Gestational Phthalate Exposure and Preschool Attention Deficit Hyperactivity Disorder in Norway

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Abstract: Prenatal phthalate exposure has been linked to altered neurobehavioral development in both animal models and epidemiologic studies, but whether or not these associations translate to increased risk of neurodevelopmental disorders is unclear. We used a nested case-cohort study design to assess whether maternal urinary concentrations of 12 phthalate metabolites at 17 weeks gestation were associated with criteria for Attention Deficit Hyperactivity Disorder (ADHD) classified among 3-year-old children in the Norwegian Mother, Father and Child Cohort Study (MoBa). Between 2007 and 2011, 260 children in this substudy were classified with ADHD using a standardized, on-site clinical assessment; they were compared with 549 population-based controls. We modeled phthalate levels both linearly and by quintiles in logistic regression models adjusted for relevant covariates and tested for interaction by child sex. Children of mothers in the highest quintile of di-iso-nonyl phthalate ($\sum$DiNP) metabolite levels had 1.70 times the odds of being classified with ADHD compared with those in the lowest quintile (95% confidence interval [CI] = 1.03 to 2.82). In linear models, there was a trend with the sum of di-2-ethylhexyl phthalate metabolites ($\sum$DEHP); each natural log-unit increase in concentration was associated with 1.22 times the odds of ADHD (95% CI = 0.99 to 1.52). In boys, but not girls, mono-n-butyl phthalate exposure was associated with increased odds of ADHD (odds ratio [OR] 1.42; 95% CI = 1.07 to 1.88). Additional adjustment for correlated phthalate metabolites attenuated estimates. These results suggest gestational phthalate exposure may impact the behavior of children as young as 3 years.

Keywords: phthalates, ADHD, Attention Deficit Hyperactivity Disorder, biomarkers, prenatal, gestational, MoBa, The Norwegian Mother, Father and Child Cohort Study

Introduction

Phthalates are high-production volume chemicals used primarily as plasticizers in a broad array of consumer products.[1,2] Sources of human exposure to phthalates vary by individual chemical. Some phthalates, including di(2-ethylhexyl) phthalate (DEHP), and increasingly, diisononyl phthalate (DiNP), are primarily consumed through contaminated food and drinking water.[3,4] Others like diethyl phthalate (DEP), di-*n*-butyl phthalate (DnBP), diiosbutyl phthalate (DiBP), and butylbenzyl phthalate (BBzP) are typically found in consumer goods and personal care products.[5,6]

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What this study adds
Epidemiologic evidence suggests prenatal exposure to phthalates is associated with emotional and behavioral difficulties in children. This is the first study of prenatal phthalate exposure to use a standardized, validated diagnostic interview to ascertain ADHD-like symptoms in preschool-aged children. Our results support prior research showing a positive association between gestational exposure to DEHP metabolites and risk of ADHD in childhood. We are the first to report an association between gestational exposure to DiNP metabolites and children's neurobehavioral development. This research is an important step toward identifying modifiable risk factors for ADHD with important public health consequences.

Because of the pervasive use of phthalates, and the ease with which they are leached from products into the environment, human exposure to phthalates is nearly ubiquitous in many countries.[7,8] In North America, phthalate metabolites are consistently detected in nationally representative populations.[7,9] In Norway, phthalates have been found at levels within ranges reported in studies worldwide, including among pregnant women.[10–14] Of particular concern is that phthalate exposure in pregnant women can result in exposure to the developing fetus, as phthalates are known to cross the placenta.[15]

There is growing epidemiologic evidence linking prenatal phthalate exposure to emotional and behavioral difficulties in children.[16–23] In prospective birth cohort studies, prenatal maternal phthalate levels have been associated with internalizing behaviors,[19–22,24–27] externalizing behaviors,[20,22,24,28,29] attention problems,[24,29] and social or peer relationship problems in the child,[19,21,25,30,31] with some studies showing stronger adverse effects among boys[20,21,27,29,32] and one among girls.[27] However, not all studies find associations between prenatal phthalates and adverse behavioral outcomes,[26,30,33,34] and there is a lack of consistency across studies on the specific phthalate implicated and on the existence and direction of sex-specific associations.

We previously reported that Norwegian mothers in the highest quintile of gestational DEHP exposure had nearly three times the odds of having a child registered with hyperkinetic disorder (HKD) based on ICD-10 codes in the Norwegian Patient Registry (NPR).[35] However, HKD requires the presence of hyperactive and inattentive symptoms, and thus is most similar to combined-type Attention Deficit Hyperactivity Disorder (ADHD) based on Diagnostic and Statistical Manual (DSM) criteria.[36,37] Although NPR registration ensures rigor in the clinical standards applied to diagnosis, referrals are likely to be biased toward more severe cases with a larger degree of impairment.[38,39] Moreover, clinical referral has been shown to depress the extent to which girls meeting diagnostic criteria are identified.[40,41] Indeed, in our prior investigation that used NPR registration for case finding,[35] girls comprised less than 30% of all ADHD cases, which may have undermined power to examine effect measure modification by child sex.

Clinically significant ADHD-like symptoms, which can result in substantial impairment and predict long-term functioning, often debut during the preschool period.[42,43] The Norwegian Mother, Father and Child Cohort (MoBa) preschool ADHD substudy was established to examine social, environmental, and behavioral factors that may be etiological determinants of preschool ADHD. Nested within a large, population-based birth cohort, this study utilized the MoBa 36-month questionnaire to ascertain child ADHD-like symptoms that may be suggestive of maladaptive behavioral development, subsequently inviting these children in for a clinical evaluation.[44,45] This approach may be less affected by referral biases in case-identification that result in underidentification of girls as well as less severe cases. We leveraged this high-quality assessment to examine the extent to which gestational phthalate exposure increased risk for preschool ADHD in a nested case-cohort subset of MoBa.

Methods

Study population

MoBa is an ongoing prospective population-based cohort study of over 100,000 mother-child pairs, enrolled between 1999 and 2008, conducted by the Norwegian Institute of Public Health.[46,47] Pregnant women were recruited at their first ultrasound appointment, at approximately 17 weeks' gestation, and responded to questionnaires at three time points during pregnancy (17, 22, and 30 weeks gestation). MoBa is also linked to the Medical Birth Registry of Norway (MBRN), providing information on pregnancy and birth records. Maternal biologic samples, including urine, were collected at approximately 17 weeks' gestation.[48] Questionnaires covering child development were obtained at multiple points after delivery.

Preschool ADHD substudy

The MoBa preschool ADHD substudy was initiated to ascertain prenatal and early childhood risk factors for this disorder. Eligibility for the preschool ADHD substudy was restricted to children who were born between April 2004 and January 2008 and who lived proximate to or within a direct flight to Oslo. Included in the 36-month MoBa questionnaire were 11 items about symptoms related to ADHD, including six items from the Child Behavior Checklist/1.5–5[49] and five items from the DSM-IV-TR criteria for ADHD.[37] Item-specific numeric scores were assigned to responses and summed to form a quantitative index. All children meeting the eligibility criteria and scoring at or above the 90th percentile on the quantitative index (n = 2798), as well as a smaller group of randomly selected children from the eligible cohort (n = 654) were invited to participate in an on-site assessment of preschool ADHD. Among those invited, 1195 children (35%) aged 3.1–3.8 years agreed to participate in the substudy and took part in a 1-day clinical assessment in Oslo, including a diagnostic interview (conducted primarily with mothers) between 2007 and 2011. Mothers of these children were slightly older, more highly educated, and had fewer children than those who chose not to participate.[50] Of those, 870 also had available maternal gestational urine samples stored in the MoBa Biobank[48] (Figure 1).

Children meeting criteria for ADHD or subthreshold ADHD were included as cases. Under the supervision of a child psychologist or psychiatrist, trained graduate psychology students conducted diagnostic interviews based on the Preschool Age Psychiatric Assessment (PAPA), designed to evaluate children aged 2–6 years of age and well-validated for use with preschoolers.[51,52] Using the PAPA, ADHD symptoms were defined as present when reported by parents to be pervasive across at least two settings.[53] Only symptoms lasting ≥3 months were counted as present. A separate rater, blind to the parent and teacher ratings, rescored audiotapes of 79 randomly selected assessment interviews. The average intraclass correlation (ICC) was 0.98 for the total number of ADHD symptoms. In addition, impairment or impact of symptoms in six functional domains (family relationships; friends; learning; play/leisure activities; child's quality of life; and family burden) was scored on a four-point Likert scale. The functional domains gave a total impairment scale score (range 0–18). Scores of ≥2 indicated presence of impairment. ADHD was defined by the presence of both (a) ≥6 symptoms on the PAPA that met DSM-IV-TR[37] criteria and (b) impairment. Children with six or more ADHD symptoms but without clear evidence of impairment, or with 3–5 ADHD symptoms and evidence of impairment, were classified as having subthreshold preschool ADHD. Among the clinically evaluated children (n =
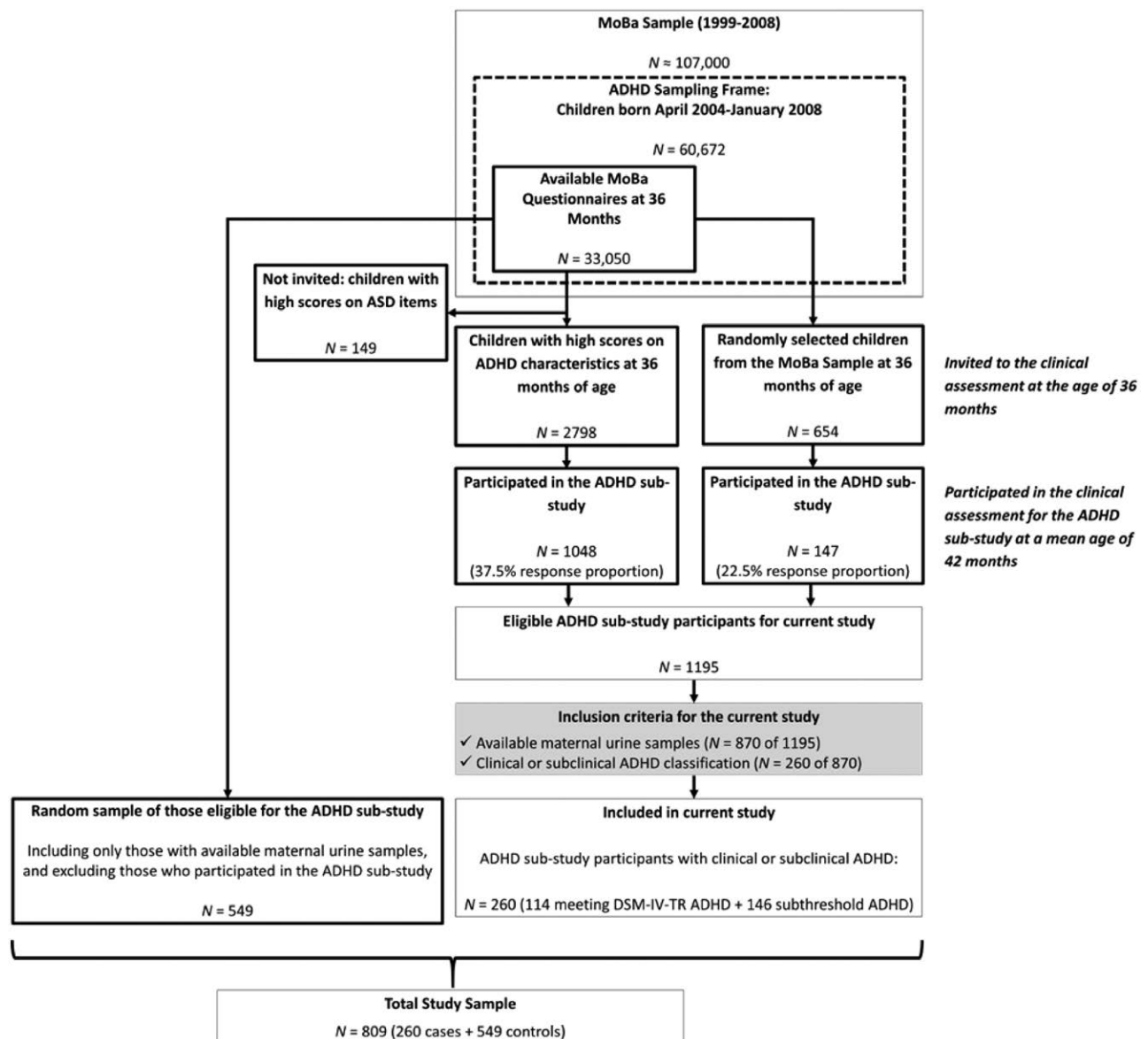
Figure 1. ADHD Substudy population selection diagram.

1195), with available urine samples (n = 870), 114 children met the criteria for preschool ADHD, and an additional 146 children met the criteria for subthreshold symptoms of preschool ADHD. Although the ADHD classifications defined by the PAPA are not equivalent to a clinical ADHD diagnosis, which would require a more intensive assessment of multiple sources of information, children meeting criteria for either above threshold or subthreshold symptoms of ADHD are included as "cases" in this study (n = 260), hereafter referred to as "preschool ADHD cases."

MoBa reference population "controls"

The controls in this nested case-cohort study were a stratified random sample of 556 children from among the 27,347 who were both eligible for the ADHD substudy and also whose mothers had available urine samples, frequency matched to preschool ADHD cases on year of birth. Because controls were randomly selected independent of their scores on the 3-year MoBa questionnaire and were not required to have completed an on-site ADHD clinical assessment, in theory, they reflect the distributions of phthalate metabolites and measured and unmeasured confounding factors among all those eligible for the ADHD substudy.[54,55] Among our randomly sampled controls, seven were also preschool ADHD cases. Given this minimal overlap, for the purpose of this study, these individuals were treated as cases only, for a total reference population of 549 noncase children.

Phthalate metabolite measurements

A detailed description of urine collection and analysis methods have been previously published.[35] Briefly, maternal urines collected during pregnancy were shipped to and processed in the MoBa Biobank.[48] Collection and processing methods have been previously validated for phthalate metabolite analysis.[11] Phthalate metabolites were analyzed at the Norwegian Institute of Public Health, using methods that have previously been described.[56] We measured 12 phthalate metabolites: monoethyl phthalate (MEP), a metabolite of DEP; mono-iso-butyl phthalate (MiBP), a metabolite of DiBP; mono-n-butyl phthalate (MnBP), a metabolite DnBP; monobenzyl phthalate (MBzP), a metabolite of BBzP; mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxoyhexyl phthalate (MEOHP), mono-2-ethyl-5-carboxypentyl

phthalate (MECPP), and mono-2-methylcarboxyhexyl phthalate (MMCHP), metabolites of DEHP; and mono-4-methyl-7-hydroxyoctyl phthalate (OH-MiNP), mono-4-methyl-7oxooctyl phthalate (oxo-MiNP), and mono-4-methyl-7-carboxyheptyl phthalate (cx-MiNP), metabolites of DiNP.

A complete description of quality control procedures has been previously described.[35] Briefly, 4–6 laboratory blinded quality control (QC) samples of pooled urine were included in every analytic batch to assess batch-to-batch variability and assay precision, along with unblinded laboratory QC materials. Cases and controls were randomly allocated to batch. To account for urinary dilution, specific gravity was measured using a pocket refractometer (PAL-10S) from Atago. The coefficient of variation was <0.1% for the in-house control urine samples. In laboratory blinded QC samples, average batch coefficients of variation were less than 5%.

Phthalate metabolite concentrations for each participant were adjusted for specific gravity and batch as previously described.[35] Following specific gravity and batch adjustment, molar sums of DEHP and DiNP metabolites were computed, and concentrations were expressed as µmol/L DEHP and ∑DiNP. Because the distributions of metabolite concentrations were heavily right-skewed, adjusted measures were subsequently natural log (ln)-transformed following standard practice. Finally, one implausibly high value (16 and 185 times the second and third highest values, respectively) for MnBP was removed. The specific gravity and batch-adjusted phthalate metabolite measures are used in all tables, figures, and statistical models.

Statistical models

Potential confounders of the relationship between gestational phthalate exposure and preschool ADHD were selected *a priori* using directed acyclic graphs (see eFigure 1; http://links.lww.com/EE/A142, which provides an example) and previous literature regarding covariates that could influence both the exposure and outcome. These covariates were child sex, maternal age at delivery, parity, maternal education, marital status, self-reported maternal smoking during the first trimester of pregnancy, maternal depression in early pregnancy, and maternal ADHD-like symptoms. Maternal depression was evaluated using the SCL-5 (short Symptom Checklist) questions from the 17-week maternal questionnaire.[57] The mean score of the depression-related questions were dichotomized so that a mean score of two or greater indicated the presence of depressive symptoms.[57–60] Maternal symptoms of ADHD were evaluated in the MoBa 36-month questionnaire using six items from the Adult ADHD Self-Report Scale, based on DSM-IV criteria, with a mean score ≥4 considered indicative of ADHD-like symptoms.[61] The level of maternal education was reported as "other education" for 19 individuals. This category was combined with ">college completed," the group to which it was the most similar in association magnitude in models in which ADHD was regressed against all categories of education (data not shown). We further conducted sensitivity analyses excluding those in the "other education" category. Owing to concerns with nonpositivity, the adjustment set was further reduced if removal improved model fit (by reducing the Akaike Information Criterion value) and changed the primary estimate by <10%. The final adjustment set included child sex, maternal age, parity, maternal education, maternal depression, and maternal ADHD-like symptoms.

Sex-specific estimates for linear models were created using the augmented product term method.[62] The threshold for statistical significance of interaction product terms was set at $P < 0.20$ *a priori*. Starting with a fully augmented product term model, sex*covariate interactions were removed if the P value for the interaction term was >0.20. The final models for all phthalates included interaction terms between sex and phthalate and between child sex and maternal education. We examined results

of a fully augmented product term model, with interaction terms between sex and every covariate, in sensitivity analyses. Sex-specific results were not estimated for quintile models owing to concerns about power and positivity.[63]

Phthalate exposure was examined both continuously and categorically (to allow detection of nonlinear and nonmonotonic associations), with thresholds defined by quintiles of individual-specific gravity and batch-adjusted phthalate concentrations in the randomly sampled control population.[54] Logistic regression models were used to calculate odds ratios (ORs) for estimates of the associations between phthalates and preschool ADHD, adjusted for covariates described above. Restricted cubic splines with knots at 20th, 40th, 60th, and 80th percentiles and Wald tests were used to assess the statistical significance of nonlinear associations. For primary analyses, phthalates were analyzed as individual exposures in single-phthalate models. In sensitivity analyses, we additionally examined models coadjusted for correlated phthalates (Pearson correlation coefficient was ≥0.40) to examine the potential for confounding by coexposures. The current analysis is based on version 9 of the MoBa quality-assured data files.

Results

Demographic characteristics of the study population are presented in Table 1. Fifty-six percent of the 260 preschool ADHD

Table 1.

Demographic characteristics of study population.

	Preschool ADHD		MoBa controls	
	N = 260		N = 549	
	N or Mean	% or SD[a]	N or Mean	% or SD[a]
Child sex				
Male	145	56%	275	50%
Female	115	44%	274	50%
Child age at clinical assessment (months)	41.6	1.2		
Maternal age at delivery (years)[b]	30.0	4.1	30.9	4.2
≤25	32	12%	46	8%
26–30	111	43%	206	38%
31–35	99	38%	218	40%
>35	18	7%	77	14%
Missing			2	
Maternal education[b]				
<College completed	92	36%	121	22%
College completed	108	42%	237	44%
>College completed	59	23%	184	34%
Missing	1		7	
Marital status[b]				
Married	113	44%	287	53%
Cohabitating	131	51%	244	45%
Other	15	6%	13	2%
Missing	1		5	
Primiparous[b]	156	60%	270	49%
Missing			2	
Self-reported smoking during pregnancy[b]	62	24%	76	14%
Missing	1		6	
Maternal self-reported symptoms during pregnancy				
Significant symptoms of depression[b,c]	42	16%	34	6%
Missing	5		14	
Significant ADHD-like symptoms[b,d]	33	13%	21	4%
Missing	2		12	

[a]Percentages may not add to 100% due to rounding.

[b]Comparing reference population to all cases, significant ($P < 0.05$) using t-test for continuous variables, chi-squared test for categorical variables, or Fisher's exact test for categorical variables with sparse cells.

[c]Mean score ≥2 indicative of presence of depression.

[d]Scores ≥4 indicative of ADHD-like symptoms.

cases were boys, whereas sex distribution was even among the 549 noncases. Mothers of children classified with preschool ADHD were more likely to be younger at delivery, less highly educated, primiparous, and self-report smoking during early pregnancy than mothers in the reference population. A total of 16% of mothers of preschool ADHD case children had a mean depression score ≥2 on the SCL-5 indicating the presence of depressive symptoms, compared with 6% of mothers of noncases. Thirteen percent of mothers of case children had significant symptoms of ADHD compared with 4% of mothers of noncases.

The distribution of gestational phthalate metabolite concentrations, stratified by case/noncase status, is presented in Table 2. The geometric mean of phthalate metabolite concentrations was similar or slightly higher among mothers of preschool ADHD cases as compared to mothers of noncases (Table 2). There were moderately strong correlations observed between some phthalates, particularly between ln-transformed MiBP, MnBP, and MBzP (Pearson r's between 0.48 and 0.61; see eFigure 2; http://links.lww.com/EE/A143, which illustrates correlations between ln-transformed phthalate metabolite measures). Ln-transformed ΣDEHP was also moderately correlated with ln-transformed ΣDiNP (r = 0.40).

After adjustment for covariates, children of mothers with higher levels of exposure to some phthalates had greater odds of preschool ADHD (Table 3). The association between ΣDiNP and preschool ADHD was significantly nonlinear (Wald P for nonlinearity < 0.05). Mothers at the highest quintile of ΣDiNP had 1.70 times the odds of a child with preschool ADHD compared with mothers at the lowest quintile (95% CI = 1.03 to 2.82), although mothers at the second quintile of ΣDiNP had 2.07 times the odds of those at the lowest quintile of having a child with preschool ADHD (95% CI = 1.27 to 3.37). We identified nonmonotonicity in the association between gestational MiBP and preschool ADHD (Wald P < 0.05). Specifically, although there appeared to be monotonic elevation in ORs with increasing quintile of exposure up to the fourth quintile, the odds dropped substantially in the fifth quintile. There were also positive trends between increasing levels of ΣDEHP and odds of preschool ADHD in both linear and quintile models. However, confidence intervals were wide. Each ln-unit increase in ΣDEHP was associated with 1.22 times the odds of preschool ADHD (95% CI = 0.99 to 1.52), although children of mothers at the highest quintile of ΣDEHP had 1.58 times the odds of preschool ADHD compared with children whose mothers were in the lowest quintile of ΣDEHP exposure (95% CI = 0.96 to 2.16). We identified no associations with MEP metabolites. Excluding children of mothers with education level of "other" somewhat strengthened estimates for MBzP and ΣDEHP, and general conclusions remained the same (see eTable 1; http://links.lww.com/EE/A144, which provides estimates from these sensitivity analyses).

Given the patterns of phthalate correlations described previously, we examined two groups of multi-phthalate models: (1) MiBP, MnBP, MBzP, coadjusted for one another; and (2) ΣDEHP, ΣDiNP, coadjusted for each other. Coadjustment for ΣDEHP and ΣDiNP somewhat attenuated estimates of association for these phthalates, and confidence intervals were wider (in part, at least, owing to lower model precision), but trends were generally similar (Table 3). Adjustment for MnBP and MBzP appeared to strengthen the nonmonotonic associations between MiBP and preschool ADHD (Table 3).

We further examined sex-specific effects using augmented product term models, with sex interaction product terms for each phthalate and for maternal education (Table 4). There were largely null findings, with the exception of statistically significant modification by child sex of the linear association between MnBP and preschool ADHD (interaction P = 0.05). Among boys, one ln-unit increase in maternal gestational MnBP was associated with 1.42 times the odds of preschool ADHD (95% CI = 1.07 to 1.88). This association persisted after additional adjustment for MBzP and MiBP. There was no evidence of an association with MnBP in girls. Adding interaction terms between sex and all other covariates did not materially change results (see eTable 2; http://links.lww.com/EE/A145), which provides estimates from these sensitivity analyses).

Discussion and conclusions

The purpose of this study was to evaluate the relationship between maternal gestational urinary concentrations of phthalate metabolites and the risk of preschool ADHD, using a high quality on-site assessment. In this nested case-cohort study, preschool-aged children of mothers with the highest quintile of gestational ΣDiNP and ΣDEHP were at increased risk of being classified with preschool ADHD, although associations were not always monotonic. The association between MnBP levels and preschool ADHD was significantly modified by child sex, with no evidence of an association among girls, and a significant positive linear relationship among boys. Finally, we observed some evidence that increasing exposure to MiBP may increase risk of ADHD; however, estimates in the highest quintile of exposure exhibited a downward trend, which may be suggestive of nonlinear effects, or alternatively, of uncontrolled confounding. Adjustment for correlated phthalates did not materially alter our observations.

These results build upon our prior research in MoBa.[35] Using ADHD diagnoses registered in the NPR, we previously reported monotonically increasing risk of ADHD in relation to gestational DEHP exposure. In this current study, we find increased risk of preschool ADHD, although of a somewhat lesser magnitude (OR per log increase in DEHP in Engel et al [2018] 1.47 [95% CI = 1.09 to 1.94]; current study OR 1.22 [95% CI = 0.99 to 1.52]). In both studies, we find no substantial modification of the DEHP association by child sex. However, in this current study, we find evidence of sex-specific effects of MnBP exposure among boys, as well as some evidence of increased risk in the highest quintile of DiNP exposure. There are several key differences in the design of these studies. First, the current study has a much more even representation of girls and boys among children classified with preschool ADHD—44% of the current cases were girls compared with fewer than 30% of those in the NPR subset. Thus we had better power to examine effect measure modification by child sex. Second, the NPR cases were on average shifted toward earlier birth years because DEHP exposure exhibits a temporally declining trend,[64–66] NPR cases were on average gestationally exposed to higher levels of DEHP than our preschool ADHD cases, which may explain why our effect estimates are somewhat attenuated in this study. During this time, DiNP was frequently used as a substitute for DEHP[67] and levels of its metabolites have increased in pregnant women in the United States and Europe.[68] The structural similarities that make DiNP a useful substitute may partially explain why these two chemicals show similarly strong associations with preschool ADHD in this study. Third, NPR cases are likely a biased subset of ADHD cases as a whole, representing a higher degree of impairment, underidentifying girls, and requiring both hyperactive and inattentive symptoms.[36,38–41] Moreover, some cases identified in the preschool period will experience a decline in symptom intensity over time.[42,69,70] Thus, ADHD cases identified in these studies may comprise slightly different, although overlapping, populations of affected children. The alignment in our overall results is therefore notable and suggests that prenatal exposure is associated with both clinically significant ADHD symptoms in the preschool period and ADHD diagnosis later in childhood.

Table 2.

Distribution of gestational phthalate concentrations[a] (µg/L) among preschool ADHD cases and MoBa controls[b].

	N	Geometric mean	Geometric SD	Min	25%	50%	75%	Max	LOQ[c]	% >LOQ
MEP (µg/L)									0.5	100.0
cases	260	113	4.37	3.92	38.8	108	288	7530		
MoBa controls	554	99.7	4.32	2.32	32.6	97.6	296	6760		
MiBP (µg/L)									0.5	100.0
cases	260	19.7	2.12	2.74	12.0	19.4	31.4	180		
MoBa controls	555	18.3	2.47	1.68	9.62	16.6	32.2	562		
MnBP (µg/L)									0.5	100.0
cases	260	20.0	2.22	3.02	12.1	19.8	33.2	379		
MoBa controls	554	18.1	2.17	2.00	11.4	17.2	31.0	4170[d]		
MBzP (µg/L)									0.2	100.0
cases	260	5.40	2.49	0.46	2.84	5.08	9.87	114		
MoBa controls	555	4.65	2.47	0.56	2.56	4.26	7.87	103		
MEHP (µg/L)									0.5	100.0
cases	260	12.1	2.12	1.96	7.51	11.1	16.6	871		
MoBa controls	555	11.4	2.11	2.23	7.12	10.4	17.4	812		
MEHHP (µg/L)									0.4	100.0
cases	260	15.6	2.54	2.01	9.05	14.0	22.1	1490		
MoBa controls	555	14.0	2.45	1.93	8.13	12.6	20.6	1700		
MEOHP (µg/L)									0.4	100.0
cases	260	10.6	2.55	1.36	5.90	9.40	15.4	1190		
MoBa controls	555	9.44	2.42	1.24	5.51	8.47	14.1	807		
MECPP (µg/L)									2.0	100.0
cases	260	23.1	2.12	7.39	14.7	19.0	28.3	2020		
MoBa controls	555	20.9	1.94	4.96	13.9	18.6	25.8	768		
MMCHP (µg/L)									2.0	100.0
cases	260	22.6	2.03	7.94	14.5	18.2	30.0	1110		
MoBa controls	555	21.0	1.85	5.23	14.0	18.1	26.3	372		
∑DEHP (µmol/L)									NA	NA
cases	260	0.29	2.13	0.08	0.18	0.25	0.37	22.4		
MoBa controls	555	0.27	2.00	0.07	0.18	0.23	0.34	14.9		
oh-MiNP (µg/L)									0.2	100.0
cases	260	1.12	2.23	0.31	0.72	0.97	1.36	138		
MoBa controls	554	1.07	2.01	0.20	0.69	0.96	1.43	60.7		
oxo-MiNP (µg/L)									0.2	98.5
cases	260	1.30	2.58	0.27	0.72	1.04	1.76	122		
MoBa controls	555	1.22	2.34	0.18	0.70	1.04	1.76	201		
cx-MiNP (µg/L)									1.0	100.0
cases	260	3.80	1.83	1.27	2.51	3.37	5.15	49.7		
MoBa controls	555	3.65	1.71	1.14	2.50	3.49	4.74	141		
∑DiNP (µmol/L)									NA	NA
cases	260	0.02	2.04	0.01	0.01	0.02	0.03	0.96		
MoBa controls	554	0.02	1.86	0.01	0.01	0.02	0.03	1.07		

[a]Standardized to specific gravity and adjusted for analytic batch. Quintiles were calculated using the distribution of phthalates in reference population.

[b]For the purpose of evaluating population distributions of phthalates only, 7 preschool ADHD cases were not excluded from the control group

[c]Limit of quantification.

[d]A value of 70,164 µg/L was discarded as implausibly high.

Children with ADHD often have impaired executive functions.[71] One mechanism through which phthalates could increase risk of ADHD diagnosis is through impacts on executive functions, which begin to develop early in life and continue development through adolescence.[72,73] Choi et al[74] examined the relationships between prenatal phthalate exposure and preschool-aged executive functions among the subset of MoBa children who returned for the preschool ADHD clinical assessment. Similar to results presented in this current paper, they found that increased MnBP levels during pregnancy were associated with deficits in executive functions among boys but not girls. However, the most consistent associations in Choi et al were for adverse effects of MBzP across all measures of executive function and for both sexes. Although we observed increased odds of preschool ADHD with increasing levels of gestational MBzP, adjustment for covariates attenuated estimates, particularly in the highest quintile of exposure. In contrast to our findings and to those of Engel et al,[35] Choi et al[74] did not observe consistently adverse associations with DEHP or DiNP.

A number of prospective birth cohort studies have examined associations between perinatal exposure to phthalate metabolites and childhood behavior. Although some recent systematic reviews of the existing body of evidence have concluded that phthalates have an overall negative effect on various aspects of neurobehavioral development,[16,18] others have concluded that the lack of consistency across studies prevents firm conclusions from being drawn.[75] A complicating feature of the phthalate literature is that exposure was often measured at different time points in pregnancy, and outcome assessment approaches have been varied. There have been very few studies that have had access to clinical assessments of children. Rather, the majority of studies have relied on parent-reported behavioral inventories that may imperfectly capture developmental problems. In contrast, we leveraged a standardized, high quality, on site assessment for preschool ADHD that used a validated diagnostic interview appropriate for preschoolers. The only other study to our knowledge with prenatal exposure and a clinical ADHD diagnosis is our prior study in MoBa.[35] These studies together support the possibility that prenatal DEHP exposure

Table 3.

Quintile of phthalate and odds of preschool ADHD

Phthalate	Quintile	N cases[d]	Model 1 crude[a] OR (95% CI)	Model 2 adjusted for covariates[b] OR (95% CI)	Model 3 adjusted for covariates and correlated phthalate metabolites[c] OR (95% CI)
MEP	1. <26.0 µg/L	44	ref.	ref.	
	2. 26.0–62.2 µg/L	44	0.96 (0.59 to 1.56)	0.91 (0.54 to 1.53)	
	3. 62.2–148 µg/L	57	1.28 (0.80 to 2.05)	1.19 (0.72 to 1.95)	
	4. 148–380 µg/L	55	1.26 (0.79 to 2.01)	1.24 (0.76 to 2.03)	
	5. >380 µg/L	53	1.18 (0.74 to 1.90)	1.05 (0.63 to 1.75)	
	Linear model[e]	253	1.06 (0.96 to 1.17)	1.03 (0.93 to 1.15)	
MiBP[f]	1. <8.76 µg/L	32	ref.	ref.	ref.
	2. 8.76–13.2 µg/L	41	1.30 (0.77 to 2.20)	1.37 (0.79 to 2.39)	1.61 (0.87 to 2.97)
	3. 13.2–20.8 µg/L	65	2.07 (1.26 to 3.39)	1.88 (1.12 to 3.18)	2.21 (1.19 to 4.10)
	4. 20.8–38.9 µg/L	75	2.32 (1.43 to 3.78)	2.37 (1.41 to 3.99)	2.77 (1.46 to 5.25)
	5. >38.9 µg/L	40	1.23 (0.73 to 2.09)	1.19 (0.68 to 2.08)	1.29 (0.65 to 2.57)
	Linear model[e]	253	1.10 (0.93 to 1.30)	1.08 (0.89 to 1.29)	0.98 (0.78 to 1.24)
MnBP	1. <9.90 µg/L	49	ref.	ref.	ref.
	2. 9.90–14.6 µg/L	41	0.83 (0.51 to 1.35)	0.76 (0.45 to 1.27)	0.54 (0.30 to 0.97)
	3. 14.6–21.9 µg/L	48	0.96 (0.60 to 1.55)	0.92 (0.56 to 1.52)	0.55 (0.29 to 1.03)
	4. 21.9–34.0 µg/L	55	1.17 (0.74 to 1.85)	1.10 (0.67 to 1.80)	0.59 (0.31 to 1.14)
	5. >34.0 µg/L	60	1.22 (0.77 to 1.93)	1.15 (0.70 to 1.89)	0.64 (0.32 to 1.30)
	Linear model[e]	253	1.17 (0.97 to 1.41)	1.18 (0.95 to 1.45)	1.13 (0.84 to 1.52)
MBzP	1. <2.19 µg/L	40	ref.	ref.	ref.
	2. 2.19–3.46 µg/L	40	1.06 (0.64 to 1.76)	0.93 (0.54 to 1.59)	0.93 (0.52 to 1.69)
	3. 3.46–5.51 µg/L	53	1.36 (0.84 to 2.22)	1.27 (0.76 to 2.13)	1.28 (0.71 to 2.30)
	4. 5.51–9.60 µg/L	54	1.40 (0.86 to 2.27)	1.40 (0.83 to 2.33)	1.41 (0.75 to 2.66)
	5. >9.60 µg/L	66	1.70 (1.06 to 2.72)	1.39 (0.83 to 2.31)	1.37 (0.71 to 2.64)
	Linear model[e]	253	1.19 (1.01 to 1.40)	1.13 (0.95 to 1.35)	1.07 (0.85 to 1.35)
∑DEHP	1. <0.16 µmol/L	41	ref.	ref.	ref.
	2. 0.16–0.21 µmol/L	52	1.34 (0.83 to 2.17)	1.26 (0.76 to 2.09)	1.28 (0.76 to 2.15)
	3. 0.21–0.27 µmol/L	49	1.23 (0.75 to 2.01)	1.23 (0.73 to 2.06)	1.15 (0.68 to 1.97)
	4. 0.27–0.38 µmol/L	47	1.21 (0.74 to 1.97)	1.23 (0.73 to 2.06)	1.19 (0.70 to 2.03)
	5. >0.38 µmol/L	64	1.59 (0.99 to 2.54)	1.58 (0.96 to 2.61)	1.51 (0.89 to 2.56)
	Linear model[f]	253	1.17 (0.96 to 1.43)	1.22 (0.99 to 1.52)	1.18 (0.93 to 1.49)
∑DiNP[f]	1. <0.012 µmol/L	42	ref.	ref.	ref.
	2. 0.012–0.016 µmol/L	76	1.82 (1.15 to 2.88)	2.07 (1.27 to 3.37)	2.04 (1.25 to 3.33)
	3. 0.016–0.020 µmol/L	35	0.88 (0.53 to 1.47)	0.89 (0.52 to 1.55)	0.86 (0.50 to 1.50)
	4. 0.020–0.027 µmol/L	42	1.01 (0.61 to 1.66)	1.13 (0.67 to 1.92)	1.07 (0.62 to 1.82)
	5. >0.027 µmol/L	58	1.37 (0.85 to 2.20)	1.70 (1.03 to 2.82)	1.54 (0.91 to 2.61)
	Linear model[e]	253	1.11 (0.89 to 1.39)	1.18 (0.94 to 1.49)	1.10 (0.85 to 1.42)

[a]Adjusted for specific gravity, analytic batch.

[b]Adjusted for specific gravity, analytic batch, child sex and maternal age, education, parity, depression during pregnancy, and ADHD-like symptoms.

[c]Adjusted for specific gravity, analytic batch, child sex and maternal age, education, parity, depression during pregnancy, ADHD-like symptoms and additionally adjusted for correlated metabolites (a) MiBP, MnBP, and MBzP co-adjusted for one another; (b) ∑DEHP and ∑DiNP coadjusted for each other).

[d]Number with no missing exposure or covariates in Model 2.

[e]Per 1 natural log-unit increase in biomarker.

[f]Associated nonlinearly (Wald test *P* < 0.10) for MiBP and ∑DiNP when modeled using Model 2 adjustment set and restricted cubic splines with knots at 20th, 40th, 60th, and 80th percentiles.

may have a long-term impact on behavior in children. However, the literature has been inconsistent as to whether associations for any given phthalate exhibit consistent evidence of sexual dimorphism. For MnBP in particular, several studies have found associations that are stronger in boys,[20,21,23,27,29,32] whereas others have not.[22,25,33,35] We cannot exclude the possibility that interactions by sex are owing to chance, particularly since there is no specific rationale to support sex interactions for MnBP alone as opposed to any of the other phthalates that were measured.

Despite a considerable amount of epidemiologic research on prenatal phthalate exposure and behavioral outcomes in children,[16] there is a more limited body of experimental evidence in animals.[76] The majority of experimental model studies have focused on DEHP,[77] with limited research on other phthalates, and have found that phthalate exposure can increase anxiety-like behaviors,[78–83] impair memory,[80,83,84] and cause hyperactivity.[85,86] However, the mechanisms underlying these effects are unclear. Phthalates are endocrine-disrupting chemicals, several of which have antiandrogenic properties.[87,88] A number of

phthalates, including DEHP, DBP, and MBP, have been linked to thyroid disruption in both animal models and human epidemiologic studies.[89–97] Maternal thyroid sufficiency is critical for fetal neurodevelopment,[98] and both maternal hyper- and hypothyroidism have been associated with ADHD.[99] In addition, evidence from pregnancy cohorts suggests phthalates perturb normal sex steroid levels in pregnant women.[92–97,100,101] Sex steroids act throughout the brain to govern various aspects of neurodevelopment and cognition,[102] and early life hormonal exposures may influence neurobiological differences in brain structural and functional development.[103–105] Given the complex nature of these hormones and the importance of normal hormone function during pregnancy on fetal brain development,[106] phthalate-induced hormone disruption during pregnancy could have long-term effects on the developing child.[107]

Our study has a number of limitations. The half lives of phthalates are relatively short, ranging from a few hours to a few days,[108–111] and the intraclass correlation coefficients (ICCs) for repeated measures of prenatal phthalate metabolite

Table 4.

Phthalate metabolite concentration and odds of preschool ADHD by child sex, using augmented product term models, with sex-interaction products for phthalate and for maternal education.

Phthalate	Cases[c]		Adjusted for covariates[a]			Adjusted for covariates and correlated phthalates[b]		
	Boys	Girls	Boys OR (95% CI)[d]	Girls OR (95% CI)[d]	P[e]	Boys OR (95% CI)[d]	Girls OR (95% CI)[d]	P[e]
MEP	142	111	1.03 (0.89 to 1.19)	1.03 (0.88 to 1.21)	0.97			
MiBP	142	111	1.17 (0.92 to 1.50)	0.97 (0.73 to 1.29)	0.33	0.98 (0.71 to 1.35)	1.00 (0.71 to 1.41)	0.93
MnBP	142	111	1.42 (1.07 to 1.88)	0.93 (0.68 to 1.28)	0.05	1.43 (0.97 to 2.10)	0.82 (0.51 to 1.31)	0.07
MBzP	142	111	1.20 (0.95 to 1.53)	1.06 (0.82 to 1.37)	0.47	1.01 (0.74 to 1.39)	1.17 (0.84 to 1.65)	0.53
∑DEHP	142	111	1.32 (1.00 to 1.74)	1.10 (0.78 to 1.55)	0.42	1.28 (0.95 to 1.73)	1.03 (0.70 to 1.51)	0.37
∑DiNP	142	111	1.22 (0.88 to 1.68)	1.17 (0.83 to 1.64)	0.86	1.10 (0.78 to 1.55)	1.15 (0.79 to 1.69)	0.85

[a]Adjusted for specific gravity, analytic batch, child sex and maternal age, education, parity, depression during pregnancy, and maternal ADHD-like symptoms.
[b]Adjusted for specific gravity, analytic batch, child sex and maternal age, education, parity, depression during pregnancy, maternal ADHD-like symptoms, and additionally adjusted for correlated metabolites (a) MiBP, MnBP, and MBzP coadjusted for one another; (b) ∑DEHP and ∑DiNP coadjusted for each other.
[c]Number with no missing exposure or covariates.
[d]Per 1 natural log-unit increase in biomarker.
[e]P for sex*phthalate interaction in linear regression models.

concentrations reported in the literature are low to moderate.[112–115] Thus, a single spot urine sample, which was used for exposure assessment in this study, is unlikely to accurately reflect a woman's exposure to phthalates across her entire pregnancy. If the putative sensitive window was not 17 weeks' gestation when the prenatal urine was collected, this lack of reproducibility in phthalate exposures over time may result in bias in the estimated exposure-outcome association. It is unknown whether there is any specific sensitive window for phthalate exposure, as the development of the brain begins very early in gestation and continues into postnatal life. However, the prenatal period in general, and the second trimester specifically, is a relevant window of vulnerability to perturbations in fetal growth that can impact long-term neurodevelopmental outcomes. Additionally, evaluating behavioral outcomes during preschool years is challenging, as some symptoms required for diagnosis of ADHD may in fact be developmentally appropriate.[53,116] However, our study leveraged a high-quality assessment with diagnostic interviews supervised by psychiatrists/psychologists, and our assessment was optimized for this period. To maximize ascertainment of preschool ADHD cases, selection for clinical assessment was primarily owing to parentally reported symptoms on the MoBa 36-month questionnaire. Additionally, a small subset of children without symptoms was randomly selected for an on-site clinical interview, six of whom were found to have subclinical or clinically significant symptoms of preschool ADHD. This suggests both a potential undercount of preschool ADHD cases and the possibility that there are members of our subcohort random sample who are also undetected preschool ADHD cases. The presence of cases in our random sample is expected and does not represent a bias in our estimates, as the purpose of the subcohort is to represent the phthalate exposure distribution in the source population. However, our preschool ADHD cases may underrepresent children whose symptoms are not as noticeable to their caretakers. Finally, there is likely some bias that is attributable to self-selection into MoBa and its follow-up studies, which could influence our results.[117] Statistical approaches for addressing self-selection often rely on the availability of population-level estimates of exposure in the target population, which are not available for phthalates in Norway. We did, however, include in our statistical model adjustment for important predictors of exposure and selection into the follow-up study that may influence findings, including maternal age, education, and parity. Statistical adjustment may mitigate any residual bias in our findings attributable to these factors.

Our study also had many important strengths. This case-cohort study was nested within a well-characterized, population-based cohort. ADHD case ascertainment relied on a standardized, on-site clinical assessment of children, an improvement in outcome measurement as compared to previous research. Previous studies of ADHD symptoms in preschoolers have relied primarily on ratings by parents, which may be less reliable. In our previous research of ADHD diagnoses, cases were determined from registry records, and any variation in diagnostic tendencies between providers could not be accounted for. In contrast, the interrater reliability of this research-quality clinical assessment was very high. Further, a number of important confounders of the relationship between maternal prenatal phthalate exposure and preschool behavior were included in statistical models, including maternal self-reported symptoms of both ADHD and depression during pregnancy, which have not been available in prior studies.

In summary, we found evidence that gestational exposure to some phthalates, including DiNP, DEHP, MiBP, and in males, MnBP, may increase the risk of ADHD-like symptoms in the preschool period. This is the first study to report an association between prenatal exposure to metabolites of DiNP, an industry substitute for DEHP, and neurodevelopmental outcome in children. ADHD represents an important health burden both to the patient[118,119] and society,[120–122] as reflected by lower than average educational attainment and future income among ADHD cases. Despite considerable research, relatively few modifiable risk factors for ADHD have been identified.[123,124] This research is an important step toward identifying modifiable risk factors for ADHD with important public health consequences.

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