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Thyroxine-binding globulin, peripheral deiodinase activity, and thyroid autoantibody status in association of phthalates and phenolic compounds with thyroid hormones in adult population

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ABSTRACT

Exposure to consumer chemicals such as phthalates and phenolic compounds has been associated with thyroid hormone disruption in humans. However, information related to factors that may influence such associations, e.g., transport and activation of the hormones, and autoimmunity status, is limited. In the present study, we employed a subpopulation of adults (n = 1,254) who participated in the Korean National Environmental Health Survey (KoNEHS) 2015–2017, and associated urinary concentrations of major phthalate metabolites, bisphenol A (BPA), and parabens, with thyroid hormone-related measures, including free and total T3 and T4, TSH, thyroxine-binding globulin (TBG), calculated peripheral deiodinase (DIO) activity, and thyroid autoantibodies of thyroperoxidase (TPO) and thyroglobulin (Tg). Phthalate metabolites were negatively associated with total T4 and free T3, and positively associated with total T3. These observations could be explained by TBG levels and calculated peripheral DIO activity that were positively associated with phthalates exposure. In contrast, BPA was positively associated with total T4 and negatively associated with total T3, without any changes in TBG concentration. Serum TPO and Tg antibodies were not associated with urinary phthalate metabolites and BPA. However, thyroid autoantibody status appeared to modulate the association of some phthalates with thyroid hormones. For parabens, little to negligible association was observed. The results of our observation show potential underlying mechanisms of phthalates-induced thyroid hormone disruption, and suggests the importance of consideration of thyroid autoimmunity status in association studies for thyroid disrupting chemicals.

1. Introduction

While traditional risk factors for thyroid dysfunction are iodine deficiency and autoimmune thyroid disease, recent attention has been directed toward endocrine disrupting chemicals as an environmental factor for thyroid dysfunction (Wiersinga 2016). Many consumer chemicals, such as phthalates and phenolic compounds which are widely used and exposed to humans, have been suggested to disrupt thyroid hormones (Gore et al. 2015). Several large-scale epidemiologic studies, including one recent *meta*-analysis have reported the association between the urinary concentrations of phthalate metabolites and blood thyroid hormone levels (Huang et al. 2017; Kim et al. 2019; Meeker and Ferguson 2011; Park et al. 2017). Bisphenol A (BPA) has been also reported to be associated with thyroid hormones in several epidemiologic studies (Meeker and Ferguson 2011; Park et al. 2017; Sriphrapradang et al. 2013). While studies are relatively limited, parabens have been reported to be associated with thyroid hormones (Koeppe et al. 2013). However, observational studies on human populations showed often inconsistent directions of association; the evidence is lacking and further studies on large population are needed.

Environmental chemicals can disrupt the hypothalamic-pituitary-thyroid (HPT) axis and thyroid hormone action through several

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mechanisms (Gore et al. 2015). Thyroid hormone is synthesized in the thyroid gland, carried by binding proteins such as thyroxine-binding globulin (TBG) and transthyretin (TTR) in the blood and is converted to active (T3) or inactive (rT3 or T2) form by deiodinase (DIO) in the peripheral tissues. Any steps among the above could be affected by chemical exposures. Previous experimental studies involving cell lines or animals have suggested several mechanisms of chemical-induced thyroid disruption. However, similar evidences in human populations are not readily available, probably because of the observational nature of epidemiological studies and difficulties of measurement.

In the present study, we measured thyroid autoantibodies and TBG, calculated DIO activity, in order to understand potential mechanisms that may help interpret the association reported between chemical exposure and thyroid measures. Thyroid autoantibodies including thyroperoxidase (TPO) antibody and thyroglobulin (Tg) antibody are related to hypothyroidism and are found in the autoimmune thyroid disease such as Hashimoto thyroiditis. TBG is a determinant of total form of thyroid hormones (i.e. total T4 and total T3). DIO activity, estimated from free T4 and total T3 approximates deiodinase ability to convert from T4 to T3 in peripheral tissues. With these measurements, the results of this study will help better understand the effects of thyroid disrupting chemicals, and generates hypothesis on potential mechanisms of thyroid disruption among humans.

2. Material and methods

2.1. Study population

The study population was a subgroup of the adults who participated in the Korean National Environmental Health Survey (KoNEHS) of 2015–2017. KoNEHS is an ongoing cross-sectional study designed to estimate the exposure levels of environmental chemicals and their associated factors. Details about the study design were described previously (Choi et al. 2017; Park et al. 2016). Total number of the adult subjects (aged 19 years or older) who participated in KoNEHS 2015–2017 was 3,787, but their thyroid hormone levels had not been measured during the survey. In the present study, the adult subjects were classified by sex and age group (19~ < 40, 20~ < 50, 50~ < 60, and ≥ 60), a total of 1,295 subjects were randomly chosen for each combination of sex and age strata, according to the distribution reported from the population census of Korea 2015 (Statistics Korea). Thyroid hormones and related factors were measured from the archived serum samples of this subpopulation (n = 1,295). After exclusion of the subjects who took thyroid medication (n = 41), the data obtained from 1,254 subjects were included in statistical analysis. The original study protocol was approved by the Research Ethics Committee of the National Institute of Environmental Research, Korea (NIER-2015-BR-006–01), and the present study design was approved by Seoul National University (IRB No. E1911/002–008).

2.2. Urinary concentrations of phthalate metabolites, bisphenol A, and parabens

The spot urine samples were collected and stored at − 20 °C. Urinary concentrations of phthalate metabolites, BPA, and parabens were measured using ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) with electrospray ionization (ESI) negative mode. Details of the extraction and analytical procedures are described elsewhere (NIER 2015; Silva et al. 2003). Phthalate metabolites included metabolites of diethylhexyl phthalate (DEHP) (mono-[2-ethyl-5-hydroxyhexyl] phthalate [MEHHP], mono-[2-ethyl-5-oxohexyl] phthalate [MEOHP], mono-[2-ethyl-5-carboxypentayl] phthalate [MECPP]), a metabolite of di-isononyl phthalate (DNP) (monocarboxyoctyl phthalate [MCOP]), a metabolite of di-isodecyl phthalate (DDP) (monocarboxy-isononyl phthalate [MCNP]), a metabolite of di-n-butyl phthalate (DBP) (mono[3-carboxylpropyl] phthalate [MCPP]), and metabolites of benzylbutylphthalate (BzBP) (mono-benzyl phthalate [MBzP] and mono-n-butyl phthalate [MnBP]). The limit of detections (LODs) for MEHHP, MEOHP, MECPP, MCOP, MCNP, MCPP, MBzP, and MnBP were determined at 0.056, 0.048, 0.141, 0.048, 0.139, 0.078, 0.066, 0.040, and 0.066 μg/L, respectively. LOD of BPA was 0.08 μg/L. LODs for methyl paraben (MeP), ethyl paraben (EtP), and propyl paraben (PrP) were 0.108, 0.107, and 0.082 μg/L, respectively.

2.3. Serum thyroid measures

Serum free T4 and total T4 concentrations were measured using radioimunoassay (RIA) with a RIAKEY Free T4 RIA Tube (Shin Jin Medics Inc., Goyang, Republic of Korea) and a OCPG07-T4 kit (Cisbio Bioassays, Codolet, France), respectively. The reference range of free T4 was 0.7–1.8 ng/dL. Serum free T3 and total T3 concentrations were measured using RIA with a BRAHMS FT3 RIA kit (Thermo Scientific, Hennigsdorf, Germany) and a T3 RIA kit (Institute of Isotopes Ltd., Budapest, Hungary), respectively. Serum thyroid-stimulating hormone (TSH) was measured using immunoradiometric assay (Shin Jin Medics Inc.). The normal reference range of TSH was defined at 0.3 – 5.0 μIU/mL, which was derived from the range of the measurements within which 95% of the general adult subjects of Korea (n = 200) fall (Korean Society for Laboratory Medicine 2014). TPO antibody, Tg antibody, and TBG were measured using BRAHMS RIA kits (Thermo Scientific). For TPO antibody and Tg antibody, values ≥ 60 U/mL were considered positive. To evaluate the thyroid homeostasis, peripheral DIO activity were calculated using the following formula (Dietrich et al. 2016): $\frac{8\times10^{-6}\times(5\times10^{-7}+\text{free T4})\times\text{total T3}}{0.026\times\text{free T4}}$ (reference range: 20–60 nmol/s).

2.4. Statistical analysis

Serum thyroid measures were compared by age, sex, BMI, smoking status, and income, using Kruskal-Wallis test. Before analysis, urinary concentrations of phthalate metabolites, BPA, and parabens were corrected by urine specific gravity for urine dilution, and results below the LOD were substituted with a value of the LOD divided by the square root of 2. Because urinary concentrations of phthalate metabolites, BPA, and parabens showed the skewed distribution, those were ln-transformed to approximate a normal distribution. Linear regression analysis was performed to assess the association between the urinary analytes and serum thyroid measures. Logistic regression analysis was conducted to determine the association between phthalate metabolites/BPA/parabens grouped in quartiles and the presence of thyroid autoantibodies. In the multiple regression analysis, covariates of age, sex (male or female), body mass index (BMI), smoking status (never, former, or current), and income (very low, low, mid-low, mid-high, high, or very high) were included. For income variable, missing values (n = 8) were observed and hence were excluded in the regression model. As one chemical was considered at a time in the regression analysis, this model was termed as single-chemical model. To evaluate the effect of exposure to multiple chemicals, multiple-chemical models were developed. For this purpose, firstly, factor analysis was performed using PROC FACTOR (SAS version 9.4) to reduce the number of variables. Subsequently, four components were chosen with the MINEIGEN criterion, i.e., eigenvalues are greater than one. Factor loadings greater than 0.4 were considered as high. These four factors were then included in the further linear regression analysis after varimax rotation, along with all the other covariates. All statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

3. Results

The demographic characteristics and serum thyroid measures of the study population was presented in Table 1. The study population was

Table 1
Demographic characteristics and serum thyroid measures of study population (n = 1,254).

Characteristic	N (%)	Free T4 (ng/dL)	Total T4 (μg/dL)	Free T3 (ng/dL)	Total T3 (ng/dL)	TSH (μlU/mL)	TBG (mg/L)	DIO (nmol/s)
Total	1,254	1.31 (1.22, 1.41)	8.13 (6.98, 9.62)	0.32 (0.28, 0.37)	143 (127, 164)	2.24 (1.63, 3.24)	16.91 (14.93, 19.16)	20.10 (17.54, 23.35)
Age (years)								
19–29	183 (14.6)	1.36 (1.27, 1.45)*	8.53 (7.44, 9.84) **	0.34 (0.29, 0.40) ***	151 (134, 171) ***	1.83 (1.30, 2.70) ***	16.77 (15.05, 18.76) ***	20.44 (17.86, 23.71)
30–39	269 (21.5)	1.32 (1.24, 1.42)	8.04 (6.94, 9.53)	0.32 (0.27, 0.37)	142 (125, 163)	2.13 (1.58, 3.09)	16.15 (13.97, 18.28)	19.79 (17.30, 22.80)
40–49	260 (20.7)	1.32 (1.22, 1.42)	8.28 (7.16, 9.78)	0.33 (0.28, 0.40)	146 (129, 167)	2.19 (1.57, 3.11)	17.02 (14.90, 19.36)	20.31 (17.86, 23.64)
50–59	240 (19.1)	1.30 (1.21, 1.38)	7.85 (6.82, 9.47)	0.31 (0.27, 0.36)	142 (126, 164)	2.53 (1.90, 3.59)	16.81 (14.86, 19.13)	20.13 (17.72, 23.31)
60–69	199 (15.9)	1.28 (1.19, 1.37)	8.18 (6.93, 9.86)	0.31 (0.27, 0.35)	138 (122, 158)	2.40 (1.90, 3.49)	17.52 (15.55, 19.93)	19.91 (17.00, 23.62)
≥70	103 (8.2)	1.26 (1.19, 1.38)	7.84 (6.55, 9.32)	0.29 (0.25, 0.34)	138 (124, 156)	2.62 (1.95, 4.00)	18.08 (16.11, 20.20)	20.11 (17.88, 23.11)
Sex								
Male	630 (50.2)	1.36 (1.27, 1.44) ***	8.20 (7.00, 9.79)	0.34 (0.30, 0.39) ***	147 (130, 168) ***	2.15 (1.56, 3.21)	16.11 (17.42, 23.20) ***	19.94 (14.22, 18.40)
Female	624 (49.8)	1.26 (1.19, 1.35)	8.06 (6.91, 9.40)	0.29 (0.26, 0.35)	139 (123, 159)	2.35 (1.68, 3.32)	17.76 (17.61, 23.46)	20.26 (15.71, 19.77)
BMI (kg/m^2)								
< 18.5	36 (2.9)	1.34 (1.17, 1.47)	8.43 (6.83, 9.56)	0.31 (0.26, 0.38)	149 (129, 167)	1.85 (1.55, 2.77)	17.42 (15.11, 19.50)	20.51 (18.55, 22.31)
18.5–23	439 (37.9)	1.31 (1.22, 1.40)	8.13 (6.89, 9.70)	0.31 (0.28, 0.36)	142 (126, 161)	2.29 (1.53, 3.29)	16.83 (14.91, 18.76)	19.96 (17.25, 23.27)
23–25	317 (63.2)	1.32 (1.22, 1.41)	7.91 (6.86, 9.43)	0.32 (0.28, 0.38)	144 (127, 166)	2.13 (1.65, 3.15)	16.73 (15.03, 19.29)	19.99 (17.96, 23.12)
≥25	462 (36.8)	1.30 (1.21, 1.41)	8.26 (7.11, 9.71)	0.32 (0.28, 0.37)	143 (127, 165)	2.32 (1.71, 3.37)	17.09 (14.86, 19.51)	20.28 (17.49, 23.61)
Smoking status								
Never	763 (60.8)	1.28 (1.20, 1.38) ***	8.10 (6.97, 9.51)	0.30 (0.27, 0.36) ***	141 (125, 161) **	2.37 (1.70, 3.36) *	17.37 (15.39, 19.38) ***	20.21 (17.57, 23.40)
Former	235 (18.7)	1.34 (1.23, 1.42)	7.97 (6.64, 9.70)	0.33 (0.28, 0.38)	144 (129, 165)	2.31 (1.79, 3.35)	16.34 (14.43, 18.61)	19.92 (17.33, 23.57)
Current	256 (20.4)	1.36 (1.29, 1.45)	8.35 (7.20, 9.79)	0.35 (0.31, 0.40)	148 (130, 169)	1.87 (1.42, 2.74)	16.14 (14.15, 18.40)	19.94 (17.49, 22.81)
Income (1,000 KRW/month)								
Very Low (< 1,000)	147 (11.7)	1.28 (1.19, 1.39)	8.09 (6.87, 9.76)	0.30 (0.26, 0.34) *	137 (122, 158) *	2.28 (1.74, 3.49)	17.30 (15.55, 19.24) **	19.71 (17.51, 23.11)
Low (< 2,000)	203 (16.2)	1.29 (1.20, 1.41)	7.90 (6.76, 9.33)	0.31 (0.28, 0.36)	144 (126, 167)	2.23 (1.65, 3.31)	17.62 (15.33, 19.90)	20.47 (17.17, 24.30)
Mid-low (< 3,000)	267 (21.3)	1.30 (1.20, 1.39)	8.20 (7.00, 9.48)	0.32 (0.28, 0.38)	144 (128, 165)	2.43 (1.66, 3.45)	17.04 (15.09, 19.16)	20.47 (17.74, 23.01)
Mid-high (< 5,000)	383 (30.5)	1.32 (1.22, 1.41)	8.09 (6.93, 9.60)	0.31 (0.27, 0.37)	144 (128, 164)	2.24 (1.64, 3.24)	16.62 (14.66, 18.97)	20.06 (17.80, 23.28)
High (< 7,000)	160 (12.8)	1.33 (1.26, 1.42)	8.23 (7.21, 9.69)	0.32 (0.29, 0.38)	145 (127, 171)	2.13 (1.57, 2.98)	16.71 (14.87, 18.95)	20.02 (17.06, 23.52)
Very high (≥7,000)	86 (6.9)	1.35 (1.23, 1.45)	8.44 (7.26, 10.25)	0.33 (0.28, 0.38)	142 (123, 162)	2.02 (1.47, 3.20)	15.99 (13.88, 18.67)	19.33 (17.20, 22.66)
Not answered	8 (0.6)	1.28 (1.18, 1.42)	9.21 (8.24, 10.19)	0.34 (0.31, 0.38)	126 (102,161)	1.50 (1.02, 2.85)	16.84 (13.57, 21.24)	18.04 (13.30, 21.98)

Data presented as geometric mean (interquartile range).
TSH, thyroid-stimulating hormone; TBG, thyroxine-binding globulin; DIO, calculated deiodinase activity; BMI, body mass index; KRW, Korean won (*ca* 1200 KRW is equivalent to 1 USD).
* $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.

Table 2
Regression coefficients and (95% confidence intervals) for serum thyroid measures according to ln-transformed urinary concentrations of phthalate metabolites, BPA, and parabens.

	Free T4 β (95% CI)	Total T4 β (95% CI)	Free T3 β (95% CI)	Total T3 β (95% CI)	TSH β (95% CI)	TBG β (95% CI)	DIO β (95% CI)
MEHHP	−0.006 (-0.013, 0.002)	−0.011 (-0.028, 0.006)	**−0.020 (-0.035, −0.004)*****	**0.023 (0.012, 0.035)*****	0.007 (-0.038, 0.052)	**0.017 (0.004, 0.031)** *	**0.029 (0.015, 0.043)** ***
MEOHP	−0.005 (-0.012, 0.002)	−0.013 (-0.028, 0.003)	**−0.029 (-0.044, 0.015)*****	**0.036 (0.026, 0.047)*****	−0.005 (-0.046, 0.036)	**0.022 (0.010, 0.035)** **	**0.041 (0.028, 0.053)*****
MECPP	−0.002 (-0.010, 0.006)	**−0.031 (-0.048, −0.013)****	**−0.025 (-0.042, −0.008)****	**0.057 (0.046, 0.069)*****	0.008 (-0.039, 0.056)	**0.023 (0.008, 0.037)** **	**0.059 (0.045, 0.073)*****
MCOP	0.001 (-0.007, 0.009)	**−0.028 (-0.046, −0.010)****	**−0.020 (-0.037, −0.003)***	**0.058 (0.045, 0.070)*****	0.026 (-0.022, 0.075)	0.014 (-0.0003, 0.029)	**0.056 (0.042, 0.071)*****
MCNP	0.006 (-0.001, 0.014)	**−0.020 (-0.036, −0.003)***	**−0.023 (-0.039, −0.007)****	**0.065 (0.054, 0.076)*****	0.031 (-0.014, 0.075)	0.013 (-0.001, 0.026)	**0.059 (0.045, 0.072)*****
MCPP	0.009 (-0.00001, 0.017)	−0.010 (-0.029, 0.009)	−0.011 (-0.029, 0.007)	**0.069 (0.056, 0.082)*****	−0.029 (-0.081, 0.022)	0.012 (-0.004, 0.027)	**0.060 (0.045, 0.076)*****
MnBP	0.005 (-0.001, 0.010)	**0.015 (0.003, 0.026)** *	**0.011 (0.00001, 0.022)***	**0.013 (0.005, 0.021)****	−0.022 (-0.053, 0.010)	−0.005 (-0.014, 0.005)	0.008 (-0.001, 0.018)
MBzP	**−0.008 (-0.014, −0.002)****	**−0.018 (-0.031, −0.006)** *	**−0.023 (-0.035, −0.010)** ***	**0.023 (0.014, 0.032)*****	−0.001 (-0.036, 0.034)	**0.013 (0.002, 0.023)** *	**0.031 (0.020, 0.041)*****
BPA	0.001 (-0.005, 0.007)	**0.014 (0.002, 0.026)** *	0.006 (-0.006, 0.017)	**−0.012 (-0.020, −0.003)****	−0.021 (-0.055, 0.012)	−0.0001 (-0.010, 0.01)	**−0.013 (-0.023, −0.003)***
MeP	0.002 (-0.003, 0.006)	0.001 (-0.008, 0.010)	0.001 (-0.008, 0.010)	**0.008 (0.001, 0.014)** *	−0.019 (-0.044, 0.006)	**0.008 (0.0005, 0.016)***	0.006 (-0.001, 0.014)
EtP	0.0004 (-0.003, 0.004)	0.0005 (-0.007, 0.008)	0.003 (-0.004, 0.011)	0.005 (-0.0002, 0.010)	0.001 (-0.019, 0.022)	0.002 (-0.004, 0.009)	0.005 (-0.002, 0.011)
PrP	−0.003 (-0.005, 0.0004)	−0.001 (-0.007, 0.006)	−0.003 (-0.009, 0.003)	−0.0003 (-0.005, 0.004)	−0.011 (-0.028, 0.006)	**0.008 (0.003, 0.014)** **	0.002 (-0.003, 0.007)

Adjusted for age, sex, BMI, smoking, and income.
TSH, thyroid-stimulating hormone; TBG, thyroxine-binding globulin; DIO, calculated deiodinase activity.
* $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.

on average 47 ± 15 years old, with 624 (50%) of female, and mean BMI of 24.3 ± 3.5 kg/m^2. Most of the subjects had normal thyroid function, but 7.2% and 1.6% had higher and lower TSH than the reference range, respectively. Serum thyroid measures were different by age, sex, BMI, smoking status, and income (Table 1). Phthalate metabolites, BPA, and parabens were detected in most subjects (greater than 90%, Table S1). Because the distribution of phthalate metabolites/BPA/parabens was also different by age, sex, BMI, smoking status, and income (Table S1), these parameters were added as covariates in the association models developed for phthalate metabolites/BPA/parabens and serum thyroid measures.

Multivariable regression analysis showed negative associations between phthalates metabolites (MECPP, MCOP, MCNP, and MBzP) and total T4 (Table 2). Phthalates metabolites (MEHHP, MEOHP, MECPP, MCOP, MCNP, and MBzP) were also negatively associated with free T3. In contrast, all phthalate metabolites showed positive associations with total T3 (Table 2 and Table S2). Consistent with an increase of total T3, TBG and calculated peripheral DIO activity were positively associated with phthalate metabolites. Unlike most phthalate metabolites, MnBP and BPA showed positive associations with total T4 (β = 0.015, p = 0.012 for MnBP; β = 0.014, p = 0.026 for BPA), and BPA showed a negative association with total T3 (β = -0.012, p = 0.007 for BPA). Among parabens, only MeP showed a positive association with serum total T3 (β = 0.008, p = 0.016; Table 2). However, TSH was not associated with any chemicals (Table 2). Among the study population, 90 (7.2%) subjects were categorized as subclinical hypothyroidism, i.e., TSH higher than the normal range with normal free T4 level. No overt hypothyroidism was identified in the present population. None of the study chemicals showed significant association with increased risk of subclinical hypothyroidism (Table S3), potentially due to low statistical power attributed to the small number of the case.

TPO antibody and Tg antibody were positive in 9.6% and 5.6% of the study population, respectively, and 12.3% of the study population had TPO or Tg antibodies. Logistic regression analysis showed no association between the measured chemicals and thyroid autoantibodies (Table 3). When classified by the presence of thyroid autoantibodies, the associations between the urinary chemicals and serum thyroid measures such as free T3 and T4 were different by the autoantibody status (Table 4). While most phthalate metabolites did not show any significant associations with free T3 among those with thyroid autoantibodies, significant negative associations were observed among those without thyroid autoantibodies, except for MnBP. MEHHP showed negative association with free T4 (β = -0.025, p = 0.049) and positive association with TSH (β = 0.229, p = 0.015) only among the subjects with thyroid autoantibodies. The associations of phthalate metabolites observed with TBG were also different by the thyroid autoantibody status.

Since multiple chemicals are exposed simultaneously and their urinary concentrations were associated (Fig. S1), factor analysis was performed to identify major factors. Factor analysis showed that four factors explain 32%, 15%, 13%, and 9% of the variance, respectively, were chosen (Table S4). Factor 1 represented the exposure to metabolites of DEHP (MEHHP, MEOHP, MECPP), MnBP, and MBzP. Factor 2 represented the exposure to MCOP, MCNP and MCPP. Factor 3 represented the exposure to MeP, EtP and PrP, and Factor 4 represented the exposure to BPA. In further multi-factor regression analysis, Factor 1 was negatively associated with free T3 (β = -0.021, p = 0.004) and positively associated with total T3, TBG, and peripheral DIO activity (β = 0.024, p < 0.001 for total T3; β = 0.014, p = 0.018 for TBG; β = 0.029, p < 0.001 for DIO; Table 5). Factor 2 were negatively associated with total T4 (β = -0.017, p = 0.018) and positively associated with free T4, total T3 and peripheral DIO activity (β = 0.007, p = 0.049 For free T4, β = 0.058, p < 0.001 for total T3; β = 0.052, p < 0.001 for DIO). Factor 3 were positively associated with TBG (β = 0.018, p = 0.004). Factor 4 was negatively associated with peripheral DIO activity (β = -0.013, p = 0.032, and positively associated

Table 3
Odds ratios (95% confidence intervals) for thyroid autoantibodies according to quartiles of urinary concentrations of phthalate metabolites, BPA, and parabens.

		Positive TPO or Tg antibody OR (95% CI)	*p*-value
MEHHP	Q1	1 (Reference)	
	Q2	1.233 (0.743–2.045)	0.418
	Q3	0.773 (0.447–1.337)	0.358
	Q4	1.148 (0.689–1.915)	0.596
MEOHP	Q1	1 (Reference)	
	Q2	1.254 (0.748–2.104)	0.391
	Q3	1.049 (0.617–1.784)	0.859
	Q4	1.105 (0.650–1.878)	0.713
MECPP	Q1	1 (Reference)	
	Q2	0.950 (0.571–1.581)	0.843
	Q3	0.884 (0.528–1.481)	0.640
	Q4	1.011 (0.612–1.670)	0.966
MCOP	Q1	1 (Reference)	
	Q2	1.575 (0.953–2.603)	0.076
	Q3	1.268 (0.758–2.121)	0.366
	Q4	1.093 (0.647–1.848)	0.739
MCNP	Q1	1 (Reference)	
	Q2	0.774 (0.466–1.285)	0.321
	Q3	1.131 (0.692–1.850)	0.623
	Q4	0.819 (0.497–1.347)	0.431
MCPP	Q1	1 (Reference)	
	Q2	0.510 (0.301–0.866)	0.013
	Q3	0.665 (0.403–1.098)	0.111
	Q4	0.865 (0.538–1.392)	0.551
MnBP	Q1	1 (Reference)	
	Q2	1.289 (0.784–2.118)	0.317
	Q3	0.698 (0.403–1.206)	0.198
	Q4	1.254 (0.771–2.041)	0.362
MBzP	Q1	1 (Reference)	
	Q2	1.331 (0.795–2.229)	0.277
	Q3	1.377 (0.831–2.281)	0.214
	Q4	1.258 (0.744–2.127)	0.392
BPA	Q1	1 (Reference)	
	Q2	0.765 (0.477–1.228)	0.267
	Q3	0.632 (0.391–1.023)	0.062
	Q4	0.654 (0.398–1.073)	0.092
MeP	Q1	1 (Reference)	
	Q2	0.927 (0.533–1.612)	0.787
	Q3	1.364 (0.806–2.309)	0.247
	Q4	1.256 (0.726–2.174)	0.415
EtP	Q1	1 (Reference)	
	Q2	0.609 (0.361–1.029)	0.064
	Q3	0.711 (0.436–1.161)	0.173
	Q4	1.095 (0.693–1.731)	0.697
PrP	Q1	1 (Reference)	
	Q2	0.700 (0.395–1.243)	0.223
	Q3	1.155 (0.684–1.949)	0.589
	Q4	0.951 (0.556–1.626)	0.853

Adjusted for age, sex, BMI, smoking, and income.
TPO, thyroperoxidase; Tg, thyroglobulin.

with total T4 and free T3 (β = 0.025, p = 0.001 for total T4; β = 0.018, p = 0.010 for free T3).

4. Discussion

4.1. Thyroid disruption by phthalates, BPA and parabens

Phthalates, BPA, and parabens showed different patterns of association with thyroid-related measurements (Table 2). Significant negative associations of phthalate metabolites with free T3 and total T4 observed in the adult population are comparable to the previous epidemiologic observations that reported decreased thyroid hormones by this group of compounds in national biomonitoring programs of the US and Korea (Table 6) (Meeker and Ferguson 2011; Park et al. 2017). In adult populations of KoNEHS 2012–2014, several phthalate metabolites in urine showed negative associations with total T4 (Park et al. 2017). In the US adult population of the National Health and Nutrition Examination Survey (NHANES) 2007–2008, similar negative associations of urinary DEHP metabolites were observed with total T4 (Meeker and Ferguson 2011).

For all phthalate metabolites, significant and consistent positive associations were observed with total T3 (Table 6). While null or the other direction of associations have often been reported (Table 6) (Huang et al. 2017; Meeker and Ferguson 2011), in the US adolescent population of NHANES 2007–2008, Meeker and Fergusson reported that the DEHP metabolites in urine were positively associated with total T3 (Meeker and Ferguson 2011). Our observations confirm that at the current level of exposure, several phthalates are associated with decreasing free T3 levels in adult human population.

For BPA, a different pattern of association was observed. Urinary BPA concentration was positively associated with total T4 and negatively with total T3 and DIO activity in our study. This association were somewhat different from the previous studies (Kim and Park 2019). In US NHANES 2007–2008 (n = 1,346), BPA was negatively associated with total T4 (Table 6) (Meeker and Ferguson 2011). Similarly, in Thai male adults (n = 1,159), BPA was negatively associated with free T4 (Sriphrapradang et al., 2013). Those two studies show a similar trend with the results of free or total T4 from our study, however, in China, BPA was negatively associated with TSH and positively associated with free T3 (n = 3,394) (Wang et al. 2013). In the previous KoNEHS of 2012–2014 (n = 6,003), BPA was negatively associated with TSH (Park et al. 2017). These conflicted results warrant validation in other populations. For example, in the same US NHANES 2007–2008, the significance between BPA and total T4 disappeared when benzophenone-3 and MEHHP were included in the same regression model (Kim et al. 2017). In addition, it should be noted that none of these previous studies had considered peripheral DIO activity, TBG, or antibody status in the study design, and hence are difficult to directly compare with the results of the present study.

For parabens, the associations with thyroid measures were not evident in the current population (Table 6). The association of parabens on thyroid hormone was first reported in NHANES 2007–2008 of the US. Parabens (EtP and PrP) were reported to be negatively associated with free T3 and free T4, especially in women (Koeppe et al. 2013). In pregnant women, significant associations between parabens and thyroid measures were also observed (Aker et al. 2019; Aker et al. 2018; Berger et al. 2018). In the present study, however, the associations were observed only between MeP and total T3.

The results of the multiple-chemical models (Table 5), which included major factors identified from the factor analysis, are comparable to and support the observations from the single-chemical models (Table 2). The factor analysis showed that phthalate metabolites, i.e., Factor 1 and Factor 2, were associated with decreased free T3 or total T4, and increased total T3 and peripheral DIO activity, consistently with the results of the single-chemical model. Factor 3, which was highly loaded with parabens, was associated with increased TBG, consistently with the results of single-chemical models for MeP and PrP. Positive association of BPA with total T4 and negative association with peripheral DIO activity were also consistent in both single- and multiple-chemical models. Major factors that were identified from the factor analysis demonstrated that target chemicals could be classified based on the shared characteristics of exposure. The chemicals grouped in the same factor are also supported by significant correlations observed between the target chemicals: For example, the correlations among MECPP, MCNP, MCPP, and MCOP, and between MeP and PrP, were significant (Fig. S1).

4.2. Thyroid disruption mediated by TBG and DIO activity

Associations of urinary phthalate metabolites with increasing total T3 and decreasing free T3 may be in part explained by increasing TBG and enhanced DIO activity in peripheral tissues. TBG is the major

Table 4
Association of ln-transformed urinary phthalate metabolites, BPA, and parabens with serum thyroid measures by the presence of thyroid autoantibodies.

	Free T4		Total T4		Free T3		Total T3	
Thyroid autoantibody status	Negative β (95% CI)	Positive β (95% CI)	Negative β (95% CI)	Positive β (95% CI)	Negative β (95% CI)	Positive β (95% CI)	Negative β (95% CI)	Positive β (95% CI)
MEHHP	−0.003 (-0.011, 0.005)	**−0.025 (-0.049, −0.001)***	−0.009 (-0.027, 0.009)	−0.019 (-0.063, 0.025)	**−0.020 (-0.036, −0.003)** *	−0.033 (-0.076, 0.011)	**0.020 (0.008, 0.032)** ***	0.020 (-0.015, 0.056)
MEOHP	−0.004 (-0.011, 0.004)	−0.010 (-0.034, 0.014)	−0.010 (-0.026, 0.006)	−0.031 (-0.073, 0.011)	**−0.029 (-0.045, −0.014)** ***	−0.030 (-0.072, 0.012)	**0.033 (0.022, 0.044)** ***	**0.048 (0.015, 0.082)** **
MECPP	−0.001 (-0.01, 0.007)	−0.005 (-0.029, 0.018)	**−0.029 (-0.048, −0.01)** **	−0.039 (-0.081, 0.002)	**−0.028 (-0.046, −0.009)** **	−0.014 (-0.056, 0.028)	**0.055 (0.042, 0.067)** ***	**0.061 (0.028, 0.094)** ***
MCOP	0.002 (-0.007, 0.01)	−0.003 (-0.032, 0.025)	**−0.025 (-0.044, −0.006)** *	**−0.056 (-0.107, −0.006)** *	−0.018 (-0.036, 0.000)	−0.032 (-0.082, 0.019)	**0.057 (0.044, 0.07)** ***	**0.049 (0.008, 0.090)** *
MCNP	0.005 (-0.003, 0.013)	0.021 (-0.007, 0.048)	**−0.023 (-0.04, 0.005)** *	0.012 (-0.038, 0.062)	**−0.028 (-0.044, −0.011)** **	0.029 (-0.021, 0.078)	**0.062 (0.05, 0.073)** ***	**0.097 (0.06, 0.134)** ***
MCPP	0.007 (-0.002, 0.016)	0.016 (-0.013, 0.044)	−0.013 (-0.034, 0.007)	0.009 (-0.042, 0.061)	−0.011 (-0.030, 0.009)	−0.017 (-0.068, 0.034)	**0.068 (0.055, 0.081)** ***	**0.076 (0.036, 0.115)** **
MnBP	0.005 (-0.001, 0.011)	0.002 (-0.013, 0.018)	0.012 (0.000, 0.025)	**0.033 (0.006, 0.060)** *	**0.014 (0.002, 0.026)** *	−0.012 (-0.039, 0.016)	**0.012 (0.003, 0.021)** **	0.010 (-0.013, 0.032)
MBzP	**−0.007 (-0.013,-0.001)** *	−0.010 (-0.027, 0.008)	**−0.015 (-0.029, −0.001)** *	**−0.039 (-0.07, −0.007)** *	**−0.022 (-0.035, −0.009)** **	−0.024 (-0.056, 0.008)	**0.020 (0.01, 0.029)** ***	**0.034 (0.009, 0.060)** **
BPA	0.001 (-0.005, 0.007)	−0.005 (-0.023, 0.012)	**0.015 (0.002, 0.028)** *	0.014 (-0.017, 0.046)	0.009 (-0.004, 0.022)	−0.012 (-0.043, 0.019)	**−0.012 (-0.021, −0.003)** *	−0.008 (-0.034, 0.017)
MeP	0.0002 (-0.004, 0.005)	0.010 (-0.003, 0.023)	−0.0008 (-0.011, 0.009)	0.004 (-0.019, 0.028)	0.0003 (-0.009, 0.010)	0.001 (-0.022, 0.024)	0.007 (0.000, 0.013)	0.015 (-0.004, 0.034)
EtP	−0.0005 (-0.004, 0.003)	0.008 (-0.003, 0.019)	−0.0001 (-0.008, 0.008)	0.005 (-0.014, 0.024)	0.001 (-0.007, 0.009)	0.014 (-0.005, 0.033)	**0.007 (0.001, 0.012)** *	−0.004 (-0.019, 0.012)
PrP	−0.003 (-0.006, 0.000)	−0.001 (-0.010, 0.008)	−0.001 (-0.008, 0.006)	−0.001 (-0.017, 0.015)	−0.004 (-0.01, 0.003)	0.0003 (-0.016, 0.016)	−0.0005 (-0.005, 0.004)	−0.001 (-0.014, 0.012)

	TSH		**TBG**		**DIO**	
	Negative β (95% CI)	Positive β (95% CI)	Negative β (95% CI)	Positive β (95% CI)	Negative β (95% CI)	Positive β (95% CI)
MEHHP	−0.018 (-0.062, 0.027)	**0.229 (0.046, 0.413)** *	0.013 (-0.002, 0.028)	0.019 (-0.013, 0.051)	**0.023 (0.008, 0.037)** **	**0.045 (0.004, 0.086)** *
MEOHP	−0.005 (-0.045, 0.036)	0.001 (-0.179, 0.181)	**0.020 (0.007, 0.034)** **	0.016 (-0.014, 0.047)	**0.036 (0.023, 0.05)** ***	**0.058 (0.02, 0.097)** **
MECPP	0.024 (-0.024, 0.072)	−0.057 (-0.236, 0.122)	**0.022 (0.006, 0.038)** **	0.017 (-0.014, 0.047)	**0.056 (0.04, 0.071)** ***	**0.067 (0.028, 0.105)** **
MCOP	0.041 (-0.007, 0.089)	−0.010 (-0.228, 0.208)	0.015 (-0.001, 0.031)	−0.004 (-0.041, 0.033)	**0.055 (0.04, 0.071)** ***	**0.052 (0.005, 0.100)** *
MCNP	**0.050 (0.006, 0.093)** *	−0.095 (-0.307, 0.117)	0.011 (-0.004, 0.025)	**0.037 (0.001, 0.072)** *	**0.057 (0.043, 0.071)** ***	**0.077 (0.031, 0.122)** **
MCPP	0.0002 (-0.051, 0.051)	−0.179 (-0.394, 0.036)	0.009 (-0.008, 0.026)	0.029 (-0.008, 0.066)	**0.061 (0.045, 0.077)** ***	**0.060 (0.013, 0.107)** *
MnBP	−0.031 (-0.062, 0.001)	0.026 (-0.091, 0.143)	−0.006 (-0.017, 0.004)	−0.002 (-0.022, 0.018)	0.007 (-0.003, 0.017)	0.008 (-0.018, 0.034)
MBzP	−0.0004 (-0.035, 0.034)	−0.022 (-0.158, 0.115)	0.012 (0.001, 0.024)	0.009 (-0.015, 0.032)	**0.027 (0.016, 0.038)** ***	**0.044 (0.014, 0.073)** **
BPA	−0.019 (-0.053, 0.014)	−0.017 (-0.15, 0.116)	−0.001 (-0.012, 0.010)	0.019 (-0.003, 0.042)	**−0.014 (-0.024, −0.002)** *	−0.003 (-0.032, 0.026)
MeP	−0.009 (-0.033, 0.016)	−0.064 (-0.163, 0.035)	0.009 (0.000, 0.017)	0.010 (-0.007, 0.027)	0.007 (-0.002, 0.015)	0.005 (-0.017, 0.027)

(*continued on next page*)

Table 4 (*continued*)

Thyroid autoantibody status	Free T4		Total T4		Free T3		Total T3	
	Negative β (95% CI)	Positive β (95% CI)	Negative β (95% CI)	Positive β (95% CI)	Negative β (95% CI)	Positive β (95% CI)	Negative β (95% CI)	Positive β (95% CI)
EtP	0.0002 (-0.021, 0.021)	−0.006 (-0.087, 0.075)	0.005 (-0.002, 0.011)	−0.01 (-0.024, 0.004)	**0.007 (0.000, 0.014)** *	−0.012 (-0.029, 0.006)		
PrP	−0.011 (-0.028, 0.006)	−0.008 (-0.077, 0.060)	**0.008 (0.002, 0.013)** **	**0.015 (0.003, 0.026)** *	0.002 (-0.003, 0.008)	−0.001 (-0.016, 0.015)		

Adjusted for age, sex, BMI, smoking, and income.
TSH, thyroid-stimulating hormone; TBG, thyroxine-binding globulin; DIO, calculated deiodinase activity.
* $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.
"Negative" includes those with neither TPO antibody nor Tg antibody (n = 1,100). "Positive" includes those with TPO antibody or Tg antibody (n = 154).

Table 5
Association between four major components determined by factor analysis and serum thyroid measures in multi-factor models.

	Free T4 β (95% CI)	Total T4 β (95% CI)	Free T3 β (95% CI)	Total T3 β (95% CI)	TSH β (95% CI)	TBG β (95% CI)	DIO β (95% CI)
Factor 1	−0.005 (-0.012, 0.002)	−0.011 (-0.025, 0.004)	**−0.021 (-0.034, −0.007)****	**0.024 (0.014, 0.034)*****	−0.009 (-0.049, 0.031)	**0.014 (0.002, 0.026)***	**0.029 (0.017, 0.041)*****
Factor 2	**0.007 (0.0001, 0.013)***	**−0.017 (-0.032, −0.003)***	−0.013 (-0.027, 0.001)	**0.058 (0.049, 0.068)*****	0.016 (-0.024, 0.056)	0.009 (-0.003, 0.021)	**0.052 (0.040, 0.063)*****
Factor 3	−0.002 (-0.009, 0.005)	−0.002 (-0.016, 0.013)	−0.001 (-0.015, 0.013)	0.006 (-0.003, 0.016)	−0.021 (-0.061, 0.019)	**0.018 (0.006, 0.03)****	0.008 (-0.004, 0.020)
Factor 4	0.004 (-0.002, 0.011)	**0.025 (0.010, 0.039)****	**0.018 (0.004, 0.032)***	−0.008 (-0.018, 0.001)	−0.028 (-0.068, 0.011)	−0.006 (-0.018, 0.006)	**−0.013 (-0.024, −0.001)***

Adjusted for age, sex, BMI, smoking status, monthly income, Factors 1, 2, 3, and 4. Factor 1 was highly loaded with DEHP metabolites, MnBP, and MBzP. Factor 2 was highly loaded with MCOP, MCNP, and MCPP. Factor 3 was highly loaded with MeP, EtP, and PrP. Factor 4 was highly loaded with BPA.
TSH, thyroid-stimulating hormone; TBG, thyroxine-binding globulin; DIO, calculated deiodinase activity.
* $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.

Table 6
Associations between phthalate metabolites/BPA/parabens and serum thyroid measured reported for general adult populations.

Population	N	Chemical	Free T4	Total T4	Free T3	Total T3	TSH	Reference
KoNEHS 2015–2017	1,254	MEHHP	–	–	↓	↑	–	This study
		MEOHP	–	–	↓	↑	–	
		MECPP	–	↓	↓	↑	–	
		MCOP	–	↓	↓	↑	–	
		MCNP	–	↓	↓	↑	–	
		MCPP	–	↓	↓	↑	–	
		MnBP	–	↑	↑	↑	–	
		MBzP	↓	↓	↓	↑	–	
		BPA	–	↑	–	↓	–	
		MeP	–	–	–	↑	–	
		EtP	–	–	–	–	–	
		PrP	–	–	–	–	–	
KoNEHS 2012–2014	6,003	MEHHP		↓		–	–	Park et al. (2017)
		MEOHP		↓		–	↑	
		MECPP		–		–	–	
		MnBP		–		↓	–	
		MBzP		–		↓	–	
		BPA		–		–	↓	
US NHANES 2007–2008	1,346	MEHHP	↓	↓	–	–	–	Meeker et al. (2011)
		MEOHP	–	↓	–	–	–	
		MECPP	–	↓	–	–	–	
		MnBP	–	–	–	–	–	
		MCPP	–	–	↓	–	–	
		BPA	–	↓	–	–	–	
US NHANES 2007–2008	1,479	MeP	–	–				Koeppe et al. (2013)
		EtP	–	↓				
		PrP	–	↓				
NAHSIT 2013	279	MEHHP	–	↓		–	–	Huang et al. (2017)
		MEOHP	↓	–		–	–	
		MECPP	–	–		–	–	
		MnBP	↑	–		–	–	
		MBzP	–	–		–	–	
Thai NHES 2009	2,340	BPA	↓(male)				–	Sriphrapradang et al. (2013)
China	3,394	BPA	↓(male), ↑(female)		↑		↓	Wang et al. (2013)

TSH, thyroid-stimulating hormone; KoNEHS, Korean National Environmental Health Survey; NHANES, National Health and Nutrition Examination Survey; NAHSIT, Nutrition and Health Survey in Taiwan; Thai NHES, Thai National Health Examination Survey.

thyroid hormone-binding protein in humans and might play an important role in phthalates-related thyroid disruption. Increasing TBG can lead to increase of total form of thyroid hormones, while leaving lesser thyroid hormones in free forms (Schussler 2000). In the present population, most measured phthalate metabolites, especially DEHP metabolites (MEHHP, MEOHP, and MECPP), were positively associated with TBG (Table 2). We could identify only one human observational study that assessed both urinary phthalate metabolites and serum TBG (Huang et al. 2017). Based on the relatively small number of Taiwanese population (n = 279), urinary concentrations of DEHP metabolites did not show any significant association with TBG or total T3 (Huang et al. 2017). However, a previous animal study showed a consistent result. In rat, DBP treatment increased serum TBG levels (Duan et al. 2018). In addition, DEHP treatment in zebrafish upregulated mRNA expression of *ttr* gene (Jia et al. 2016), which is the main thyroid hormone-binding protein in zebrafish. For *ttr* gene transcription, however, the opposite direction of observation has also been reported for DEHP in zebrafish or rat (Liu et al. 2015; Zhai et al. 2014).

Positive associations between urinary phthalate metabolites and calculated peripheral DIO activity may also explain the increased total T3 in the present population. Deiodinase catalyzes the conversion from inactive T4 to active T3, and most circulating T3 in blood is derived from peripheral T4 deiodination (Gereben et al. 2008). The present observation suggests that change of DIO activity might play an important role in thyroid disruption by phthalates. Although, we did not directly measure DIO activity, the calculated activity is known to be well-correlated with peripheral DIO activity (Dietrich et al. 2016), so these findings provide clinical evidence that DIO activity is among possible mechanisms of thyroid disrupting chemicals. To date, no epidemiologic studies looked at the association between chemical exposure and DIO activity. However, our observation is comparable to the report of an experimental study involving a long-term exposure to low-dose DEHP in rat (Dong et al., 2017). Three and 6 months long exposure to low-dose DEHP (150 mg/kg/day) in rats showed a tendency to up-regulate *dio1* expression (Dong et al., 2017). However, short-term (1 month) exposure to DEHP (500–750 mg/kg/day) significantly down-regulated *dio1* mRNA expression or reduce DIO activity in the liver (Liu et al. 2015; Zhang et al. 2018).

BPA in which presents a different pattern of association with total T4 and T3, or TBG showed no association in contrast to phthalates. These observations suggest that the direction and mechanisms of thyroid disruption for BPA might be different from those of phthalates.

4.3. Thyroid disruption by thyroid autoantibody status

Different patterns of associations between urinary phthalate metabolites and the thyroid measures by the status of thyroid autoantibodies suggest that thyroid autoantibodies should be considered in the association studies for thyroid disrupting chemicals. In the present population, while no direct associations were observed between chemical exposure and thyroid autoantibody status (Table 3), the associations with free T3, free T4, and TBG appeared to be influenced by the autoantibody status (Table 4).

Associations between phthalate exposure and thyroid autoantibodies have rarely been assessed in human population. Because thyroid autoimmunity is an important cause of thyroid dysfunction, if chemicals can induce thyroid autoimmunity, it can also reduce thyroid hormone production. In a human crossover-crossback study design, it was demonstrated that treatment with DBP-coated drugs could lower thyroid autoantibody levels in humans (Nassan et al. 2019). But this

observation cannot be directly applied to the general population because this study was based on small number of males (n = 70) with inflammatory bowel disease, and the level of exposure was expected to be much greater than those occurring in the general population. In previous animal studies, DBP treatment to rats increased the production of Tg antibody and chronic lymphocytic thyroiditis induced by Tg (Duan et al. 2018; Wu et al. 2017). Recently, a hypothesis has been raised that exposure to environmental chemicals such as BPA is related to the development of autoimmune diseases (Aljadeff et al. 2018). Several human population studies have been conducted on the link between BPA and thyroid autoantibodies, but the results were inconsistent. In a Thai study based on the Thai 4th National Health Examination Survey (n = 2,361, aged ≥ 15 years old), BPA was reported to be positively associated with TPO and Tg antibodies (Chailurkit et al. 2016). However, in an adult population of Shanghai China (n = 3,394, aged 40 and older), BPA was not associated with TPO antibody (Wang et al. 2013).

Our observations of different association by the presence of thyroid autoantibodies (Table 4) suggest potential modifying effects of thyroid autoantibody status. Considering that small number of the subjects with thyroid autoantibodies ("positive") may lead to low statistical power, the associations observed among the antibody positive subjects should be interpreted with caution. Indeed, many significant associations that were observed among the antibody negative subjects disappeared among the antibody positive group. However, the associations between MEHHP and freeT4/TSH observed only among the antibody positive subjects suggest potential modifying effects of the thyroid autoantibody status on the susceptibility to chemical exposure. Such modifying effects of the thyroid autoantibody status have rarely been assessed in a human population, especially for phthalates. Recently, for perfluoroalkyl substances (PFAS), different directions of association by the thyroid autoantibodies were reported (Itoh et al. 2019). Among mother-newborn infant pairs of Hokkaido, Japan, the associations observed between PFAS concentrations and thyroid hormones in cord blood serum were different by the thyroid autoantibody status of the mother (Itoh et al. 2019). In boys, positive association with TSH and negative association with free T3 were only observed among those whose mothers were negative in thyroid autoantibodies. When the mothers were positive in thyroid autoantibodies, a negative association was observed only between perfluorodecanoic acid (PFDA) and TSH. In the adult population of the US NHANES 2007–2008, the association between PFAS and thyroid hormones were modified when both TPO antibody was positive and iodine status was low (Webster et al. 2016).

5. Conclusions

Among the general adult population who was randomly chosen from a nationally representative adult population of Korea, significant associations supporting thyroid disrupting effects of phthalates and BPA were observed. Thyroid disruption by phthalates could be explained by changes in serum TBG and peripheral DIO activity observed in the present study, but not for BPA. In addition, we found suggestive evidence that the thyroid autoantibody status could modulate the associations between some phthalate exposure and thyroid hormones at the current levels of exposure. While cross-sectional nature of the observational study that may not allow causal interpretation of the association should be noted as a disadvantage of the present study, there are certain advantages; this study is based on a reasonable number of population which was randomly chosen from a nationally representative population of KoNEHS 2015–2017, and provides several hypotheses on mechanisms of thyroid disruption by environmental chemicals, which can be further tested in other populations.

CRediT authorship contribution statement

Sohyeon Choi: Formal analysis, Writing - original draft. **Min Joo Kim:** Investigation, Writing - original draft. **Young Joo Park:** Conceptualization, Methodology. **Sunmi Kim:** Formal analysis. **Kyungho Choi:** Conceptualization, Supervision. **Gi Jeong Cheon:** Investigation. **Yoon Hee Cho:** Writing - review & editing. **Hye Li Jeon:** Investigation. **Jiyoung Yoo:** Resources, Validation. **Jeongim Park:** Writing - review & editing, Supervision.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105783.

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