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Prenatal Phthalates, Maternal Thyroid Function, and Risk of Attention-Deficit Hyperactivity Disorder in the Norwegian Mother and Child Cohort

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Background: There is growing concern that phthalate exposures may have an impact on child neurodevelopment. Prenatal exposure to phthalates has been linked with externalizing behaviors and executive functioning defects suggestive of an attention-deficit hyperactivity disorder (ADHD) phenotype.

Objectives: We undertook an investigation into whether prenatal exposure to phthalates was associated with clinically confirmed ADHD in a population-based nested case–control study of the Norwegian Mother and Child Cohort (MoBa) between the years 2003 and 2008.

Methods: Phthalate metabolites were measured in maternal urine collected at midpregnancy. Cases of ADHD ($n = 297$) were obtained through linkage between MoBa and the Norwegian National Patient Registry. A random sample of controls ($n = 553$) from the MoBa population was obtained.

Results: In multivariable adjusted coexposure models, the sum of di-2-ethylhexyl phthalate metabolites ($\sum$DEHP) was associated with a monotonically increasing risk of ADHD. Children of mothers in the highest quintile of $\sum$DEHP had almost three times the odds of an ADHD diagnosis as those in the lowest [OR = 2.99 (95% CI: 1.47, 5.49)]. When $\sum$DEHP was modeled as a log-linear (natural log) term, for each log-unit increase in exposure, the odds of ADHD increased by 47% [OR = 1.47 (95% CI: 1.09, 1.94)]. We detected no significant modification by sex or mediation by prenatal maternal thyroid function or by preterm delivery.

Conclusions: In this population-based case–control study of clinical ADHD, maternal urinary concentrations of DEHP were monotonically associated with increased risk of ADHD. Additional research is needed to evaluate potential mechanisms linking phthalates to ADHD. https://doi.org/10.1289/EHP2358

Introduction

There is growing concern that phthalate exposures, particularly during the prenatal period, may have an impact on child neurobehavioral development (Bennett et al. 2016). Prenatal exposure to phthalates has been associated with both externalizing (Engel et al. 2010; Kobrosly et al. 2014; Lien et al. 2015) and internalizing (Engel et al. 2010; Whyatt et al. 2012) behaviors using validated behavioral screening instruments, as well as with deficits in executive function as measured by both parental report (Engel et al. 2010) and performance-based assessments (Factor-Litvak et al. 2014), although not all studies have found evidence of associations (Gascon et al. 2015). Among the neurobehavioral domains identified in multiple studies are inattention (Engel et al. 2010; Kobrosly et al. 2014), aggression (Engel et al. 2010; Kobrosly et al. 2014; Lien et al. 2015), conduct problems (Engel et al. 2010; Kobrosly et al. 2014; Lien et al. 2015), and emotional reactivity/regulation (Engel et al. 2010; Whyatt et al. 2012), as well as impairments in working memory (Engel et al. 2010; Factor-Litvak et al. 2014). Sex differences in the associations of phthalates with neurobehavioral end points have often been noted, although some studies have found stronger associations among boys (Engel et al. 2010; Kobrosly et al. 2014), whereas others have found stronger associations among girls (Whyatt et al. 2012). The constellation of phthalate-associated behaviors highlighted across studies has led many researchers to note overlap with symptoms of attention-deficit hyperactivity disorder (ADHD).

Despite the observed overlap in affected neurobehavioral domains, there is less consensus on the specific phthalate responsible for neurodisruptive effects, and no prior study has accounted for the correlation among phthalates by mutual adjustment. Some studies have reported significant associations with dibutyl phthalates (Engel et al. 2010; Kobrosly et al. 2014; Lien et al. 2015; Whyatt et al. 2012) and/or di-2-ethylhexyl phthalate (DEHP) (Kobrosly et al. 2014; Lien et al. 2015); others have highlighted butyl benzyl phthalate (BBzP) (Whyatt et al. 2012). Moreover, as of now there have been no studies with biomarkers of exposure in the prenatal period and access to clinically confirmed neurobehavioral end points, such as ADHD diagnoses from a clinical provider. Rather, the bulk of the literature relies on parent-reported symptoms. Because the ages of the children examined have varied substantially across and within studies, relying solely on parental reports to identify nonnormative behavior may be problematic.

A number of mechanisms have been proposed to explain how phthalates may negatively affect brain development (Miodovnik et al. 2014), although few have been thoroughly examined in humans or in animal models. One prominent concern is phthalate-induced maternal thyroid hormone disruption. Phthalates have

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been associated with changes in circulating thyroid hormone levels in adults (Huang HB et al. 2017; Meeker et al. 2007; Meeker and Ferguson 2011; Park et al. 2017) and in pregnant women (Huang PC et al. 2007, 2016; Johns et al. 2015, 2016; Kuo et al. 2015; Gao et al. 2017; Yao et al. 2016). The most consistent finding across studies has been an inverse association between metabolites of DEHP and thyroxine and/or free thyroxine (Meeker and Ferguson 2011; Park et al. 2017; Huang PC et al. 2016; Johns et al. 2015; Gao et al. 2017; Yao et al. 2016). Maternal prenatal thyroid hormone is essential for fetal neurodevelopment (Moog et al. 2017; Morreale de Escobar et al. 2004), and clinically diagnosed thyroid hormone disorders (hyperthyroidism and hypothyroidism) in the perinatal period have been linked with ADHD in offspring (Andersen et al. 2014; Instanes et al. 2015). Additionally, both higher and lower levels of thyroid hormone concentrations, even within population reference ranges, have been associated with ADHD-like behaviors (Ghassabian et al. 2011, 2012; Modesto et al. 2015; Päkkilä et al. 2014). Perinatal phthalate exposure has also been associated with preterm delivery (Ferguson et al. 2014a, 2014b), which is itself a risk factor for ADHD (Murray et al. 2016; Sucksdorff et al. 2015).

A true causal association of phthalate exposure with child neurodevelopment would have major public health significance. Phthalates are ubiquitous in consumer products (Schettler 2006), are components of many food processing and packaging materials (Serrano et al. 2014; Sakhi et al. 2014), and can be found in both pharmaceuticals (Kelley et al. 2012; Hernández-Díaz et al. 2013), and personal care products (Calafat et al. 2015; Sakhi et al. 2017). Therefore, to address this critically important public health question, we undertook a prospective, nested case–control study in the Norwegian Mother and Child Study (MoBa) to examine the hypothesis that prenatal biomarkers of phthalate exposure are associated with clinical ADHD in offspring. We further considered whether any associations were mediated by maternal thyroid function or preterm delivery or were modified by child sex.

Methods

Study Population

A total of 112,762 children were born to MoBa enrollees between 1999 and 2008 (Magnus et al. 2006, 2016). Pregnant women were recruited at their first ultrasound appointment, which occurred at approximately 17 wk gestation. Written informed consent was obtained from each MoBa participant upon recruitment. Mothers returned questionnaires three times during pregnancy: a general health and behavior questionnaire at 17 and 30 wk and a food frequency questionnaire at 22 wk gestation. Following the birth of their child, mothers returned questionnaires on child health and development at 6, 18, and 36 months of age. From this originally enrolled population, individuals were eligible for our study if they were pregnant in 2003 or later ($n = 60{,}835$ remaining), completed the 36-mo questionnaire ($n = 34{,}190$ remaining), did not have Down syndrome or cerebral palsy ($n = 34{,}099$ remaining), had maternal urine and blood samples collected ($n = 28{,}097$ remaining), had singleton pregnancies ($n = 27{,}347$ remaining), and resided in geographic areas eligible for the ADHD substudy (described below ($n = 24{,}035$ remaining). The final eligible population was 24,035, from which we randomly sampled our Norwegian Patient Registry (NPR) cases and controls.

Selection of ADHD Cases

Clinically diagnosed cases of ADHD born in 2003 or later were obtained from the NPR. The NPR is a national database containing all persons with diagnoses recorded from 2008 onward, from government-funded facilities, which captures an estimated 90–95% of ADHD diagnoses (Surén et al. 2012). We selected cases if they had at least two registrations of "Hyperkinetic disorder" [*The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines* (ICD-10) codes F90, F90.0, F90.1, F90.8 or F90.9; WHO 1993]. We required two registrations in order to exclude erroneous registrations or false diagnoses. Registrations for hyperkinetic disorder before the age of 5 y are exceedingly rare (Surén et al. 2012). The ICD-10 criteria for ADHD are "early onset; a combination of overactive, poorly modulated behavior with marked inattention and lack of persistent task involvement; and pervasiveness over situations and persistence over time of these behavioral characteristics" (WHO 1993). In total, 297 cases were randomly sampled from the eligible registrations.

Selection of Controls

Families with the index child born at one of the larger hospitals in Norway between April 2004 and January 2008 and who completed the 36-mo MoBa questionnaire were eligible to participate in the MoBa Preschool ADHD Substudy (Rohrer-Baumgartner et al. 2014). From this eligible population, we randomly sampled a control population of 553 mother–child pairs. We nested our control group within the population eligible to participate in the Preschool ADHD Substudy so that future studies could utilize the same control population for preschool ADHD cases, which were diagnosed via a systematic neuropsychological evaluation of the child at 3.5 y old (Skogan et al. 2014). Apart from eligibility criteria, no other information from the Preschool ADHD Substudy was entered into this analysis.

Phthalate Metabolite Measurements

Maternal urine collected at approximately 17 wk gestation was shipped overnight, unrefrigerated, to the central biorepository in Oslo, Norway for immediate processing. Urine was transported in a commercially available urine transport tube with a preservative to prevent bacterial growth (chlorhexidine plus ethyl paraben and sodium propionate) (UAP Vacutainers; Becton-Dickinson) (Rønningen et al. 2006). In a previous quality control (QC) study in MoBa, no impact was found on the measurement of phthalates from this preservative (Ye et al. 2009). Analysis of urine for phthalate metabolites was conducted at the Norwegian Institute of Public Health. Methods have been previously described (Sabaredzovic et al. 2015). Briefly, on-line column switching liquid chromatography coupled with tandem mass spectrometry was used to measure 12 phthalate metabolites: monoethyl phthalate (MEP), a metabolite of diethyl phthalate; mono-iso-butyl phthalate (MiBP), a metabolite of di-iso-butyl phthalate; mono-*n*-butyl phthalate (MnBP), a metabolite of di-*n*-butyl phthalate; 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-7-oxooctyl phthalate (oxo-MiNP), and mono-4-methyl-7-carboxyheptyl phthalate (cx-MiNP), metabolites of di-iso-nonyl phthalate (DiNP). A QC sample of pooled urine was created to assess batch-to-batch variability and assay precision. In each analytic batch, procedural blank samples, two in-house control urine samples and 4–6 QC pooled urine aliquots were included. External reference samples from the National Institute of Standards and Technology [NIST; Standard Reference Material (SRM) 3673] were also analyzed in every fourth analytical batch. Cases and controls were randomly allocated across analytic batches. The analyst was blinded to QC, case, and control samples. To account for urinary

dilution, specific gravity was measured using a pocket refractometer (PAL-10S) from Atago. In brief, 180 μL of the urine sample was placed onto the prism surface, and the specific gravity was measured with the refractometer. The coefficient of variation (CV) was <0.1% for the in-house control urine samples. In laboratory-blinded QC samples, average batch CVs were <5%.

Prenatal Maternal Thyroid Function

Maternal blood collected in ethylenediamine tetraacetic acid (EDTA) tubes at 17 wk gestation was shipped overnight, unrefrigerated, to a central biospecimen processing lab (Rønningen et al. 2006). Plasma was separated and stored in 1-mL cryovials at −80°C and was shipped frozen on dry ice to ARUP Laboratories (Salt Lake City, Utah) for analysis of thyroid hormone concentrations. Thyroid stimulating hormone (TSH) was measured using a quantitative chemiluminescent immunoassay on a Roche Cobas e602 blood analyzer. Triiodothyronine (T3) and thyroxine (T4) were also measured using quantitative electrochemiluminescent immunoassays on the Roche Cobas e602 analyzer. Intra- and inter-assay CVs for T3, T4, and TSH were <5%. We previously established the reliability of MoBa maternal plasma for measurement of thyroid hormone concentrations, considering delays in processing and storage and freeze-thaw cycles (Villanger et al. 2017).

Ethics

Data collection for MoBa was approved by the Norwegian Data Inspectorate and the Norwegian Committee for Medical and Health Research Ethics (REC). The present study was approved by the Norwegian REC and the Institutional Review Board at University of North Carolina Chapel Hill.

Statistical Analysis

The QC pool CV for each phthalate metabolite, computed as the ratio of the standard deviation across QC pools to the mean across QC pools, was assessed separately for each batch as well as overall.

Phthalate metabolite concentrations for each participant were standardized to specific gravity using the procedure described by Hauser et al. (2004). Suppose P_{ij} represents the measured value of phthalate metabolite i for participant j. Then, letting P^*_{ij} represent the corresponding specific gravity adjusted measurement (Equation 1),

$$P^*_{ij} = P_{ij} \times (c/(SG_j - 1)), \quad (1)$$

where SG_j denotes the specific gravity for participant j, and c is a common normalizing constant computed as the geometric mean of specific gravity across all participants minus 1.

To account for potential batch effects, individual measurements were batch-adjusted using a scaled variation of the Ratio-G batch adjustment method (Luo et al. 2010). Consider again the specific gravity–adjusted measurement P^*_{ij}, and suppose it was processed in batch k. Letting the corresponding specific gravity– and batch-adjusted measurement be denoted P^{**}_{ij} (Equation 2),

$$P^{**}_{ij} = P^*_{ij} \times (meanQC_l/meanQC_{lk}), \quad (2)$$

where $meanQC_l$ represents the geometric mean of phthalate metabolite i across all QC pools, and $meanQC_{lk}$ represents the geometric mean of phthalate metabolite i across the QC pools from batch k. The specific gravity– and batch-adjusted phthalate metabolite measures are used in all tables, figures, and statistical models.

Following specific gravity and batch adjustments of all phthalate metabolites, the molar sums for DEHP and DiNP were computed (hereafter referred to as $\sum$DEHP and $\sum$DiNP, respectively). Each component phthalate metabolite was first converted from μg/L to μmol/L by dividing it by its molecular mass. After conversion, the component phthalates were then summed to produce $\sum$DEHP and $\sum$DiNP measures in μmol/L.

The present analysis is based on version 9 of the MoBa quality-assured data files. Covariate data were obtained from the 17- and 30-wk prenatal questionnaires. We selected potential confounders *a priori* by using directed acyclic graphs based on current knowledge of covariates that could influence both phthalate levels and ADHD. In statistical models exploring the relationship between ADHD and maternal urinary phthalate concentrations, adjustments were made for the following covariates: maternal age at delivery, sex of the child, maternal education (obtained from the 17-wk questionnaire), marital status, prenatal maternal smoking in the first or second trimester of pregnancy (self-reported), parity, maternal depression during pregnancy (self-reported on the 30-wk questionnaire), and year of birth.

In order to obtain inference about the relationship between each phthalate metabolite and ADHD after adjustment for all other phthalate levels, we regressed ADHD on (transformations of) all phthalates simultaneously and assumed no interactions among the phthalates. Two participants were excluded from analyses because a single phthalate metabolite was missing because of analytic interference; because our statistical approach involved coadjustment for all phthalate metabolites, they were dropped from the model. One additional participant was excluded because of unusually low values for all phthalate metabolites. The logged phthalate metabolites demonstrated moderate pairwise correlation; therefore, a Bayesian modeling framework, which provides more stable estimates than frequentist models in the presence of correlated exposures (MacLehose et al. 2007), was selected. In all Bayesian models, normal prior distributions with zero mean and 0.5 variance were chosen for each of the regression coefficients. Because pairwise correlations between the logged phthalates were only moderate, mixture prior distributions, which improve estimation with highly correlated predictors, were deemed to be unnecessary (MacLehose et al. 2007).

The associations between the phthalate metabolites and ADHD were first assessed by fitting a Bayesian logistic regression model with binary ADHD status as the outcome and the quintiles of all the phthalates simultaneously as predictors in a complete case analysis framework. As a follow-up, a second Bayesian logistic regression model was fit; this model considered all logged phthalates simultaneously as linear predictors. A model containing the interactions between each of the logged phthalates and child's sex was fit to investigate effect modification by these factors. We considered effect measure modification by sex to be significant if the 90% credible interval of the phthalate by sex interaction term excluded the null value. Based on the size of our study population, we estimated that we had 90% power to detect an additive interaction term as low as 0.105, corresponding to an interaction term odds ratio (OR) of ∼1.1.

Finally, for phthalate metabolites exhibiting associations with ADHD, mediation analyses were performed for each thyroid function biomarker measure and for preterm delivery (delivery <37 completed weeks of gestation) to explore the possibility that the impact of maternal phthalate exposure on child ADHD is mediated by these factors. Natural direct effect (NDE) and natural indirect effect (NIE) ORs were computed for each phthalate and thyroid hormone combination, and for each phthalate and preterm delivery, using the methods described by Vanderweele and Vansteelandt (Vanderweele and Vansteelandt 2010; Valeri and Vanderweele 2013).

For participant j let Y_j represent binary ADHD status, A_j represent continuous log phthalate metabolite measure, M_j represent

the mediator under consideration (either a thyroid hormone measure or preterm delivery), $\boldsymbol{C}_{1j}$ represent the set of covariates for the ADHD-phthalate models described above, and $\boldsymbol{C}_{2j}$ represent a relevant set of confounders of the phthalate–mediator relationship. The following two models were fit (Equations 3 and 4):

$$\text{logit}(Y_j|A_j,M_j,C_j) = \theta_0 + \theta_1 A_j + \theta_2 M_j + \boldsymbol{\theta}_3' \boldsymbol{C}_{1j}, \quad (3)$$

$$g(M_j|A_j,C_j) = \beta_0 + \beta_1 A_j + \boldsymbol{\beta}_2' \boldsymbol{C}_{2j}, \quad (4)$$

where the first is called the outcome model, and the second is called the mediator model; g is the appropriate link function, chosen to be E(X) for the continuous thyroid hormone measures and logit(X) for binary preterm delivery. The thyroid hormone measures were square root–transformed to ensure adherence to linear modeling assumptions, and both the log phthalate and the square root thyroid hormone were centered to aid interpretation. For the thyroid hormones, the linear mediator model was fit using inverse probability weights to account for the case–control design of our study.

The NDE and NIE ORs corresponding to a change in log phthalate from its mean to one unit above the mean were calculated by plugging frequentist parameter estimates into $\exp(\theta_1)$ and $\exp(\theta_2\beta_1)$ for the thyroid hormones and $\exp(\theta_1)$, respectively, and Equation 5 for preterm delivery:

$$\left(1+\exp\left(\beta_0+\boldsymbol{\beta}_2'\boldsymbol{C}_2^*\right)\right)\left(1+\exp\left(\theta_2+\beta_0+\beta_1+\boldsymbol{\beta}_2'\boldsymbol{C}_2^*\right)\right)/$$
$$\left(1+\exp\left(\beta_0+\beta_1+\boldsymbol{\beta}_2'\boldsymbol{C}_2^*\right)\right)\left(1+\exp\left(\theta_2+\beta_0+\boldsymbol{\beta}_2'\boldsymbol{C}_2^*\right)\right), \quad (5)$$

where $\boldsymbol{C}_2^*$ represents a chosen set of covariate values. Analogous NDE and NIE ORs were also calculated based on an outcome model containing an interaction between the phthalate and the mediator, as advised by Vanderweele and Vansteelandt (Vanderweele and Vansteelandt 2010). This interaction term increases model flexibility and helps to account for the extent of mediation (Vanderweele 2015). Assumptions of mediation analysis include correct model specification and no unmeasured confounding of the exposure–outcome, mediator–outcome, and exposure–mediator relationships (Vanderweele and Vansteelandt 2010). In preliminary analyses, we found evidence of a U-shaped relationship between T4 and ADHD (data not shown), and the Vanderweele and Vansteelandt method does not easily account for nonlinear mediator forms. Therefore, we conducted a sensitivity analysis wherein we assessed mediation separately among those below and above the median T4 level.

All analyses were performed using R statistical software (R Core Team; Van Buuren and Groothuis-Oudshoorn 2011).

Results

Characteristics of ADHD cases and controls can be found in Table 1. Mothers of cases were slightly younger than mothers of controls, and they were also more likely to report lower educational attainment, less likely to report being married at the time of enrollment, more likely to have reported smoking during their first or second trimester, and more likely to report having experienced depression during pregnancy. Cases were also more likely to be boys.

The distributions of the maternal urinary phthalate metabolites measured herein are presented in Table 2. The concentrations are adjusted for batch and standardized to the geometric mean of specific gravity. Although all raw measured values were greater than the limit of quantification (LOQ), after adjustment for batch and specific gravity, some of the lower concentrations fell below the analytic LOQ. For all phthalate metabolites except DiNP metabolites, concentrations among controls were lower than among cases, which is explained in part by an imbalance in birth year by case/control status (Table 1). For DiNP metabolites, the reverse pattern was observed. Average exposures were in general highest for MEP and lowest for DiNP metabolites.

Table 1. Characteristics of study population in nested case–control study of attention-deficit hyperactivity disorder in the Norwegian Mother and Child Cohort (MoBa), 2003–2008.

Characteristic	MoBa Controls Mean ± SD or *n* (%)	MoBa NPR ADHD Cases Mean ± SD or *n* (%)
Total N	553	297
Maternal age at delivery (years)	30.9 ± 4.19	29.2 ± 5.08
Missing (*n*)	2	2
Child Sex		
Boy	273 (49.6)	213 (72.2)
Girl	278 (50.4)	82 (27.8)
Missing (*n*)	2	2
Maternal education		
<College	123 (22.5)	160 (59.7)
College	238 (43.6)	74 (27.6)
>College	169 (31.0)	25 (9.3)
Other	16 (2.9)	9 (3.4)
Missing (*n*)	7	29
Marital status		
Single/Other	14 (2.6)	18 (6.7)
Cohabitating	245 (44.7)	144 (53.5)
Married	289 (52.7)	107 (39.8)
Missing (*n*)	5	28
Smoking in 1st or 2nd trimester		
Yes	78 (14.3)	94 (34.8)
No	469 (85.7)	176 (65.2)
Missing (*n*)	6	27
Primiparous		
Yes	270 (49.0)	141 (47.8)
No	281 (51.0)	154 (52.2)
Missing (*n*)	2	2
Reported depression during pregnancy		
Yes	6 (1.1)	16 (5.4)
No	547 (98.9)	281 (94.6)
Missing (*n*)	0	0
Year of Birth		
2003–2004	55 (10.0)	131 (44.1)
2005	130 (23.5)	87 (29.3)
2006	194 (35.1)	44 (14.8)
2007–2008	174 (31.5)	35 (11.8)
Missing (*n*)	0	0

Note: ADHD, attention-deficit hyperactivity disorder; NPR, Norwegian Patient Registry; SD, standard deviation.

After adjustment for covariates, neither MEP, MiNP, MnBP, MBzP, nor $\sum$DiNP was associated with ADHD in Bayesian multivariable adjusted models, which included adjustment for phthalate coexposures (Table 3, Figure 1; see also Table S1). However, $\sum$DEHP was positively associated with ADHD. Across quintiles of exposure, ORs increased monotonically (Figure 1; see also Table S1). Children of mothers in the highest quintile of $\sum$DEHP had almost three times the odds of an ADHD diagnosis as those in the lowest quintile [OR = 2.99 (95% CI: 1.47, 5.49)]. When $\sum$DEHP was modeled as a log-linear term, for each log-unit increase in exposure, the odds of ADHD increased by 47% [OR = 1.47 (95% CI: 1.09, 1.94)] (Table 3). Adjustment for year of birth substantially attenuated estimates of association for MEP, MiBP, MnBP, $\sum$DEHP, and $\sum$DiNP; however, associations for $\sum$DEHP remained statistically significant in year-adjusted models (Table 3; see also Table S1). In sensitivity analyses, we examined associations in single-phthalate models, in models with mutual adjustment only within classes of high- or low-molecular-

Table 2. Phthalate metabolite distribution in a nested case–control study of attention-deficit hyperactivity disorder in the Norwegian Mother and Child Cohort (MoBa), 2003–2008.

Exposure and outcome	Geometric mean	Geometric SD	Min	25%	50%	75%	Max	LOQ	% >LOQ	Average batch-specific CV
MEP (μg/L)								0.5	100.0	3.20
Case	133	4.50	5.09	40.9	132	406	10,500			
Control	98.7	4.49	0.05	32.3	98.7	297	6,760			
MiBP (μg/L)								0.5	100.0	5.86
Case	21.2	2.33	3.21	12.0	21.5	36.8	407			
Control	18.0	2.58	0.02	9.61	16.5	31.4	562			
MnBP (μg/L)								0.5	100.0	4.02
Case	25.1	2.13	4.18	14.4	25.0	43.4	214			
Control	18.1	2.44	0.03	11.4	17.0	30.6	70,200			
MBzP (μg/L)								0.2	100.0	4.93
Case	7.28	2.72	0.76	3.34	6.74	14.8	151			
Control	4.57	2.59	<0.01	2.54	4.25	7.84	103			
MEHP (μg/L)								0.5	100.0	5.66
Case	13.7	1.89	2.16	8.74	13.2	20.1	156			
Control	11.2	2.21	0.02	7.11	10.3	17.2	812			
MEHHP (μg/L)								0.4	100.0	3.74
Case	16.9	2.25	1.71	9.52	16.6	26.5	324			
Control	13.8	2.54	0.03	8.06	12.6	20.5	1,700			
MEOHP (μg/L)								0.4	100.0	3.82
Case	11.3	2.23	1.36	6.67	10.8	17.6	179			
Control	9.29	2.51	0.02	5.51	8.41	14.0	807			
MECPP (μg/L)								2.0	100.0	1.22
Case	23.6	1.84	7.42	15.5	21.2	32.2	327			
Control	20.6	2.04	0.04	13.8	18.5	25.6	768			
MMCHP (μg/L)								2.0	100.0	2.79
Case	23.2	1.84	7.86	15.2	20.5	29.8	463			
Control	20.6	1.95	0.03	14.0	18.1	26.1	372			
$\sum$DEHP (μmol/L)								NA	NA	NA
Case	0.31	1.85	0.07	0.21	0.28	0.41	3.30			
Control	0.27	2.10	<0.01	0.18	0.23	0.34	14.9			
OH-MiNP (μg/L)								0.2	100.0	4.99
Case	0.92	1.96	0.33	0.59	0.86	1.22	138			
Control	1.06	2.10	<0.01	0.69	0.95	1.42	60.7			
oxo-MiNP (μg/L)								0.2	98.5	6.58
Case	1.09	2.18	0.33	0.62	0.95	1.58	122			
Control	1.20	2.45	<0.01	0.70	1.04	1.76	201			
cx-MiNP (μg/L)								1.0	100.0	2.79
Case	3.22	1.63	1.30	2.27	2.96	4.45	36.0			
Control	3.61	1.80	0.01	2.50	3.49	4.73	141			
$\sum$DiNP (μmol/L)								NA	NA	NA
Case	0.02	1.75	0.01	0.01	0.02	0.02	0.96			
Control	0.02	1.95	<0.01	0.01	0.02	0.03	1.07			

Note: Concentrations are expressed to three significant digits. Phthalate metabolites were measured in 297 cases and 552 controls. The LOQ was not available for $\sum$DEHP and $\sum$DiNP because they are molar sums of phthalate metabolites, and therefore were not directly measured. CV, coefficient of variation; cx-MiNP, mono-4-methyl-7-carboxyheptyl phthalate; DEHP, di-2-ethylhexyl phthalate; DiNP, di-iso-nonyl phthalate; LOQ, limit of quantification; MBzP, monobenzyl phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MEOHP, mono-2-ethyl-5-oxoyhexyl phthalate; MEP, monoethyl phthalate; MiBP, mono-iso-butyl phthalate; MMCHP, mono-2-methylcarboxyhexyl phthalate; MnBP, mono-*n*-butyl phthalate; NA, not available; OH-MiNP, mono-4-methyl-7-hydroxyoctyl phthalate; oxo-MiNP, mono-4-methyl-7oxooctyl phthalate. Values were adjusted for batch and standardized to the geometric mean of specific gravity.

weight phthalates specifically, and in a model in which specific gravity was instead included as a covariate in the model (see Tables S2 and S3). There was modest confounding by correlated phthalates present in the single-phthalate models, and adjustment for specific gravity as a covariate resulted in a substantial decrease in the precision of estimates. We additionally examined whether adjustment for maternal or paternal income affected our models, and there were no substantial changes. We also constructed alternative models in which we adjusted for month and year of urine collection and found no differences compared with models adjusted for birth year (see Table S4).

We observed no notable effect modification by child sex, with the possible exception of MnBP (Table 3). Among boys, the association between MnBP and ADHD was OR = 0.98 (95% CI: 0.70, 1.34), whereas among girls, the point estimate was somewhat elevated [OR = 1.33 (95% CI: 0.75, 2.20)]; however, neither of the stratum-specific associations excluded the null value, and the 90% credible interval for the phthalate by sex interaction term included the null, suggesting no meaningful interaction. Notably, the association between $\sum$DEHP and ADHD was strong in both boys and girls, as well as overall, although the estimate was slightly stronger, and less precise, among girls (Table 3).

We found no evidence of mediation of the $\sum$DEHP-ADHD relationship by any of the measured maternal thyroid function biomarkers (Table 4). This finding was true for both mediation models (with and without the exposure–mediator interaction terms). In a sensitivity analysis, we assessed mediation separately among those below and above the median T4 level and again found no mediation (see Table S5). We also investigated mediation of the $\sum$DEHP-ADHD relationship by preterm delivery and detected no significant mediation in models with and without the thyroid hormone–preterm interaction term (Table 4).

Discussion

In this prospective, nested case–control study, we found evidence that maternal prenatal exposure to $\sum$DEHP was monotonically associated with increased risk of ADHD in offspring. We did not

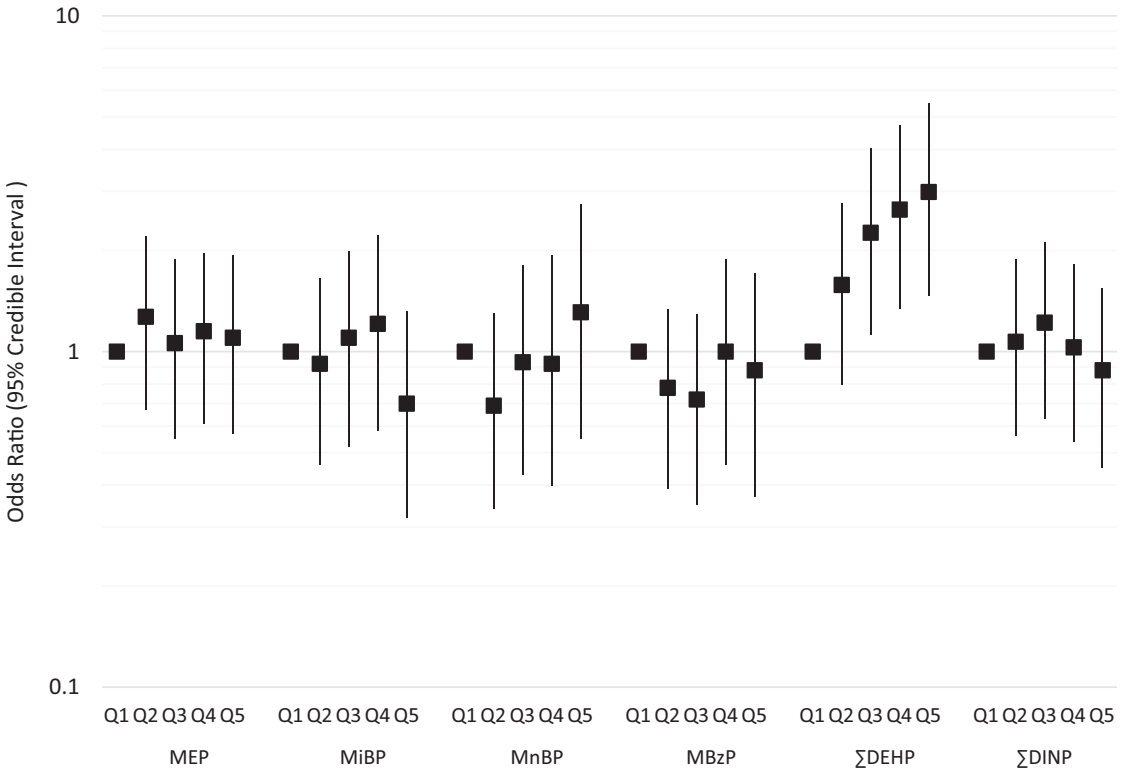

Figure 1. Odds ratios and 95% credible intervals for quintiles of phthalate metabolite concentrations in a nested case–control study of attention-deficit hyperactivity disorder in the Norwegian Mother and Child Cohort, 2003–2008. This plot displays the results of a multivariable adjusted model, where phthalate metabolite quintiles are mutually adjusted. This model was adjusted for analytic batch, specific gravity, maternal age at delivery, sex of the child, maternal education, marital status, prenatal smoking, parity, maternal depression during pregnancy, and year of birth. ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; ∑DiNP, sum of di-iso-nonyl phthalate metabolites; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MiBP, mono-iso-butyl phthalate; MnBP, mono-*n*-butyl phthalate.

identify evidence of significant heterogeneity in these associations by child sex, nor did we identify evidence that this association was mediated through either maternal thyroid function or preterm delivery.

Among the previous studies that have examined prenatal phthalate exposures in relation to childhood neurobehavioral development (Engel et al. 2010; Kobrosly et al. 2014; Lien et al. 2015; Whyatt et al. 2012; Gascon et al. 2015; Miodovnik et al. 2011; Philippat et al. 2015; Braun et al. 2014), several, but not all, have highlighted potentially troubling associations with DEHP exposures (Kobrosly et al. 2014; Lien et al. 2015; Philippat et al. 2015). Lien et al. (2015) examined measured biomarkers of DEHP exposure during pregnancy in relation to child behavior and found that increased concentration of DEHP metabolites was associated with more externalizing problems. Kobrosly et al. (2014) reported more somatic complaints in children with increased prenatal concentrations of DEHP metabolites. Although individual phthalate metabolite associations were not provided, Engel et al. (2010) reported that increased concentrations of the sum of high-molecular-weight phthalate metabolites (inclusive of DEHP, as well as MBzP and mono-(3-carboxypropyl) phthalate (MCPP), a metabolite of di-*n*-octyl phthalate) were associated with poorer scores on the adaptability scale of the behavioral assessment scale for children (BASC). Interestingly, a Swedish study of the indoor environment and autism spectrum disorder (ASD) reported that presence of vinyl flooring, a source of DEHP, in the parents' bedroom during pregnancy significantly increased odds of an ASD diagnosis (Larsson et al. 2009). Furthermore, in a population-based case–control study of ASD and developmental delay, Philippat et al. (2015) found no association between house-dust levels of DEHP and ASD, although they did find that higher DEHP concentrations in house dust were associated with increased odds of developmental delay. However, not all studies have found associations between prenatal DEHP exposure and behavior (Whyatt et al. 2012; Gascon et al. 2015; Miodovnik et al. 2011; Braun et al. 2014). We also note that our study assessed more DEHP metabolites has been than examined in the prior literature. The total DEHP exposure captured by all five metabolites after 24 h and 44 h of an oral dose is 67% and 74%, respectively (Koch et al. 2005). Both MECPP and MMCHP have longer elimination half-lives (MECPP, 12–15 h; MMCHP, 24 h) than MEHHP and MEOHP

Table 3. Interactions between linear phthalate exposure and child sex in a nested case–control study of attention-deficit hyperactivity disorder in the Norwegian Mother and Child Cohort (MoBa), 2003–2008.

Phthalate	Combined ($n = 802$)[a] OR (95% CI)	Boys ($n = 458$)[b] OR (95% CI)	Girls ($n = 344$)[b] OR (95% CI)
MEP	1.02 (0.90, 1.16)	0.99 (0.85, 1.15)	1.10 (0.87, 1.36)
MiBP	0.92 (0.70, 1.20)	0.96 (0.68, 1.29)	0.87 (0.54,1.29)
MnBP	1.04 (0.77, 1.40)	0.98 (0.70, 1.34)	1.33 (0.75, 2.20)
MBzP	1.21 (0.92, 1.55)	1.21 (0.87, 1.62)	1.18 (0.75, 1.81)
∑DEHP	1.47 (1.09, 1.94)	1.41 (1.00, 1.95)	1.62 (0.95, 2.58)
∑DiNP	0.85 (0.61, 1.15)	0.83 (0.57, 1.18)	0.85 (0.48, 1.35)

Note: CI, credible interval; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; ∑DiNP, sum of di-iso-nonyl phthalate metabolites; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MiBP, mono-iso-butyl phthalate; MnBP, mono-*n*-butyl phthalate; OR, odds ratio.

[a]Models adjusted for analytic batch, specific gravity, child sex, mother's age, mother's education level, mother's marital status, mother's smoking status, parity, maternal depression during pregnancy, and year of birth.

[b]Stratum-specific estimates derived from models that additionally include sex by phthalate interaction terms.

Table 4. Natural direct effect (NDE) and natural indirect effect (NIE) odds ratios and 95% confidence intervals for mediation of ∑DEHP by thyroid hormones and preterm delivery.

	No interaction		Interaction	
	NDE[a]	NIE	NDE[a]	NIE
Model parameter	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Thyroid stimulating hormone (TSH)[b]	1.45 (1.11, 1.88)	1.00 (0.99, 1.01)	1.43 (1.10, 1.86)	1.00 (0.98, 1.02)
Triiodothyronine (T3)[b]	1.46 (1.12, 1.90)	1.00 (0.98, 1.02)	1.51 (1.14, 2.00)	1.00 (0.95, 1.05)
Thyroxine (T4)[b]	1.46 (1.13, 1.90)	1.00 (0.99, 1.01)	1.47 (1.13, 1.92)	0.99 (0.97, 1.02)
Preterm delivery[c]	1.45 (1.12, 1.88)	1.00 (1.00, 1.00)	1.44 (1.11, 1.87)	1.00 (0.99, 1.02)

Note: CI, confidence interval; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; OR, odds ratio.
[a]The NDE is conditional on values of the mediator model covariates. For the thyroid hormones, the NDEs are computed for the following covariate specifications: iodine deficient (≤150), sample average maternal age, nonsmoking mother, nonprimiparous, and year of birth 2005. For preterm delivery, the NDEs are computed for the following covariate specifications: sample average maternal age, married mother, nonsmoking mother, and year of birth 2005.
[b]Mediation models adjusted for iodine intake (dichotomized at 150), mother's age, mother's smoking status, parity, and year of birth and outcome models adjusted for child sex, mother's age, mother's education level, mother's marital status, mother's smoking status, parity, maternal depression during pregnancy, and year of birth.
[c]Mediation models adjusted for mother's age, mother's education level, mother's smoking status, and year and outcome models adjusted for child sex, mother's age, mother's education level, mother's marital status, mother's smoking status, parity, maternal depression during pregnancy, and year of birth.

(10 h for both MEHHP and MEOHP). Owing to their longer elimination half-lives, both MECPP and MMCHP are excellent biomarkers of time-weighted DEHP body burden. In addition, MMCHP is the major metabolite excreted during the second day of exposure to DEHP (Koch et al. 2005). Therefore, including this additional DEHP metabolite may improve the reliability of our estimates of DEHP exposure compared with those in the existing literature, potentially reducing misclassification.

There has been considerable concern about adverse developmental effects of perinatal exposure to DEHP for over a decade (Shelby 2006; Kavlock et al. 2006; CPSC 2014; NRC 2008), particularly in reference to the development of the male reproductive tract (Shelby 2006). Although most of the experimental research on the developmental effects of phthalates has focused on reproductive toxicity, principally relating to antiandrogenic activity, there is a small but growing body of experimental literature exploring the effects of perinatal exposure to DEHP on neurodevelopment. Gestational DEHP exposure in mice has been linked to decreases in neurogenesis and in the proliferation of neural stem cells in the developing neocortex (Komada et al. 2016), although another study found an increase in neurite length but no difference in the number of cortical neurons (Lee et al. 2016). In rats, gestational DEHP exposure was associated with a dose-dependent impairment of learning and spatial memory along with alterations in gene expression in the neonatal rat brain (Lin et al. 2015), particularly highlighting effects on two genes important for neuron proliferation (Lin et al. 2015). Perinatal DEHP exposure in rats has also been associated with an altered brain lipid metabolome (Xu et al. 2007). Moreover, in an *in vitro* study, MEHP exposure (a metabolite of DEHP) inhibited cell proliferation and differentiation of neuronotypic PC12 cells via cell cycle arrest (Chen et al. 2011). Perinatal DEHP exposure has also been associated with aggravation of anxiety and depression-like behaviors in pubertal and adult mice (Xu et al. 2015; Quinnies et al. 2017). Although little is known about the tissue distribution of DEHP following exposure, phthalates are known to cross the placenta (Jensen et al. 2015; Jensen et al. 2012; Singh et al. 1975). Additionally, although DEHP has low affinity for brain tissue, more radiolabeled DEHP was found in the brain of 3-d old mice than in the brain of older mice, suggesting that the blood–brain barrier may have increased permeability to DEHP in neonates (Miles-Richarson and Bosch 2002). Overall, however, this body of experimental literature is quite small, and experimental designs have differed in the doses administered and in the periods of exposure examined, as well as in the outcomes assessed.

In contrast with prior studies (Engel et al. 2010; Kobrosly et al. 2014; Lien et al. 2015; Whyatt et al. 2012), we found no evidence that prenatal exposure to low-molecular-weight phthalates (e.g., MEP, MiBP, MnBP) was associated with clinically confirmed ADHD and no evidence of interactions by sex for any of our measured phthalates. There are several plausible explanations for these findings. First, it is possible that the differences between our studies are simply attributable to variability around an overall null association between these phthalates and ADHD. Second, it is possible that focusing on clinically diagnosed cases misses subtle behavioral differences that can be more powerfully assessed using instruments that allow for dimensionality in the severity of symptoms. Third, ADHD is a heterogeneous disability (Thapar and Cooper 2016). Established neuropsychological screening approaches assess a range of symptoms and classify individuals into ADHD subtypes on the basis of their presence or absence. We only had access to the binary diagnosis of ADHD; however, it is conceivable that some phthalates are only associated with specific subtypes of ADHD, and this etiological heterogeneity could potentially attenuate associations in our study. Finally, it may also be relevant that the timing of exposure measurement in our study differs from that of most of the previous studies. Our urine sample was taken at 17 wk gestation, whereas most of the prior studies assessed exposure late in the third trimester. If there are sensitive windows of brain development that are critical for the development of ADHD, then timing of exposure measurement may be a key explanatory factor. However, there is at present no literature that specifically examines timing of phthalate exposure in relation to ADHD.

We acknowledge several limitations in our study. First, phthalates are rapidly metabolized and have been shown to exhibit low to moderate reliability across pregnancy in several studies, with the best reliability often found for MEP, MiBP, and MnBP, and the worst reliability often found for DEHP (Adibi et al. 2008; Baird et al. 2010; Braun et al. 2012; Teitelbaum et al. 2008; Townsend et al. 2013). For DEHP specifically, intraclass correlation coefficients for repeated biomarker measurements from urine collected over a period of weeks (Adibi et al. 2008; Baird et al. 2010), months (Braun et al. 2014; Teitelbaum et al. 2008), or years (Townsend et al. 2013) has ranged from a low of 0.08 to a high of 0.38. Our study only had access to one spot urine sample that was collected at approximately 17 wk gestation. Thus, we cannot represent this single measurement as reflective of pregnancy-wide exposures. Second, to some extent, MoBa under-represents young mothers, those living alone, and women who report smoking during pregnancy (Nilsen et al. 2009). However, a prior study found this self-selection to have little impact (Nilsen et al. 2013), and we considered these factors in our models, so we do not expect such under-representation to be a major source of bias in our study. Additionally, although phthalate metabolite and thyroid function biomarker concentrations were measured, covariate data were largely obtained via maternally completed questionnaires, which

may have error, particularly for behaviors carrying a social stigma (such as prenatal smoking).

Perhaps not a weakness, but a challenge, is the significant impact of population-level shifts in exposures to phthalates that have occurred in recent years (Koch et al. 2017). DEHP exposures were generally highest in the early years of our study and have dropped over time. Irrespective of exposure, older children have had more opportunity to be identified as having ADHD; this creates the potential for confounding by year (which accounts for both age of the child and exposure period). To address confounding by time, we adjusted for year of birth in our analyses. We also constructed alternative models in which we adjusted for month and year of urine collection and found no differences when comparing them with models adjusted for birth year (see Table S5). However, it is possible that there remains some residual confounding by year that we cannot address within the present design, and accounting for this bias would attenuate our $\sum$DEHP associations. It is also possible that including year in our models results in over-adjustment for population shifts in exposure. Another limitation of this study is that we did not consider the extent to which genetic features may confound or modify these associations or the extent to which other environmental toxicant exposures may confound these estimates. Future studies that examine populations enrolled over a narrower time range, that include multiple urine samples collected during pregnancy to more validly estimate pregnancy-wide phthalate exposures, and that include information on genetic risk factors for ADHD and other toxicant coexposures are required to address these concerns.

Our study also has several strengths. To our knowledge, this is the only study of prenatal exposure to phthalates and risk of ADHD that had a clinically defined end point. Our study was nested in a well-characterized prospective birth cohort with extensive questionnaire data that enabled us to obtain a wide range of relevant covariate information. Linkage with the NPR enabled us to focus on cases that were by definition severe enough to result in clinical identification. Although we believe this is a notable strength of our study, it is also true that we cannot generalize our results to ADHD cases that are not clinically recognized and that clinical recognition itself may suggest that our cases are on the more severe end of the disease spectrum or have more comorbidities that require specialist management. Our study also produced estimates for phthalate associations that were adjusted for the presence of other phthalates in the mixture using a Bayesian approach. Although accounting for the phthalate mixture is a strength, it is possible that alternative statistical methods for analyzing exposure mixtures may produce slightly different estimates. Finally, we examined the potential for mediation of the association between DEHP (the only phthalate with a significant main effect) and ADHD by thyroid hormones and measures of thyroid function, some of which have been associated with ADHD in offspring in previous studies (Ghassabian et al. 2011, 2012; Modesto et al. 2015; Päkkilä et al. 2014). A lack of evidence for mediation of the DEHP association suggests the possibility that this phthalate may be affecting ADHD through another mechanism, although we cannot exclude the possibility that other phthalates may be operating through a thyroid mechanism or that our ability to fully interrogate this pathway may have been negatively influenced by the fact that phthalate metabolites and thyroid function were measured only once during pregnancy. We also considered the potential for mediation by preterm birth, given prior evidence that elevated prenatal DEHP was associated with increased risk of preterm birth (Ferguson et al. 2017), and preterm birth was associated with subsequent risk of ADHD (Murray et al. 2016; Sucksdorff et al. 2015); again, we found no evidence of mediation through this pathway. Although we did evaluate interactions between DEHP and the potential mediators (thyroid function and preterm birth), the validity of our mediation analyses depends on strong assumptions that cannot be verified with certainty, including the absence of uncontrolled confounding of exposure–mediator and mediator–outcome relationships (Valeri and Vanderweele 2013).

Indoor exposure to phthalates is a significant concern, in part because phthalates are not chemically bound and therefore may be released into air or other media over time (Mitro et al. 2016). Some limited regulations pertaining to consumer products in the United States and in the European Union (EU)/European Economic Area (EEA) (which includes Norway) exist, specifically focused on prohibiting DEHP, as well as BBzP, in children's toys and child care articles at levels >0.1%, and in the EU/EEA, additionally prohibiting these phthalates and DnBP in both child care articles and cosmetics. The EU/EEA has additional regulations pertaining to the use of DiNP and other phthalates in children's products, with more regulations covering other phthalates and consumer products set to take effect in the next several years. However, the 2014 Chronic Hazard Advisory Panel on Phthalates and Phthalate Replacements concluded that food, beverages, and drugs, not toys and personal care products, comprised the greatest sources of phthalates to all subpopulations worldwide (CPSC 2014). Although the European Food Safety Authority (EFSA) has set tolerable intakes for DEHP, DnBP, and BBzP (EFSA 2005a, 2005b, 2005c, 2005d, 2005e), dietary exposure to phthalates in the Norwegian adult population is comparable to that in other countries around the world and comes from similar food sources (Sakhi et al. 2014). Therefore, population exposures will continue without more stringent regulations that specifically address food and pharmaceutical sources.

Conclusion

In summary, in this prospective, population-based case–control study, prenatal DEHP exposure was associated with increased risk of ADHD. Population usage of DEHP is on the decline worldwide as a result of health concerns and some regulatory actions; however, it remains a measurable and prevalent exposure in contemporary populations (Koch et al. 2017). Given the accumulating evidence of developmental impacts, both to the male reproductive system and potentially to the developing nervous system, more health-protective regulations may be in order.

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