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Pregnancy exposure to common-detect organophosphate esters and phthalates and maternal thyroid function

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Abstract

Background.—Contemporary human populations are exposed to elevated concentrations of organophosphate esters (OPEs) and phthalates. Some metabolites have been linked with altered thyroid function, however, inconsistencies exist across thyroid function biomarkers. Research on OPEs is sparse, particularly during pregnancy, when maintaining normal thyroid function is critical to maternal and fetal health.

Aim.—To characterize pregnancy exposure to OPE and phthalates in relation to maternal thyroid function, using a cross-sectional investigation of pregnant women nested within the Norwegian Mother, Father, and Child Cohort.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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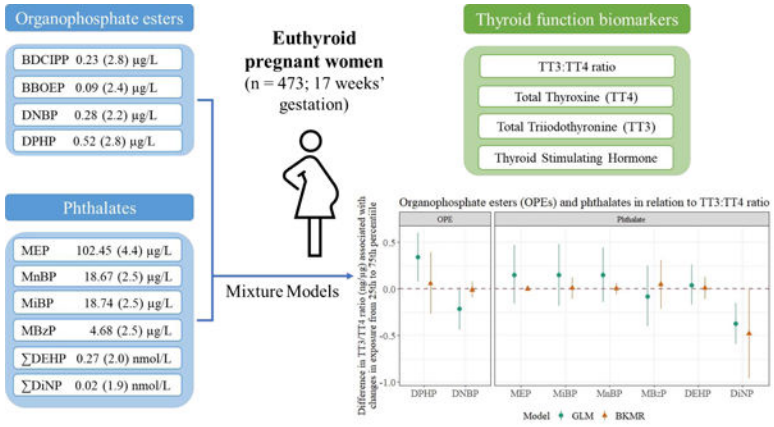
Methods.—We included 473 pregnant women, who were euthyroid and provided bio-samples at 17 weeks' gestation (2004–2008). Four OPE and six phthalate metabolites were measured from urine; six thyroid function biomarkers were estimated from blood. The relationships between thyroid function biomarkers and log-transformed concentrations of OPE and phthalate metabolites were characterized using two approaches that both accounted for confounding by co-exposures: co-pollutant adjusted general linear model(GLM) and Bayesian Kernal Machine Regression (BKMR).

Results.—We restricted our analysis to common-detect OPEs and phthalates (>94%): diphenyl phosphate (DPHP), di-n-butyl phosphate (DNBP), and all phthalate metabolites. In GLM, pregnant women with di-iso-nonyl phthalate (DiNP) concentrations in the 75th percentile had a 0.37 ng/μg lower total triiodothyronine (TT3): total thyroxine (TT4) ratio (95% credible interval: [−0.59, −0.15]) as compared to those in the 25th percentile, possibly due to small but diverging influence on TT3 (−1.99 ng/dL [−4.52, 0.53]) and TT4 (0.13 μg/dL [−0.01, 0.26]). Similar trends were observed for DNBP and inverse associations were observed for DPHP, monoethyl phthalate, mono-iso-butyl phthalate, and mono-n-butyl phthalate. Most associations observed in co-pollutants adjusted GLMs were attenuated towards the null in BKMR, except for the case of DiNP and TT3:TT4 ratio (−0.48 [−0.96, 0.003]).

Conclusions.—Maternal thyroid function varied modestly with DiNP, whereas results for DPHP varied by the type of statistical models.

Graphical Abstract



Keywords

Diphenyl phosphate; maternal thyroid function; pregnancy; mixtures; MoBa

Introduction

Organophosphate esters (OPEs) are widely used as plasticizers or flame retardants, with a steady increase in their production since the early 2000s (van der Veen and de Boer, 2012). Such temporal trends are partly due to OPEs' recognition as replacements for a class of chemicals undergoing phase-out (EPA, 2013; EU, 2003), i.e., polybrominated diphenyl ethers (PBDEs). The desirable property of OPEs is that they are rapidly metabolized and do

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not bioaccumulate; however, they also do not form covalent bonds and therefore easily leach or volatilize into the surrounding environment. Consequently, metabolites of several common-use OPEs have been detected frequently in human populations (Castorina et al., 2017; Feng et al., 2016; Hoffman et al., 2017b; Ingle et al., 2019; Kosarac et al., 2016; Ospina et al., 2018; Romano et al., 2017; Wang et al., 2019b; Zota et al., 2014). Particularly for diphenyl phosphate (DPHP), a metabolite of one of the most commonly-used OPEs, increasing human exposure has been reported over time (Hoffman et al., 2017a). Widespread exposure to OPEs raises concerns since recent studies suggest thyroid disruption properties (Hill et al., 2018; Kim et al., 2015; Liu et al., 2019; Wang et al., 2013; Zhang et al., 2016).

Epidemiological investigations on OPEs and thyroid function are relatively sparse. Some OPEs have been associated with thyroid function in sub-fertile men (Meeker et al., 2013; Meeker and Stapleton, 2010) and office workers (Preston et al., 2017), particularly DPHP and total triiodothyronine (TT3), though null findings have also been reported (Gravel et al., 2020; Wang et al., 2019a). Further limited is our understanding in pregnant women, with only 1 recent publication on pregnant women that observed potential thyroid disruption by DPHP but not with triiodothyronine (Yao et al., 2020). More research is needed to better understand the impact of OPE exposure during pregnancy since thyroid physiology drastically changes with the start of pregnancy (Glinoer et al., 1990; Moleti et al., 2014), and maintaining normal thyroid function in pregnant women are critical to maternal and fetal health (Allan et al., 2000; Andersen et al., 2014; Chan and Kilby, 2000; Gilbert et al., 2012; Karakosta et al., 2012; Päkkilä et al., 2014; Stagnaro-Green et al., 2011).

Characterizing the impact of OPEs is complicated by the correlated nature of exposure to multiple environmental agents since humans are simultaneously exposed to a mixture of chemicals. Phthalates, which share common source products as OPEs (Bornehag et al., 2005; Ionas et al., 2014; Liang and Xu, 2014; Yang et al., 2020) and are widespread (Wittassek and Angerer, 2008), has also been associated with changes in thyroid homeostasis (Gao et al., 2017; Huang et al., 2007a; Huang et al., 2007b; Huang et al., 2016; Johns et al., 2016; Johns et al., 2015; Kim et al., 2019; Kuo et al., 2015; Meeker and Ferguson, 2011; Romano et al., 2018; Villanger et al., 2020; Yao et al., 2016). Specifically, in a previous investigation of pregnant women in the Norwegian Mother, Father, and Child Cohort (MoBa), a factor dominated by mono-iso-butyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), and monobenzyl phthalate (MBzP), and another factor dominated by di-iso-nonyl phthalate (DiNP) were associated with measures of triiodothyronine (Villanger et al., 2020). However, the specific phthalate metabolite within the factor, that is strongly associated with thyroid function, remains unclear. Moreover, few studies of phthalates have attempted to account for correlated chemical exposures during pregnancy in relation to thyroid function, apart from within-class correlations among phthalates (Romano et al., 2018; Villanger et al., 2020). Attempts to isolate effects of correlated exposures across chemical classes have also been limited in the investigations of OPEs and thyroid function, where other flame retardants but not other plasticizers, have been considered (Gravel et al., 2020; Preston et al., 2017).

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We sought to characterize the relationships between pregnancy exposure to OPEs and phthalates and maternal thyroid function in pregnant women, applying mixtures approach to a cross-sectional subset of the MoBa.

Methods

Study population

MoBa is an ongoing prospective population-based cohort study of Norwegian-speaking women, conducted by the Norwegian Institute of Public Health (Magnus et al., 2016; Magnus et al., 2006). Between 1999–2008, pregnant women across Norway were recruited at their routine prenatal ultrasound visit (≈17 gestational weeks; GW) and contributed urine and blood samples upon providing a written consent (Rønningen et al., 2006). A total of 114,500 children, 95,200 mothers, and 75,200 fathers are enrolled.

The current study utilized a subset of MoBa enrollees who met the eligibility criteria: gave birth to a singleton without Down's syndrome and cerebral palsy between April 2004 – January 2008 and resided within proximity to Oslo. A total of 33,050 pregnant women were eligible, and 555 mothers with available urine and blood specimen who completed the 36-month postnatal questionnaire were sampled, frequency-matched to an external population by birth year (Engel et al., 2018). A total of 539 mothers who had measured concentrations of thyroid function biomarkers and urinary OPE and phthalate metabolites were eligible for the current study.

Measurement of OPE and phthalate metabolites in urine

Maternal urine samples were collected at 17 GW and shipped unrefrigerated to a central ISO-certified lab in Oslo overnight (Biobank), where the samples were stored at −80°C (Paltiel et al., 2014). OPE and phthalate metabolites were analyzed at the Norwegian Institute of Public Health, in randomly-assigned batches that contained quality control (QC) samples.

Four OPE metabolites, i.e., DPHP, di-n-butyl phosphate (DNBP), bis(2-butoxyethyl) hydrogen phosphate (BBOEP), and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), were measured in the urine samples using ultra performance liquid chromatography (UPLC) coupled with quadrupole-time-of-flight (QTOF) by a modified method published previously (Cequier et al., 2014). The modification was applied in the sample preparation procedure and was adapted from an earlier published method (Cequier et al., 2016). In brief, labeled internal standards, 300 μL of water, and 40 μL of formic acid were added to 300 μL of the urine sample. The OPE metabolites were extracted using Strata-X-AW 96-well plates (Phenomenenx, U.S.A.), which were conditioned first with 0.5 mL of MeOH and subsequently with 0.5 mL of H_2O, both containing 1% formic acid. Samples were loaded, eluted by gravity, and washed with 0.5 mL of MeOH to remove neutral interferences. The OPE metabolites were then eluted with 0.5 mL of acetone containing 5% triethylamine. Fifty microliters of water were added and the samples were evaporated with a gentle stream of nitrogen (10 L/hour) for 1 hour. Ten microliters were injected into the UPLC system as described elsewhere (Cequier et al., 2014). UPLC was performed using Acquity® C18 BEH

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c1olumn (50mm× 2.1 mm× 1.7 μm) from Waters Corp. (Milford, MA, U.S.A.). The metabolites were identified and quantified with tandem mass spectrometry using a Xevo® G2-S QTOF from Waters Corp. (Milford, MA, U.S.A.). All assays were conducted in batches, each of which contained 36–39 urine samples along with 8 in-house QC samples (3 spiked at 5 ng/mL, 3 spiked at 15 ng/mL, and 2 blanks) and 10–11 laboratory-blinded QC aliquots from a homogenized urine pool. The limit of detection (LOD) ranged from 0.3 μg/L (DPHP) to 0.17 μg/L (BDCIPP) and the limit of quantification (LOQ) from 0.1 μg/L (DPHP) to 0.5 μg/L (BDCIPP). Whereas the LOD quantifies the minimal analyte value that can be reliably distinguished from noise, the LOQ incorporates predefined goals for detection at a given level of analytic accuracy, thereby typically reflecting a higher minimal standard (Armbruster and Pry, 2008). For the in-house spiked QC samples, the average of batch-specific coefficients of variations (CVs) were low for DPHP, DNBP, and BBOEP (<10% at 15ng/mL; <13% at 5ng/mL), while slightly higher for BDCIPP (14.7% at 15ng/mL; 16.4% at 5ng/mL). Laboratory-blinded pooled QC urine samples exhibited more variability, which is likely due to low OPE concentrations. Average concentrations of pooled urine QC samples (DPHP: 0.30μg/mL; DNBP: 0.10ng/mL; BBOEP: 0.08ng/mL; BDCIPP: 0.26ng/mL) were many orders of magnitude lower than the spiked concentrations and only slightly above LOD(Supplementary Table 1.)

The analytic approach and quality control procedures for the measurement of phthalate metabolites have been previously reported (Engel et al., 2018; Villanger et al., 2020). Briefly, we used on-line column switching liquid chromatography coupled with tandem mass spectrometry (Sabaredzovic et al., 2015) for the measurement of MiBP, MnBP, MBzP, monoethyl phthalate (MEP), 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), mono-2-methylcarboxyhexyl phthalate (MMCHP), mono-4-methyl-7-hydroxyoctyl phthalate (OH-MiNP), mono-4-methyl-7oxooctyl phthalate (oxo-MiNP), and mono-4-methyl-7-carboxyheptyl phthalate (cx-MiNP). The secondary metabolites of di(2-ethylhexyl)phthalate (DEHP) and DiNP were converted to molar concentrations and summed to estimate the total DEHP (∑DEHP) and DiNP (∑DiNP) exposure, respectively.

To account for urinary dilution in each sample, we measured specific gravity, as defined by the ratio of the density of urine to water, using a pocket refractometer (PAL-10S) from Atago. Each individual's concentrations of OPE metabolites were standardized for specific gravity using the equation below. Phthalate metabolite concentrations were standardized to specific gravity and batch-effect using our previously described approach (Engel et al., 2018).

Measurement of thyroid function biomarkers

Pregnant women provided blood samples at the same date they provided urine samples, approximately 17 GW. The collected blood samples were shipped unrefrigerated to the Biobank overnight for processing and storage at −80°C. Our previous quality control study assessed the impact of processing delays on thyroid function biomarkers and found it had a minimal impact (Villanger et al., 2017). TT3, triiodothyronine uptake, total thyroxine (TT4),

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thyroid stimulating hormone (TSH), and thyroid peroxidase autoantibodies (TPOAb) were measured from plasma using electrochemiluminescent immunoassays on the Roche Cobas e602 analyzer (Salt Lake City, Utah, USA). The inter-and intra-assay CVs were below 7% for TPOAb; <5% for TSH, triiodothyronine uptake, TT3, and TT4.

Although TT3 and TT4 are reflective of the thyroid hormones in the blood, the majority of which are bound to plasma proteins, the hormones circulating in the free or unbound state are also important endpoints due to their relevance to fetal neurodevelopment. However, the direct measurement of the free thyroid hormones in plasma is likely to inaccurately reflect pregnancy concentrations due to large changes in the levels of plasma binding proteins and total thyroid hormones, both of which are highly variable in pregnant women (Lee et al., 2009; Thienpont et al., 2013). Alternatively, indices of free triiodothyronine and thyroxine (FT3i; FT4i) can be calculated with triiodothyronine uptake (equation 1). Triiodothyronine uptake was measured using previously described approach using electrochemiluminescent immunoassay (Villanger et al., 2017), and can measure the binding capacity of thyroxine-binding globulin in blood (Stockigt, 2001). These indices and the gold-standard (free thyroxine measurement in serum) have shown spearman correlations of 0.97–0.99 in our previous investigation (Villanger et al., 2017). FT4i, TSH, and TPOAb were used to identify participants with abnormal thyroid function biomarkers concentrations, which were considered in the construction of the euthyroid study population as described in the analytic approach.

$$P_{ij}^{*} = P_{ij} \times \frac{SG_{GM} - 1}{SG_{j} - 1} \qquad \text{(equation 1)}$$

: Specific gravity standardized concentration of i^{th} OPE metabolite in j^{th} individual's urine

: Raw concentration of i^{th} OPE metabolite in j^{th} individual's urine

GM: Geometric mean of specific gravity in the total study population

: Specific gravity of j^{th} person.

We also calculated the ratio of TT3 toTT4 (TT3:TT4), which may reflect a mechanism of thyroid homeostasis that is different from hyper- or hypo-activation of the thyroid gland (Baral et al., 2017; Mortoglou and Candiloros, 2004).

Covariate Assessment

We obtained covariate data from the MoBa questionnaire that was mailed to participants at 15 GW, from the food frequency questionnaire that mothers completed at ~22 GW, and from data linkage with the Medical Birth Registry of Norway (MBRN). From the 15 GW questionnaire, we obtained maternal characteristics reported by mothers: preexisting thyroid disease, thyroid medication, education, depression before or during pregnancy, smoking during the first or second trimester of pregnancy, and alcohol intake during pregnancy.

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Maternal iodine and selenium intakes during pregnancy were estimated from a food frequency questionnaire that covers maternal dietary intake since becoming pregnant, which was completed by pregnant women at 22 GW (Brantsaeter et al., 2007). Briefly, pregnant women responded to a semi-quantitative questionnaire that is intended to characterize diet during the first four months of pregnancy via 255 food items and additional dietary supplements. The dietary iodine and selenium intakes calculated from the food frequency questionnaire (g/day) were moderately correlated with those from four-day weighed food diaries ($\hat{\rho}$ for iodine: 0.46; $\hat{\rho}$ for selenium: 0.28) or 24-hour urine ($\hat{\rho}$ for iodine: 0.38) (Brantsæter et al., 2008; Brantsaeter et al., 2007).

Maternal age at delivery, preexisting thyroid disease, and parity were obtained by linkage with MBRN. We also obtained the year and month of biosample collection.

Ethics Data collection for MoBa was approved by the Norwegian Data

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by the Norwegian Data Inspectorate and the Norwegian Committee for Medical and Health Research Ethics (REC). The current study was approved by the Norwegian REC and the Institutional Review Board at the University of North Carolina Chapel Hill.

Analytic approach

Our primary analysis was restricted to the euthyroid population, which excluded women with 1) self-reported pre-existing thyroid disease diagnosis (N=25); 2) self-reported taking thyroid medication (N=15); or 3) measured biomarkers of TSH, TPOAb, and FT4i concentrations that could imply thyroid dysfunction (N=15; TSH<0.19 and/or FT4i>14.03; FT4i<7.73; TSH>4.06 and TPOAb>9). This restriction resulted in a euthyroid study population of 489 women out of 539 eligible pregnant women. We undertook a complete case analysis of 473 euthyroid women with complete data since missingness was minimal (N=16; 3%) and limited to maternal smoking during pregnancy (n = 6), age (n =2), education (n =7), parity (n =2), dietary iodine (n = 6), and dietary selenium (n =6). Given the infrequent detection of some OPE metabolites in the current study population, we retained only the highly-detected OPE metabolites (>94%) and substituted concentrations below LOD with LOD/√2 (Hornung and Reed, 1990).

A directed acyclic graph was constructed and minimally sufficient adjustment sets were identified. These adjustment sets included year, maternal age, education, parity, dietary iodine, dietary selenium, depression, smoking, and the urinary concentrations of phthalate metabolites. We applied two different approaches to consider confounding by co-exposure while adjusting for all covariates in the minimally sufficient adjustment set. First, we modeled the relationship between log-transformed OPE and phthalate metabolites and thyroid function biomarkers using co-pollutants adjusted general linear model (GLM). All results are presented as the absolute difference in thyroid function biomarkers per interquartile range increase in logged-exposure and their 95% confidence intervals. We

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additionally conducted Bayesian Kernal Machine Regression (BKMR; R package ═bkmr'), which allows flexible modeling of dose-response in the presence of multiple correlated exposures (Bobb, 2017). From the BKMR models, we extracted using the default (—approximate‖) and —exact‖ method the absolute difference in thyroid function biomarkers expected with increasing an OPE or phthalate metabolite from its 25th to the 75th percentile while keeping all other metabolites constant at their 25th percentile and adjusting for confounders. We also present their corresponding 95% credible intervals as well as the posterior inclusion probabilities (PIPs).

Sensitivity analyses were conducted to examine the robustness of the findings. First, we examined the relationships between OPE metabolites and thyroid function biomarkers in the total population with complete data (i.e., inclusive of non-euthyroid participants; N=522). We also explored the impact of exposure transformation and alternative definitions of OPE-phthalate mixtures in BKMR. Batch-effect was examined using a leave-one-out approach, where the main analysis was repeated with successive removal of one batch at a time.

All analyses were performed with R v.4.0.0, using version 9 of the MoBa quality assured dataset.

Results

Descriptive characteristics of the study population

The majority of women were in their 30s, completed college or more, did not report depression before or during pregnancy, did not report smoking during pregnancy, and had low dietary intakes of iodine and selenium (Table 1).

DPHP (96%>LOD), DNBP (94%>LOD), and BBOEP (51%>LOD) were detected in more than half of the urine samples (Table 2). The DPHP concentrations exceeded the LOQ in most cases (93%), while only 18% of the detectable BBOEP concentrations were above LOQ. The correlations across OPE metabolites and between OPE and phthalate metabolites were low ($i \widehat{<} 0.30$), although moderately high correlations were shown across some phthalate metabolites (($i \widehat{=} 0.64$); Supplementary Fig. 2)

Potential thyroid function disruption of OPE and phthalates from mixtures models

In co-pollutants adjusted GLM and BKMR models that both considered confounding by co-occurring metabolites and covariates, we observed an inverse association between ∑DiNP and TT3:TT4 ratio. Specifically, pregnant women with ∑DiNP concentration in the 75th percentile had a 0.37 ng/μg [−0.59, −0.15] lower TT3:TT4 ratio compared to those in the 25th percentile when using GLM; while the association was slightly larger using BKMR (exact: −0.48 ng/μg [−0.96, 0.003]; approx: −0.57 ng/μg [−0.90, −0.24]; PIP: 0.869; Table 3; Supplementary Fig. 3). In GLM models that separately considered TT3 or TT4 concentrations as dependent variables, higher ∑DiNP was associated with imprecise and small but diverging difference in thyroid hormones (TT3: −1.99 ng/dL [−4.52, 0.53]; TT4: 0.13 μg/dL [−0.01, 0.26]; Table 3). These directions of association were also found in BKMR models, however, the estimates were near-null (exact TT3: −0.16 ng/dL [−1.74, 1.41]; exact TT4: 0.01 μg/dL [−0.08, 0.09]; Table 3) and PIP were low (TT3: 0.009; TT4:

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0.010; Supplementary Fig. 3). Similar trends, although smaller and more imprecise, were observed for MEP and MnBP in GLM models, which were attenuated to near-null in BKMR. A different pattern of association was observed for MBzP using GLM, where imprecise and small positive associations were observed with individual thyroid hormone biomarkers but the associations with TT3:TT4 ratio were near null (Table 3). In BKMR, we observed no notable relationships with any other phthalate metabolites and thyroid function biomarkers (Table 3).

Among the OPE metabolites, we observed that DPHP showed similar patterns of associations across thyroid function biomarkers as DiNP in GLM, although the directions of association were inverse. Specifically, pregnant women with DPHP concentration in the 75th percentile had a 0.34 ng/μg [0.08, 0.60] higher TT3:TT4 ratio as compared to those in the 25th percentile; while imprecise and small but diverging differences were observed with the individual thyroid hormones (TT3: 1.32 ng/dL [−1.68, 4.32]; TT4: - 0.14 μg/dL [−0.30, 0.02]; Table 3). However, all associations were attenuated to near-null with BKMR (DPHP and TT3:TT4 ratio: exact: 0.06 ng/μg [−0.27, 0.39]; approx: 0.32 ng/μg [0.04, 0.61]; PIP: 0.135; Table 3; Supplementary Fig. 3). Similar but weaker and inverse associations were observed for DNBP when using GLM, which was also attenuated to near-null in BKMR (Table 3).

Sensitivity analysis

When the primary analyses were repeated inclusive of 49 non-euthyroid women (n=522), we found inferentially similar associations (Supplementary Table 2). We observed that the shape and magnitude of the dose-response function for some phthalate metabolites and TT3:TT4 ratio were somewhat sensitive to exposure transformation methods (Supplementary Fig. 3). The interpretation of results remained consistent when alternative definitions of mixtures were used (Supplementary Fig. 4) or in the investigation of batch-effect by successive removal of analytic batches (data not shown).

Discussion

We characterized the relationships between urinary OPE and phthalate metabolites and maternal thyroid function among pregnant, euthyroid women, using two approaches to account for confounding by co-exposure. Using co-pollutants adjusted GLM, we observed that higher DPHP during pregnancy was associated with small but diverging differences in individual thyroid hormones and a higher TT3:TT4 ratio; while inverse but stronger associations were observed for ∑DiNP. We also found slightly higher concentrations of thyroid hormones with higher MBzP. However, when BKMR was employed, most associations attenuated towards the null, except for ∑DiNP and TT3:TT4 ratio. Interestingly, despite the relatively low correlations between phthalate and OPE metabolites, we observed substantial attenuation of associations for the majority of metabolites when using BKMR.

Subtle but diverging differences in individual thyroid hormones and substantial differences in the TT3:TT4 ratio could be suggestive of a thyroid disruption mechanism that is distinct from hyper- or hypo-active stimulation of the thyroid gland. TT3, the active form of thyroid hormones, is produced at an approximate rate of 40 nmoles per day in euthyroid adults; of

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which only 5nmoles are directly secreted from the thyroid gland, and the remainder is derived from peripheral conversion of TT4 (Fish et al., 1987). The higher TT3:TT4 ratio observed with elevated DPHP in GLM could be a consequence of more peripheral conversion (Haddow et al., 2016; Knight et al., 2016), or increased production of triiodothyronine by the thyroid gland, which can be observed in iodine-deficient (de Escobar et al., 2007; Lazarus, 2000) or hyperthyroid individuals (Laurberg et al., 2007). Since over 70% of our study participants had low dietary iodine intake (<150 μg/day), preferential secretion of triiodothyronine and peripheral conversion of thyroxine to triiodothyronine are both plausible explanations for our results. Mechanisms underlying peripheral conversion have been reported in experimental settings, which involves the up-regulation of deiodinase type2 (*dio2*) gene expression or abundant delivery of thyroxine to target tissues (Hill et al., 2018; Liu et al., 2019). For example, up-regulated *dio2* has been observed in the thyroid gland, brain, and liver of adult female zebrafish after 14-day exposure to triphenyl phosphate (TPHP), which is one of the parent compounds for DPHP (Liu et al., 2019). DPHP and its parent compounds have also been reported to enhance the binding of T4 to transthyretin, a transport protein that delivers T4 to target cells (Hill et al., 2018). Further, there may exist multiple additional target points for OPEs and phthalates to affect the hypothalamic-pituitary-thyroid axis (Schmutzler et al., 2007), which regulates the thyroid gland through complex feedback loops (Dietrich et al., 2012).

To date, epidemiological investigation of DPHP and DNBP on thyroid disruption among pregnant women has only been conducted in one recent study in China (Yao et al., 2020). Among 360 pregnant women who participated in antenatal care in China (2016), they reported that an interquartile range higher concentrations of DPHP and DNBP were associated with elevated TSH. Although we observed similar directions of associations, the estimates were near-null and very imprecise in our study. Rather, we observed potential links between DPHP and TT3:TT4 ratio using the conventional statistical models, which has not been investigated in the previous study. Such heterogeneous findings could be due to differences in covariate measurements, study population, and analytic approach. Neither studies utilized the gold standard for measuring unbound thyroid hormones, however, we measured total thyroid hormones as well as alternatively estimated FT3i and FT4i using a previously validated measure against the gold-standard (Villanger et al., 2017). Also, the majority of our study participants provided biosamples in 16–17 GWs, which allowed us to investigate potential acute impacts of OPE exposures at approximately 17 GW on maternal thyroid function. The participants' GWs were much wider in the study by Yao (18%≤ 12 GW; 54% 13–28 GW; 29%>29 GW). Other differences include the criteria for euthyroid population construction and the measurement of iodide (dietary vs biomarker-based), which is an important predictor for thyroid function. Lastly, the statistical approach also varied between the two studies, where we applied mixtures methods to account for co-pollutant confounding.

Additional studies of non-pregnant populations examined sub-fertile men (Meeker et al., 2013; Meeker and Stapleton, 2010), office workers (Preston et al., 2017), rural community residents (Wang et al., 2019a), and electronic waste recycling workers (Gravel et al., 2020), of which only a subset included female participants (Gravel et al., 2020; Preston et al., 2017; Wang et al., 2019a). Most studies reported higher TT3 and some also reported imprecise but

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slightly higher free or total T4 (Gravel et al., 2020; Meeker et al., 2013; Meeker and Stapleton, 2010; Preston et al., 2017). We also observed imprecise but slightly higher TT3 in GLM, however, we additionally observed a slightly lower TT4 in GLM and no notable relationship in BKMR. Given the imprecise and modest estimates that were variably observed across studies, we cannot rule out an overall null association between thyroid function and DPHP. However, it should be noted that our study approach differed in potentially important ways from prior studies. We excluded non-euthyroid individuals since their measured thyroid may have been affected by medical interventions, we included a comprehensive set of thyroid function biomarkers including free indices and the TT3:TT4 ratio; and we accounted for confounding by phthalate exposures, another class of thyroid-active compounds. Differences in analytic methods may in part explain heterogeneity in results across studies, together with the biological differences in the populations as attributed to biological sex and pregnancy. Since pregnancy induces changes to thyroid physiology (Glinoer et al., 1990; Moleti et al., 2014), it is possible that OPE's impact on thyroid function is different in pregnant populations as compared to non-pregnant populations.

Our study is unique in that we applied mixtures perspective to investigate two families of rapidly metabolized, thyroid-active chemicals on thyroid homeostasis measured at 17 weeks of pregnancy. Further, the application of BKMR was able to reduce the dimension of correlated exposures and identify the major drivers of any associations. We also observed potential thyroid disruption by specifically ∑DiNP and MBzP using BKMR and/or GLM, which is in line with our previous investigation of phthalates that was conducted using a larger sub-population within MoBa (Villanger et al., 2020). In the previous study, TT3 was positively associated with a latent factor dominated by DEHP and DINP while negative associations were observed with a latent factor dominated by MiBP, MnBP, and MBzP. The associations observed for MBzP imply overactive thyroid function and are also consistent with experimental evidence of thyroid hyperfunction (Breous et al., 2005). It is possible that associations observed for DiNP could be attributable to their T3 antagonist activities resulting from competitively binding to the thyroid receptor (Ghisari and Bonefeld-Jorgensen, 2009); however, we caution that these families of toxicants have short half-lives, and toxicological and epidemiological research on DiNP remain sparse.

Several other studies have also investigated the relationship between phthalate exposure and thyroid function during pregnancy, however, the results remain inconclusive (Cathey et al., 2019; Huang et al., 2007b; Huang et al., 2016; Johns et al., 2016; Johns et al., 2015; Romano et al., 2018). Notable differences in thyroxine or TSH had been reported in relation to MEP, MBP, or MCPP, although the influential metabolite was not always consistent across studies. This is in contrast to our study, where we did not observe notable differences in TSH; rather imbalance between TT3 and TT4 was observed in relation to ∑DiNP in both GLM and BKMR while elevated TT3 and TT4 were observed with higher MBzP in GLM. Similar to our study, MBzP was positively associated with TT4 in serum in studies in Puerto Rico (Cathey et al., 2019; Johns et al., 2015), Boston (Johns et al., 2016), Cincinnati (Romano et al., 2018), and Taiwan (Huang et al., 2007b), but not in a study in Taiwan where MBzP was mostly non-detectable (Huang et al., 2016). The relationship was particularly strong in cross-sectional investigations using urine collected at 16–20 GW (Johns et al., 2016; Johns

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et al., 2015; Romano et al., 2018), which is in line with our findings and suggests that the strength of associations may be specific to GW.

Our study has several strengths. We examined the impact of OPE exposure on thyroid function in a vulnerable population with limited research, specifically pregnant women, whose affected thyroid function can influence not only maternal health but also fetal development (Allan et al., 2000; Andersen et al., 2014; Chan and Kilby, 2000; Gilbert et al., 2012; Karakosta et al., 2012; Päkkilä et al., 2014; Stagnaro-Green et al., 2011). By nesting our study within a large pre-existing pregnancy cohort, MoBa, we were able to take advantage of important determinants of thyroid health, including validated measures of habitual iodine intake, and conduct analyses that were limited to euthyroid individuals. The MoBa participants also had various thyroid function biomarkers that were previously validated for pregnant women (Villanger et al., 2017), which enabled us to rigorously characterize the relationship between gestational thyroid function and OPE metabolites. We included OPE metabolites that have not been previously investigated in epidemiological settings, despite their ubiquity, and flexibly modeled the exposure-response relationships utilizing BKMR, which allows for non-linear associations and utilizes variable selection to accommodate correlated exposures. Although phthalates are recognized as an independent risk factor for thyroid health and may share the exposure pathway with OPEs due to their similar usage as plasticizers, they have not been considered as confounders in previous investigations. Lastly, this is the largest study of its kind and is the first to be conducted in a European population, spanning an earlier period of years (2003–2007) compared to most previous studies (Gravel et al., 2020; Preston et al., 2017; Wang et al., 2019a; Yao et al., 2020), which allowed us to examine the health impact of OPEs exposure in low-exposure settings.

Our study also had some limitations. First, DPHP lacks specificity as a biomarker of OPE exposure since it aggregates exposures to multiple parent OPEs, including resorcinol bis-diphenyl phosphate (Ballesteros-Gomez et al., 2015), ethylhexyl diphenyl phosphate (Van den Eede et al., 2016), and TPHP (Su et al., 2015; Van den Eede et al., 2016). If only a subset of DPHP parent compounds exhibits thyroid disrupting properties, the associations estimated with DPHP may not accurately reflect that of the thyroid active compound. However, both DPHP as well as TPHP, have been reported to exhibit thyroid-disrupting properties in vitro (Hill et al., 2018), in which case using DPHP as an integrated biomarker can be helpful to identify relevant associations. A consequence of OPE exposure on thyroid function would be noteworthy because maternal thyroid function is particularly important in the first trimester when the fetus is entirely reliant on maternal supply (Burrow et al., 1994). Failure to maintain normal thyroid function can affect fetal brain development and increase the risk of pregnancy complications (Allan et al., 2000; Andersen et al., 2014; Berbel et al., 2009; Chan and Kilby, 2000; Gilbert et al., 2012; Karakosta et al., 2012; Päkkilä et al., 2014; Stagnaro-Green et al., 2011). Another limitation is that MoBa only collected one urine and blood sample during pregnancy, at the same visit which occurred in mid-pregnancy. Since thyroid physiology is highly variable throughout pregnancy, we are unable to identify potential thyroid-disruption at different periods of pregnancy (Glinoer et al., 1990; Moleti et al., 2014) or lagged-effects of exposure. In addition, phthalates and OPEs exhibit low to moderate reliability over months to a year due to their short half-lives (Carignan et al., 2017;

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Hoffman et al., 2014; Ingle et al., 2019; Meeker et al., 2013; Preston et al., 2017; Romano et al., 2017), which limits the extent of generalizing our results beyond the 17-week gestational window. However, we have a narrow range of gestational weeks at biosample measurement and the variability of OPE and phthalate metabolites are relatively stable over several hours to days (Carignan et al., 2017; Cequier et al., 2015; Hoffman et al., 2014; Wang et al., 2019b). Further, both the exposure and outcome biomarkers have short half-lives. Therefore, the co-incident measurements of exposure and outcome may yet be relevant to the investigation of acute thyroid function disruption of OPE and phthalate exposures during mid-gestation exposure Dietary measures were obtained from a food frequency questionnaire that was collected at approximately 22 weeks' gestation, which asked women to reflect back on diet over the course of pregnancy. While dietary intake has been shown to be relatively stable over the course of pregnancy (Crozier et al., 2009; Cuco et al., 2006), we cannot exclude the possibility of some misclassification as a result of dietary recall. Lastly, we did not adjust for PBDEs, another family of thyroid-active chemicals. Although PBDEs have also been detected in MoBa pregnant women (Caspersen et al., 2016; Haug et al., 2018), the concentrations are at least an order of magnitude lower than that in the United States (Buttke et al., 2013) and previous studies of PBDEs in Norway did not find associations with neonatal thyroid function (Eggesbo et al., 2011) nor ADHD (Lenters et al., 2019). Therefore, it is possible that PBDE exposure in this study population may not exceed the threshold to exhibit adverse health effects.

Conclusion

In this cross-sectional investigation, exposure to ∑DiNP in mid-pregnancy was associated with imbalances between T3 and T4. Similar but opposite directions of associations were observed for DPHP, although the estimates and the level of uncertainty varied by statistical models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- OPEs, phthalates, and thyroid function during mid-gestation were cross-sectionally investigated
- Potential imbalance between total triiodothyronine (TT3) and total thyroxine (TT4) was observed
- In general linear regression, DPHP and DINP were associated with TT3:TT4 ratio
- In BKMR, a lower TT3:TT4 ratio was observed with higher DINP

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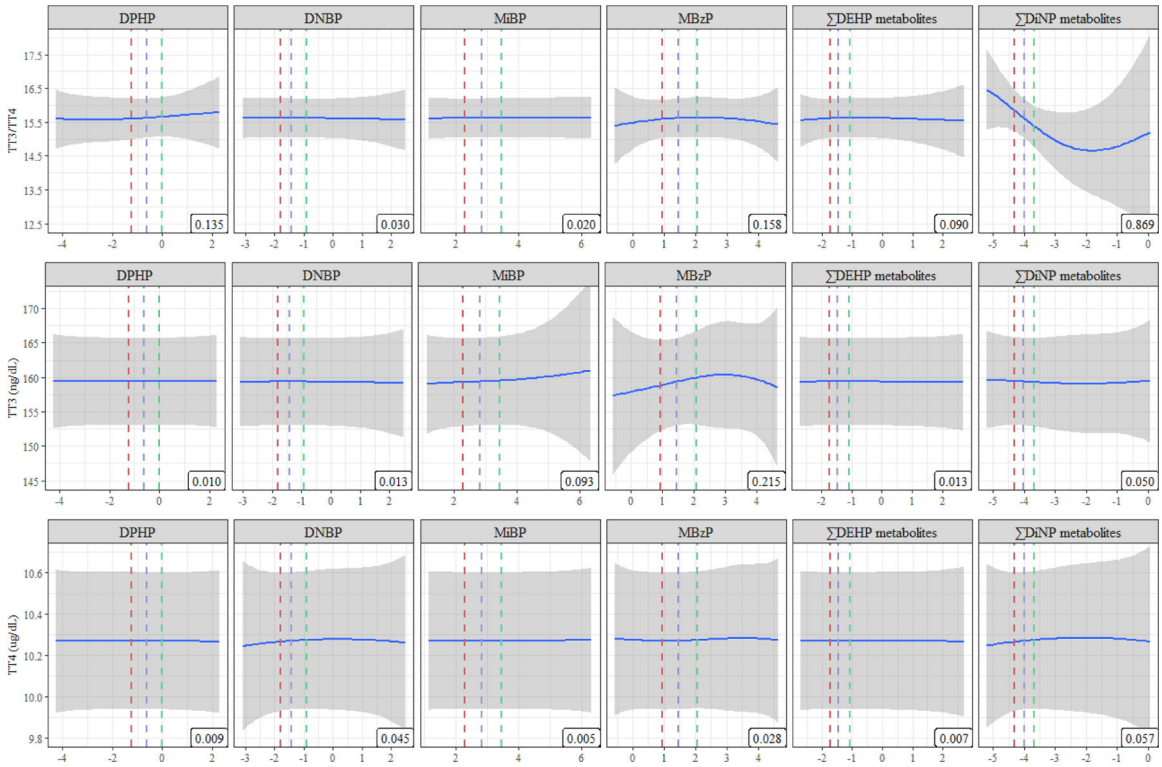

Figure 1.

Relationships between select organophosphate ester and phthalate metabolites and thyroid function biomarkers during mid-gestation using Bayesian Kernel Machine Regression.

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Table 1

Descriptive characteristics of the euthyroid study population (N=473).

Characteristic	Category	N (%)
Maternal age	<20	3(1%)
	20–29	176(37 %)
	30–39	285 (60 %)
	40≤	9(2%)
Maternal education	> College completed	148 (31 %)
	College completed	207 (44 %)
	< College completed	108 (23 %)
	Other education	10 (2 %)
Parity	Nulliparous	234 (49 %)
	Multiparous	239 (51%)
Depression before/during pregnancy	Yes	27 (6 %)
	No	446 (94%)
Dietary iodine intake	≥150 microgram/day	134 (28 %)
	<150 microgram/day	339 (72 %)
Dietary selenium intake	≥60 microgram/day	144 (40%)
	<60 microgram/day	329 (70%)
Smoking reported at 17 weeks	None during pregnancy	405 (86%)
	Any during pregnancy	68 (14 %)
Year of sample collection	2003	11 (2 %)
	2004	76 (16 %)
	2005	150 (32 %)
	2006	161 (34 %)
	2007	75 (16 %)
Month of sample collection	May - August	210 (44%)
	September – November	159 (34%)
	December – April	104 (22%)

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Table 2

Descriptive characteristics of the exposure and outcome biomarkers in the euthyroid study participants (N=473).

Class	Biomarker	GM±SD	Median (25th - 75th percentile)
Thyroid Function*	TSH (mU/L)	1.60 ± 1.6	1.63 (1.20 – 2.18)
	TT3 (ng/dL)	163.20 ± 1.2	163 (147 – 181)
	TT4 (μg/dL)	10.40 ± 1.1	10.36 (9.53 – 11.39)
	TT3:TT4 ratio (ng/μg)	15.86 ± 2.3	15.81 (14.17 – 17.34)
	FT3i (ng/dL)	162.17 ± 1.1	162 (147.07 – 178)
	FT4i (μg/dL)	10.33 ± 1.1	10.29 (9.42 – 11.34)
	T3 uptake (%)	27.82 ± 1.1	28 (27 – 29)
OPE (SG-standardized)**	DPHP (μg/L)	0.52 ± 2.8	0.55 (0.29 – 0.99)
	DNBP (μg/L)	0.28 ± 2.2	0.24 (0.17 – 0.40)
	BBOEP (μg/L)	0.09 ± 2.4	0.08 (<LOD - 0.15)
	BDCIPP (μg/L)	0.23 ± 2.8	<LOD (<LOD - 0.30)
Phthalates (SG- and batch-standardized)	MEP (μg/L)	102.45 ± 4.4	101.18 (32.97 – 305.21)
	MiBP (μg/L)	18.74 ± 2.5	17.07 (9.74 – 32.20)
	MnBP (μg/L)	18.67 ± 2.4	17.53 (11.79 – 30.98)
	MBzP (μg/L)	4.68 ± 2.5	4.26 (2.56 – 7.85)
	MEHP (μg/L)	11.27 ± 2.1	10.28 (7.07 – 16.61)
	MEHHP (μg/L)	14.26 ± 2.5	12.89 (8.52 – 21.13)
	MEOHP (μg/L)	9.60 ± 2.4	8.78 (5.71 – 14.37)
	MECPP (μg/L)	21.08 ± 2.0	18.61 (14.06 – 25.84)
	MMCHP (μg/L)	21.22 ± 1.9	18.33 (14.07 – 26.89)
	∑DEHP (mmol/L)	0.27 ± 2.0	0.24 (0.18 – 0.34)
	OH-MiNP (μg/L)	1.07 ± 2.1	0.95 (0.69 – 1.44)
	oxo-MiNP (μg/L)	1.24 ± 2.4	1.04 (0.70 – 1.78)
	cx-MiNP (μg/L)	3.69 ± 1.7	3.54 (2.46 – 4.77)
	∑DiNP (mmol/L)	0.02 ± 1.9	0.02 (0.01 – 0.03)

*Arithmetic mean and standard deviation presented instead of GM ± SD.

**DPHP LOD: 0.03 (97%>LOD); DNBP LOD: 0.07 (94%>OD); BBOEP LOD: 0.05 (52%>LOD); BDCIPP LOD: 0.17 (21%>LOD).

Notes: only OPE metabolites were measured below LOD for some participants, and therefore was substituted with LOD/√2.

Abbreviations: triiodothyronine, T3; thyroxine, T4; Thyroid stimulating hormone, TSH; Diphenyl phosphate, DPHP; Di-n-butyl phosphate, DnBP; Bis(2-butoxyethyl) hydrogen phosphate, BBOEP; Bis(1,3-dichloro-2-propyl) phosphate, BDCIPP; specific gravity, SG; geometric mean, GM; geometric standard deviation, SD; monoethyl phthalate, MEP; mono-iso-butyl phthalate, MiBP; mono-n-butyl phthalate, MnBP; monobenzyl phthalate, MBzP; molar sum of di(2-ethylhexyl)phthalate metabolites, ∑DEHP; molar sum of di-iso-nonyl phthalate metabolites, ∑DiNP

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Table 3

Absolute difference in thyroid hormones associated with a difference in log-transformed concentration of each individual metabolite from the 25th to 75th percentile in euthyroid pregnant women in MoBa 2003–2008 (N=473), while keeping adjustment factors constant*.

Model	Organophosphate ester metabolites				Phthalate metabolites			
	DPHP	DNBP	MEP	MiBP	MnBP	MBzP	∑DEHP	∑DiNP
TT3/TT4 (ng/μg)								
GLM	0.34 (0.08, 0.60)	−0.21 (−0.44, 0.02)	0.15 (−0.16, 0.47)	0.15 (−0.18, 0.48)	0.15 (−0.14, 0.44)	−0.08 (−0.40, 0.25)	0.04 (−0.17, 0.26)	−0.37 (−0.59, −0.15)
BKMR (exact)	0.06 (−0.27, 0.39)	−0.01 (−0.09, 0.08)	0.0001 (−0.01, 0.01)	0.01 (−0.11, 0.12)	0.002 (−0.06, 0.06)	0.05 (−0.21, 0.31)	0.01 (−0.11, 0.13)	−0.48 (−0.96, 0.003)
BKMR (approx)	0.32 (0.04, 0.61)	−0.16 (−0.39, 0.07)	0.01 (−0.08, 0.11)	0.16 (−0.13, 0.45)	0.07 (−0.13, 0.28)	0.02 (−0.32, 0.35)	0.01 (−0.23, 0.26)	−0.57 (−0.90, −0.24)
TT3 (ng/dL)								
GLM	1.32 (−1.68, 4.32)	−0.84 (−3.44, 1.76)	0.69 (−2.88, 4.26)	1.63 (−2.16, 5.43)	0.96 (−2.38, 4.29)	2.43 (−1.28, 6.14)	−0.47 (−2.94, 2.01)	−1.99 (−4.52, 0.53)
BKMR (exact)	0.02 (−0.62, 0.67)	−0.002 (−0.36, 0.35)	0.0005 (−0.09, 0.09)	0.22 (−1.64, 2.08)	0.05 (−0.85, 0.95)	1.12 (−3.52, 5.77)	0.003 (−0.35, 0.35)	−0.16 (−1.74, 1.41)
BKMR (approx)	0.71 (−1.80, 3.22)	−0.49 (−2.64, 1.66)	0.06 (−1.26, 1.38)	1.91 (−1.86, 5.69)	0.44 (−2.32, 3.20)	2.48 (−1.32, 6.28)	−0.39 (−2.22, 1.45)	−1.36 (−3.72, 0.99)
TT4 (μg/dL)								
GLM	−0.14 (−0.30, 0.02)	0.11 (−0.03, 0.25)	−0.07 (−0.26, 0.12)	0.02 (−0.18, 0.23)	−0.03 (−0.21, 0.15)	0.18 (−0.01, 0.38)	−0.07 (−0.20, 0.06)	0.13 (−0.01, 0.26)
BKMR (exact)	−0.001 (−0.03, 0.03)	0.01 (−0.07, 0.09)	−0.0001 (−0.01, 0.01)	−0.0001 (−0.02, 0.02)	−0.00003 (−0.01, 0.01)	0.005 (−0.06, 0.07)	0.0001 (−0.01, 0.01)	0.01 (−0.08, 0.09)
BKMR (approx)	−0.11 (−0.25, 0.03)	0.10 (−0.03, 0.24)	−0.03 (−0.16, 0.09)	0.005 (−0.13, 0.14)	−0.01 (−0.10, 0.08)	0.14 (−0.03, 0.31)	−0.03 (−0.12, 0.06)	0.11 (−0.02, 0.23)
TSH (mU/L)								
GLM	0.05 (−0.05, 0.14)	−0.02 (−0.10, 0.06)	−0.02 (−0.13, 0.10)	0.04 (−0.08, 0.16)	−0.02 (−0.12, 0.09)	−0.02 (−0.14, 0.10)	0.02 (−0.06, 0.10)	0.03 (−0.05, 0.12)
BKMR (exact)	0.001 (−0.02, 0.02)	-0.0002 (−0.02, 0.02)	0.00004 (−0.01, 0.01)	0.001 − 0.02, 0.03)	0.003 (−0.03, 0.04)	0.0002 (−0.02, 0.02)	0.002 (−0.02, 0.03)	−0.003 (−0.06, 0.05)
BKMR (approx)	0.03 (−0.05, 0.12)	−0.01 (−0.08, 0.06)	−0.01 (−0.10, 0.08)	0.02 (−0.07, 0.12)	0.001 (−0.10, 0.09)	−0.01 (−0.10, 0.08)	0.01 (−0.06, 0.08)	0.01 (−0.07, 0.10)

*All models included log-transformed concentrations of 2 OPE and 6 phthalate metabolites simultaneously while adjusting for year, dietary selenium, dietary iodine, parity, depression, season of urine collection, education, age, and smoking during pregnancy.

BKMR estimates were calculated by contrasting the posterior outcome levels at 25th and 75th exposure percentiles; GLM estimates were calculated by scaling the regression coefficients by interquartile range.

Abbreviations: triiodothyronine, T3; thyroxine, T4; Thyroid stimulating hormone, TSH; Diphenyl phosphate, DPHP; Di-n-butyl phosphate, DNBP; Bis(2-butoxyethyl) hydrogen phosphate, BBOEP; Bis(1,3-dichloro-2-propyl) phosphate, BDCIPP; specific gravity, SG; geometric mean, GM; geometric standard deviation, SD; monoethyl phthalate, MEP; mono-iso-butyl phthalate, MiBP; mono-n-butyl phthalate, MnBP; monobenzyl phthalate, MBzP; di(2-ethylhexyl)phthalate, ∑DEHP; di-iso-nonyl phthalate, ∑DINP; general linear model, GLM; Bayesian kernel machine regression, BKMR.

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