHHP, mEOHP, and mECPP to approximate exposure to the parent compound DEHP (∑DEHP) (μmol/g creatinine).

2.3 ASD Symptom Measures

ARCH-CDC collected child development and behavior data utilizing multiple validated, parent-reported questionnaires including the Social Responsiveness Scale-2nd edition (SRS-2) (9) and the CBCL (12). The SRS-2 converges with clinical measures of ASD (16);

it includes 65 items that assess behaviors consistent with child ASD symptoms. The SRS-2 total t-score is a sum of the items normed for child age and sex; scores less than 60 indicates behaviors within normal limits, scores between 60 and 65 indicate modest impairment, and scores above 65 indicate severe impairment (9). The CBCL is a parent-report checklist that assesses general behavior problems including internalizing behaviors (depression, anxiety, somatic complaints, and social withdrawal) and externalizing behaviors (aggression and rule-breaking behaviors) (12).

Our outcome was continuous age- and sex-standardized SRS-2 total t-scores. When models excluded the CBCL internalizing and externalizing t-scores, we considered SRS-2 a measure of ASD including variation from co-occurring internalizing and externalizing problems. When models included CBCL internalizing and externalizing t-scores as covariates, we considered adjusted SRS-2 scores as measures of ASD symptoms excluding variation from co-occurring internalizing and externalizing problems.

2.4 Covariates

We identified relevant covariates through literature review and specified assumptions with directed acyclic graphs (17). We ascertained prenatal covariates from the prenatal interview. Mothers completed the Broad Autism Phenotype Questionnaire (BAPQ) during the ARCH-CDC visit to measure their own Broad Autism Phenotype (BAP), which captures genetic liability for ASD (18, 19).We included the following maternal characteristics: BAPQ total score, age at birth, pre-pregnancy body mass index (BMI), prenatal education level, and prenatal household income. CBCL scores were only included in models without variation from co-occurring internalizing and externalizing problems

2.5 Statistical Analysis

We used SAS version 9.4 for analysis (SAS Institute, Cary NC). We calculated medians and ranges of creatinine-corrected urinary phthalate metabolites by child sex. We calculated means and standard deviations for SRS-2 t-scores, internalizing and externalizing t-scores, maternal age, maternal BMI, and maternal BAPQ and tested for differences using Kruskal-Wallis tests. Frequencies and percentages were calculated for maternal race and ethnicity, maternal education, and household income, including a category for missing observations, and we tested for differences using χ^2 tests.

About 6.5% of our participants were missing data for at least one covariate, so we used multiple imputation (10 imputations) to impute values for missing covariates using SAS multiple imputation procedures. We generated linear regression models that regressed SRS-2 t-scores on ln-transformed urinary phthalate metabolite concentrations/sum. The unadjusted model and adjusted models one, two, and three represent ASD symptoms with variation for internalizing and externalizing problems. Model one controlled for maternal age, BMI, education, and household income. Model two controlled for model one covariates and maternal BAPQ total score. Models 3 and 4 represent ASD symptom models without variation from internalizing and externalizing problems. Model three controlled for model one covariates and the CBCL internalizing and externalizing scales. Model four controlled for model one covariates, maternal BAPQ total score, and the CBCL internalizing and

externalizing t-scores. Additionally, we stratified analyses by sex and generated models for boys and for girls separately. We back-transformed β-estimates to represent the change in SRS-2 t-score for each doubling of analyte/sum concentration by multiplying the β-estimates by log(2). We considered *P*-values < 0.05 statistically significant.

3. Results

3.1 Description of Participants and Phthalate Metabolites

The mothers of the boys in our sample had significantly lower median pre-pregnancy BMI compared to mothers of girls (23.2 kg/m^2 compared to 29.6 kg/m^2) (Table 1). A substantial proportion of our sample had household incomes under $25,000 a year, and the percentage was higher among the mothers of girls (67.5%) than among mothers of boys (51.4%). The mothers of boys had a lower median BAPQ total score compared to the mothers of girls (median 2.4 compared to 2.9). The median boys' SRS-2 total age- and sex-standardized t-score was 5 points lower than the median of the girls (49.0 compared to 54.0).

The DEHP metabolite mEHP was the only metabolite with values lower than the LOD (21%) (Table 2). Prenatal concentrations of all urinary phthalate metabolites were similar in mothers of boys and girls (Table 2).

3.2 Regression Model Results

Overall and among girls, prenatal concentrations of urinary phthalate metabolites were not significantly associated with SRS-2 age- and sex-standardized t-score (Table 3). Among boys, prenatal mEP concentration was associated with SRS-2 t-scores in models three and four. In model three, SRS-2 t-scores increased 0.8 points (95%CI: 0.1, 1.5) and in model four, SRS-2 t-scores increased 0.9 points (95%CI: 0.1, 1.7) for each doubling of mEP concentration. Though not significant, estimates from models two, three, and four suggest an inverse association of prenatal miBP concentration with SRS-2 total scores among boys.

4. Discussion

We found mEP was associated with SRS-2 sex- and age-adjusted t-scores among boys in models that included CBCL internalizing and externalizing scores.

4.1 ASD Symptoms Without Adjustment for CBCL Internalizing and Externalizing Scores

In our study, models that excluded CBCL internalizing and externalizing scores were not statistically significant. Other studies that have used the SRS without adjustment for other childhood behavior problems show mixed results. A study that used the SRS found no associations of mBP, miBP, and DEHP metabolites with total SRS t-scores. They did find evidence of effect modification of the association of mEP with SRS total t-score by child sex, showing that each two standard-deviation increase in mEP was associated with a decrease in SRS t-scores in boys only (8). In another study that used the SRS, low-molecular weight phthalates (sum of monomethyl phthalate, mEP, mBP, and miBP) were associated with increases in SRS t-score among 7 to 9 year-olds (7). In our study, prenatal mEP concentrations were not significantly associated with SRS-2 t-score in the unadjusted model

and adjusted models one and two, though the point estimates suggested there may be an effect that we were underpowered to detect. Importantly, we were unable to control for important covariates such as maternal smoking during pregnancy. However, we were able to account for maternal BAP (BAPQ total score), which captures genetic liability for ASD and which may control for differences in reporting of child behaviors similar to those of the parent reporter, as parental ASD traits are associated with child SRS t-scores (20, 21).

4.2 ASD Symptoms Adjusted for CBCL Internalizing and Externalizing Scores

Results of models that included the CBCL internalizing and externalizing scores, which removed variance from internalizing and externalizing problems, were non-significant for ∑DEHP, mBP, and miBP. We found mEP was significantly associated with SRS-2 t-scores among boys only. Few studies have evaluated the association of prenatal phthalate exposure with ASD diagnosis in general population samples. One prenatal cohort recruited mothers of children with ASD diagnoses to study the risk of ASD diagnosis for the child of their current pregnancy (5). The study found each log-increase in prenatal urinary mEP concentration was associated with a 1.4 fold increase in risk of non-typical development, defined as an Autism Diagnostic Observation Schedule score within three points of the ASD diagnosis cut-off and/or a Mullen Scales of Early Learning score 1.5 to 2 standard deviations lower than the average. Additionally, there was a non-significant 1.2-fold risk increase of ASD diagnosis for each log-increase in mEP (5). The study also noted important modification of mEP and sum of DEHP exposures by child sex, with increased risk of ASD and non-typical development among boys, while there was no increased risk in girls (5). Our findings suggest prenatal phthalate exposures may have sex-specific associations with ASD symptoms in low-risk children, though it is critical to assess this in a larger sample.

4.3 Limitations

The sample size was small and selected from a convenience sample of pregnancies in one Michigan city. It is possible that the median girls SRS-2 t-scores are higher than expected because of the small sample size and the fact that we did not have a population-based sample (9). This is also the likely cause of the differences in maternal BMI, BAPQ total score, and household income. Confidence intervals were wide, indicating instability of associations, and the small sample size limits generalizability and power to detect associations, especially in the stratified analyses. However, our sex-specific results were consistent with associations noted in a study of children at high-risk for ASD (5). We analyzed a single spot-urine, which is a less than ideal reflection of phthalate exposure across pregnancy (22).

4.4 Strengths

Metabolites were detected at values greater than the LOD, except mEHP. We used multiple imputation to impute values for missing covariates. The data from pregnancy were collected prospectively, and many mothers enrolled in the first trimester. We included children born at 37 weeks gestation or later which allowed us to assess the association between phthalate metabolite concentrations and ASD symptoms in a lower-risk group.

5. Conclusions

In our small sample, associations of prenatal urinary phthalate metabolites and SRS-2 t-score varied based on the inclusion or exclusion of variables that adjust SRS-2 t-scores for internalizing and externalizing problems. Our findings support further investigation of these associations in a larger sample.

Acknowledgements

The authors would like to thank Dr. Kristen Upson for her advice.

Funding

This research was supported by the Environmental influences on Child Health Outcomes (ECHO), a nationwide research program supported by the National Institutes of Health (NIH), Office of the Director to enhance child health under Cooperative Agreement Number 5UH3OD023285-04 (Haggerty, Paneth, Ruden, Talge) and Award Number U2CES026542-01 (Kannan, Karthikraj), and the MSU Center for Research in Autism, Intellectual and Neurodevelopmental Disabilities (Ingersoll). The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Abbreviations used:

ARCH	Archive for Research on Child Health
ASD	Autism Spectrum Disorder
BAP	Broad Autism Phenotype
BAPQ	Broad Autism Phenotype Questionnaire
CBCL	Child Behavior Checklist
DBP	dibutyl phthalate
DiBP	di-isobutyl phthalate
DEP	diethyl phthalate
DEHP	di-(2-ethylhexyl) phthalate
LOD	limit of detection
mBP	monobutyl phthalate
mEP	monoethyl phthalate
mEHP	mono(2-ethylhexyl) phthalate
mEHHP	mono(2-ethyl-5-hydroxyhexyl) phthalate
mEOHP	mono(2-ethyl-5-oxohexyl) phthalate
mECCP	mono(2-ethyl-5-carboxypentyl) phthalate
miBP	mono-isobutyl phthalate

SRS	Social Responsiveness Scale
SRS-2	Social Responsiveness Scale-2nd edition

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Highlights:

- Phthalates, which are present in plastics, cosmetics, and other consumer products, are not covalently bound and thus can easily leach into the environment and enter the human body.
- Several phthalate metabolites were found in 100% of the urine from pregnant women in our study.
- Maternal prenatal urinary mEP concentration was associated with ASD symptoms in boys after controlling for other behavioral problems.

Table 1.

Characteristics of participants in the ARCH Child Development Cohort by child sex

Characteristics	Boys	Girls	*P*
Mother			
Age at birth[a]	27.0 (19,39)	24.5 (19, 38)	0.30
Pre-pregnancy BMI (kg/m^2)[b]	23.2 (17.7, 40.8)	29.6 (16.5, 50.1)	<0.01
Household income[b]			0.07
Less than $25,000/year	19 (51.4)	27 (67.5)	
$25,000/year or higher	18 (48.7)	11 (27.5)	
Missing	0 (0.0)	2.0 (5.0)	
Education at Assessment[b]			0.36
Less than college graduate	25 (67.6)	30 (75.0)	
College graduate or higher	12 (32.4)	9 (22.5)	
Missing	0 (0.0)	1 (2.5)	
Race/Ethnicity[b]			
Non-Hispanic White	28 (75.6)	26 (65.0)	0.31
Other including Hispanic and Multiracial	9 (24.3)	14 (35.0)	
BAPQ Total Score[a]	2.4 (1.6, 3.6)	2.9 (1.3, 4.1)	<0.01
Missing[b,c]	1 (2.7)	2 (5.0)	
Child			
CBCL Internalizing t-Score[a]	45.0 (29.0, 67.0)	47.0 (33.0, 78.0)	0.79
Missing[b,c]	0 (0.0)	1 (2.5)	
CBCL Externalizing t-Score[a]	44.0 (32.0, 63.0)	50.0 (28.0, 73.0)	0.46
Missing[b,c]	0 (0.0)	1 (2.5)	
SRS-2 Total t-Score[a]	49.0 (41.0, 82.0)	54.0 (40.0, 74.0)	0.01

[a]Median and range, *P*-value Kruskal-Wallis test.

[b]Frequency and percent, *P*-value X^2 test.

[c]Missing observations not included in median and range.

Abbreviations: ARCH, Archives on Research for Child Health; BAPQ, Broad Autism Phenotype Questionnaire; BMI, body mass index; CBCL, Child Behavior Check List; SRS-2, Social Responsiveness Scale-2nd Edition

Table 2.

Medians and ranges of maternal creatinine-corrected prenatal urinary phthalate concentrations in the ARCH Child Development Cohort sample by child sex

Parent Compound	Metabolite (μg/g creatinine)	LOD	%>LOD	Mothers of Boys Median (Range)	Mothers of Girls Median (Range)
DEHP	mEHP	0.45	79%	1.4 (0.0, 22.1)	1.2 (0.1, 82.8)
	mEHHP	0.06	100%	6.3 (2.4, 51.1)	5.7 (1.4, 101.8)
	mEOHP	0.03	100%	3.8 (1.1, 28.3)	3.0 (0.9, 47.1)
	mECPP	0.03	100%	9.8 (3.1, 90.6)	9.5 (3.1, 128.6)
DBP	mBP	0.15	100%	8.6 (2.8, 31.4)	6.1 (2.3, 20.9)
DiBP	miBP	0.10	100%	4.3 (1.4, 49.1)	2.9 (0.8, 15.4)
DEP	mEP	0.06	100%	38.3 (6.8, 2399.3)	49.2 (6.0, 879.3)

Abbreviations: DBP, dibutyl phthalate; DiBP, di-isobutyl phthalate; DEP, diethyl phthalate; DEHP, di-(2-ethylhexyl) phthalate; LOD, limit of detection; mBP, monobutyl phthalate; mEP, monoethyl phthalate; mEHP, mono(2-ethylhexyl) phthalate; mEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; mEOHP mono(2-ethyl-5-oxohexyl) phthalate; mECCP, mono(2-ethyl-5-carboxypentyl) phthalate; miBP, mono-isobutyl phthalate.

Table 3.

Linear regression models of associations of prenatal phthalate metabolite concentrations or sums and Social Responsiveness Scale 2nd Edition t-Score in the ARCH Child Development Cohort

Metabolites and Sum	Unadjusted (90%CI)	Model 1 (90%CI)	Model 2 (90%CI)	Model 3 (90%CI)	Model 4 (90%CI)
ΣDEHP					
All[a]	0.4 (−1.2, 2.1)	0.2 (−1.4, 1.8)	−0.3 (−1.7, 1.1)	−0.4 (−1.8, 0.9)	−0.5 (−1.8, 0.8)
Boys[b]	2.0 (−0.2, 4.2)	1.7 (−0.6, 4.0)	1.1 (−1.1, 3.3)	−0.8 (−2.4, 0.7)	−0.8 (−2.4, 0.8)
Girls[c]	−0.6 (−2.9, 1.6)	−0.4 (−2.3, 1.5)	−0.7 (−2.5, 1.1)	−0.3 (−2, 1.4)	−0.4 (−2.1, 1.3)
mBP					
All[a]	−0.1 (−2.6, 2.4)	−0.3 (−2.7, 2.0)	−0.4 (−2.5, 1.7)	−1.4 (−3.4, 0.6)	−1.1 (−3.0, 0.9)
Boys[b]	1.7 (−1.4, 4.8)	1.2 (−2.0, 4.4)	0.7 (−2.2, 3.6)	−0.6 (−2.7, 1.4)	−0.6 (−2.6, 1.5)
Girls[c]	−0.3 (−4.1, 3.5)	0.2 (−3.1, 3.6)	−0.2 (−3.4, 3.0)	−0.3 (−3.3, 2.8)	−0.3 (−3.4, 2.7)
miBP					
All[a]	−0.3 (−2.2, 1.6)	−0.3 (−2.1, 1.5)	−0.7 (−2.3, 0.8)	−1.0 (−2.5, 0.5)	−1.0 (−2.5, 0.4)
Boys[b]	0.3 (−2.1, 2.7)	0.0 (−2.4, 2.4)	−1.4 (−3.6, 0.8)	−1.1 (−2.6, 0.3)	−1.3 (−2.8, 0.1)
Girls[c]	0.2 (−2.6, 3.1)	0.3 (−2.1, 2.7)	0.2 (−2.1, 2.5)	0.3 (−1.9, 2.4)	0.3 (−1.9, 2.4)
mEP					
All[a]	1.0 (−0.2, 2.1)	0.9 (−0.2, 2.0)	0.3 (−0.7, 1.3)	0.7 (−0.2, 1.6)	0.4 (−0.5, 1.3)
Boys[b]	1.1 (−0.1, 2.3)	0.9 (−0.3, 2.2)	0.4 (−0.9, 1.6)	**0.8 (0.1, 1.5)**	**0.9 (0.1, 1.7)**
Girls[c]	1.1 (−0.9, 3.0)	1.1 (−0.6, 2.8)	0.8 (−0.8, 2.4)	0.7 (−0.9, 2.2)	0.6 (−0.9, 2.1)

Model 1 covariates: maternal education, household income, maternal age, and pre-pregnancy body mass index. Model 2 covariates: model 1 and maternal BAPQ total score. Model 3 covariates: model 1 and CBCL internalizing and externalizing t-scores. Model 4 covariates: model 1, maternal BAPQ total score, and CBCL internalizing and externalizing t-scores. Bolding indicates $P<0.05$. Phthalate metabolites were creatinine-corrected and ln-transformed. Beta estimates were back-transformed to represent change in SRS-2 t-score for each doubling of exposure.

Abbreviations: ARCH, Archives on Research for Child Health; BAPQ, Broad Autism Phenotype Questionnaire; CBCL: Child Behavior Checklist; CI, confidence interval; DEHP, di-(2-ethylhexyl) phthalate; LOD, limit of detection; mBP, monobutyl phthalate; mEP, monoethyl phthalate; miBP, mono-isobutyl phthalate.

[a]Sample size = 77,

[b]Sample size = 37,

[c]Sample size = 40