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Considering common sources of exposure in association studies - Urinary benzophenone-3 and DEHP metabolites are associated with altered thyroid hormone balance in the NHANES 2007–2008

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ABSTRACT

Epidemiological studies have shown that thyroid hormone balances can be disrupted by chemical exposure. However, many association studies have often failed to consider multiple chemicals with possible common sources of exposure, rendering their conclusions less reliable.

In the 2007–2008 National Health and Nutrition Examination Survey (NHANES) from the U.S.A., urinary levels of environmental phenols, parabens, and phthalate metabolites as well as serum thyroid hormones were measured in a general U.S. population (≥ 12 years old, n = 1829). Employing these data, first, the chemicals or their metabolites associated with thyroid hormone measures were identified. Then, the chemicals/metabolites with possible common exposure sources were included in the analytical model to test the sensitivities of their association with thyroid hormone levels.

Benzophenone-3 (BP-3), bisphenol A (BPA), and a metabolite of di(2-ethylhexyl) phthalate (DEHP) were identified as significant determinants of decreased serum thyroid hormones. However, significant positive correlations were detected (p-value < 0.05, r = 0.23 to 0.45) between these chemicals/metabolites, which suggests that they might share similar exposure sources. In the subsequent sensitivity analysis, which included the chemicals/metabolite with potentially similar exposure sources in the model, we found that urinary BP-3 and DEHP exposure were associated with decreased thyroid hormones among the general population but BPA exposure was not. In association studies, the presence of possible common exposure sources should be considered to circumvent possible false-positive conclusions.

1. Introduction

Thyroid hormones, such as triiodothyronine (T_3) and thyroxine (T_4), are crucial for normal cellular differentiation and neurodevelopment during early life stages, and they also regulate important physiological functions such as energy metabolism in adults (Gore et al., 2015). Therefore, tight regulation of thyroid hormone balances is essential throughout an organism's life. Numerous chemicals have been associated with disruptions in thyroid hormone balances in many epidemiological studies. However, most of these studies are focused on the statistical association of a single chemical or a very limited number of chemicals (Chevrier et al., 2013; Wang et al., 2013).

Since humans are simultaneously exposed to numerous chemicals, and many of these chemicals may affect thyroid hormone balances through additive or independent modes of action, statistical associations based on a limited number of chemicals, e.g., based on one chemical-one effect association studies, may lead to false conclusions. Therefore, multiple chemicals that may have similar potential effects should be considered simultaneously in association studies. Due to advances in analytical techniques that permit sensitive detection of multiple chemicals in a biological sample with a limited volume, more comprehensive chemical exposure profiles can be obtained and employed in association studies. Several statistical methods, e.g., the environment-wide association approach (Patel et al., 2010), semi-Bayesian shrinkage methods (Braun et al., 2014), and elastic-net regression (Lenters et al., 2016; Lenters et al., 2015), have been suggested for association studies with multiple chemicals.

Another problem of association studies that employ a single or a limited number of chemicals is the lack of consideration of exposure sources. Because many chemicals can be released from common exposure sources, if one chemical is present at high levels in a given body fluid, other chemicals could be also high. Therefore, a seemingly

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Table 1
Associations between thyroid hormones and urinary concentrations of phenols, parabens, and phthalate metabolites that were previously reported.

Chemical/metabolite	Country	Population	N	Direction of change by increasing exposure levels	Reference
Environmental phenols					
BPA	U.S.	Pregnant women	181	Cord TSH in girls decrease but no change in boys	Romano et al. (2015)
BPA[a]	Thailand	Males aged 18–94 yrs	1159	Free T_4 decrease	Sriphrapradang et al. (2013)
BPA	China	Males aged ≥ 40 yrs	1354	Free T_3 increase, free T_4 and TSH decrease	Wang et al. (2013)
BPA	China	Females aged ≥ 40 yrs	2040	Free T_3 and free T_4 increase, or TSH decrease	Wang et al. (2013)
BPA	U.S.	Pregnant women	335	Maternal total T_4 decrease, or neonatal TSH decrease only in boys	Chevrier et al. (2013)
BPA	U.S.	Adults aged ≥ 20 yrs	1346	Total T_4 decrease	Meeker and Ferguson (2011)
BPA	U.S.	Men recruited through an infertility clinic	167	TSH increase	Meeker et al. (2010)
TCS	Belgium	Overweight and obese adults	151	Free T_4 decrease	Geens et al. (2015)
TCS	U.S.	Adolescents aged 12–19 yrs	352	Total T_3 increase	Koeppe et al. (2013)
Parabens					
EtP, PrP	U.S.	Adults aged ≥ 20 yrs	1479	Total T_4 decrease	Koeppe et al. (2013)
EtP	U.S.	Adult females aged ≥ 20 yrs	702	Free T_3, free T_4, and total T_4 decrease	Koeppe et al. (2013)
PrP	U.S.	Adult females aged ≥ 20 yrs	702	Free T_3 and free T_4 decrease	Koeppe et al. (2013)
BuP	U.S.	Adult females aged ≥ 20 yrs	702	Free T_3 decrease	Koeppe et al. (2013)
DEHP metabolites					
Sum of MEHP, MEOHP, MEHHP, and MECPP	U.S.	Pregnant women	81	Free T_4 at 24–28 weeks decrease	Johns et al. (2015)
MECPP	Belgium	Non-obese females	30	TSH increase	Dirtu et al. (2013)
MEHP	U.S.	Adults aged ≥ 20 yrs	1346	Total T_4 decrease	Meeker and Ferguson (2011)
MEHHP, MEOHP, MECPP	U.S.	Adults aged ≥ 20 yrs	1346	Total T_4 decrease and TSH increase	Meeker and Ferguson (2011)
MEHP	U.S.	Adolescents aged 12–19 yrs.	329	Total T_3 and TSH increase	Meeker and Ferguson (2011)
MEHHP, MEOHP, MECPP	U.S.	Adolescents aged 12–19 yrs.	329	Total T_3 increase	Meeker and Ferguson (2011)
Sum of MEHP, MEOHP, MEHHP, and MECPP	Denmark	Children aged 4–9 yrs	758	Free T_3 decrease in both sexes	Boas et al. (2010)
Sum of MEHP, MEOHP, MEHHP, and MECPP	Denmark	Children aged 4–9 yrs	342	Free and total T_3 decrease in girls	Boas et al. (2010)
MEHP	U.S.	Men recruited through an infertility clinic	408	Total T_3 decrease and no association with TSH and free T_4	Meeker et al. (2007)
MEHP	Taiwan	Pregnant women	75	No significant correlation with TSH, T_3, and T_4	Huang et al. (2007)

[a] Serum.

significant association of a given chemical could be due to the influence of other chemicals that share common exposure sources. Previously, we investigated associations between dozens of persistent organic pollutants (POPs) and thyroid hormones among pregnant women and their newborn infants (Kim et al., 2013, 2015). When only one chemical was considered at a time in a regression model, several POPs were independently identified as significant determinants of thyroid hormone levels. However, when a potential commonality of exposure sources was considered in a sensitivity analysis model, the significance of some POPs disappeared (Kim et al., 2013, 2015). These observations suggest that without considering exposure characteristics, the conclusions of association studies could possibly lead to false positives. Therefore, in association studies, considering multiple environmental chemicals along with respective sources of exposure is necessary.

Environmental phenols, parabens, and phthalates have been widely used in consumer products and have been detected in humans worldwide. These chemicals or their metabolites in urine samples have also been reported to have significant associations with serum thyroid hormones among humans (Table 1). In adults from the U.S.A., the urinary bisphenol A (BPA) concentration was negatively associated with total T_4 (Meeker and Ferguson, 2011). Among adult females of the same population, detection of ethyl paraben (EtP) or butyl paraben (BuP) was associated with a decrease in serum thyroid hormones (Koeppe et al., 2013). Exposure to di(2-ethylhexyl) phthalate (DEHP), which is a phthalate with a high molecular weight, was also associated with decreased thyroid hormones and increased thyroid stimulating hormone (TSH) levels (Meeker et al., 2007; Meeker and Ferguson, 2011).

However, these reported associations may not reflect the realistic exposure scenarios of the general population because many of these chemicals may share similar exposure sources or common uses and therefore occur together in humans (Table 2). BPA and DEHP had been often used in the manufacture of plastics and could easily contaminate food (CDC, 2009a; Kang et al., 2006). Benzophenone-3 (BP-3, 2-hydroxy-4-methoxybenzophenone) is an active ingredient of UV protectant, and it has been used not only in sunscreens and cosmetic products but also in plastic containers (Kim and Choi, 2014). Triclosan (TCS, 2, 4, 4′-trichloro-2′-hydroxydiphenyl ether), and major parabens, such as methyl paraben (MeP), EtP, propyl paraben (PrP), and BuP, have been used as antimicrobial agents in personal care products, including cosmetics, lotions, shampoo, and soaps (Dann and Hontela, 2011; Soni et al., 2005). Therefore, it is not surprising that urinary levels of BPA, parabens, and phthalate metabolites in humans are significantly correlated with one another in many cases (Asimakopoulos et al., 2014; Calafat et al., 2009).

The aim of this study is to consider multiple chemical exposures in association models and to identify urinary chemicals that may be associated with thyroid hormone changes among a general population using National Health and Nutrition Examination Survey (NHANES) 2007–2008. BPA, four DEHP metabolites, TCS, and four parabens measured in urine were chosen based on their previously reported associations with serum thyroid hormones reported in the same population (Koeppe et al., 2013; Meeker and Ferguson, 2011). In addition, BP-3 levels in urine were added to the analytical model because of its possible endocrine-disrupting potential, which has been reported in animal and cell experiments (Kim and Choi, 2014). The results of this study will help identify chemicals that might be responsible for thyroid hormone alterations among many chemicals that may share common exposure sources. In addition, the analytical approach we employed to consider multiple chemicals in the association model can be applied to similar environmental epidemiological studies in which common exposure sources are expected for the chemicals that are being considered.