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Associations of urinary perchlorate, nitrate and thiocyanate with central sensitivity to thyroid hormones: A US population-based cross-sectional study

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ABSTRACT

Background: Perchlorate, nitrate, and thiocyanate are three well-known sodium iodine symporter inhibitors, however, associations of their individual and concurrent exposure with central thyroid hormones sensitivity remain unclear.

Objectives: To investigate the associations of urinary perchlorate, nitrate, thiocyanate, and their co-occurrence with central thyroid hormones sensitivity among US general adults.

Methods: A total of 7598 non-pregnant adults (weighted mean age 45.9 years and 52.9% men) from National Health and Nutritional Examination Survey 2007–2012 were included in this cross-sectional study. Central sensitivity to thyroid hormones was estimated with the Parametric Thyroid Feedback Quantile-based Index (PTFQI). Ordinary least-squares regression, weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) models were performed to examine the associations of three anions and their co-occurrence with PTFQI.

Results: The weighted mean values of urinary perchlorate, nitrate, thiocyanate, and perchlorate equivalent concentration (PEC) were 5.48 μg/L, 57.59 mg/L, 2.65 mg/L, and 539.8 μg/L, respectively. Compared with the lowest quartile, the least-square means difference (LSMD) of PTFQI was −0.0516 (LSMD ± SE: −0.0516 ± 0.0185, $P < 0.01$) in the highest perchlorate quartile. On average, PTFQI decreased by 0.0793 (LSMD ± SE: −0.0793 ± 0.0205, $P < 0.001$) between the highest and lowest thiocyanate quartile. Compared with those in the lowest quartile, participants in the highest PEC quartile had significantly decreased PTFQI levels (LSMD ± SE: −0.0862 ± 0.0188, $P < 0.001$). The WQS of three goitrogens, was inversely associated with PTFQI (β: −0.051, 95% CI: −0.068, −0.034). In BKMR model, PTFQI significantly decreased when the levels of three anions were at or above their 60th percentiles compared to the median values.

Conclusions: Higher levels of urinary perchlorate, thiocyanate, and co-occurrence of three goitrogens were associated with increased central thyroid hormones sensitivity among US general adults. Further studies are warranted to replicate our results and elucidate the underlying causative mechanistic links.

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1. Introduction

A wide range of metabolic activities, including lipid oxidation (Brent, 2012) and glucose homeostasis (Chidakel et al., 2005), as well as cell proliferation (Davis et al., 2016; Liu et al., 2019) and embryonic development (Vissenberg et al., 2015; Liu et al., 2019), are recognized to be regulated by thyroid hormones. Altered thyroid hormones are adverse conditions associated with diabetes, cancer, and premature death (Gauthier et al., 2020). Coordination of central negative feedback regulation, deiodinases, and thyroid hormone receptor in the peripheral tissue plays a critical role in the homeostasis of thyroid hormones (Biondi et al., 2019; Liu et al., 2021). Thyroid hormones are inversely correlated with thyroid stimulating hormone (TSH) due to negative feedback (Gauthier et al., 2020). Compared with single parameters, central sensitivity to thyroid hormones, which was evaluated based on the interaction between free thyroxine (FT4) and TSH, was preferred to systematically evaluate the regulation of thyroid hormone homeostasis (Nie et al., 2020). Moreover, impaired central sensitivity to thyroid hormones has recently been identified as a risk factor for metabolic disorders for its positive associations with diabetes, metabolic syndrome, and diabetes-related and total mortality (Laclaustra et al., 2019; Alonso et al., 2021; Mehran et al., 2021).

Since the late 1990s, much concern had been raised about long-term, low-dose exposures of perchlorate, nitrate, and thiocyanate (NRC, 2005; Lisco et al., 2020). Perchlorate, nitrate, and thiocyanate have been recognized as goitrogens due to the capability of competitively inhibiting the transportation of iodine at sodium iodine symporter (NIS) (Pearce and Braverman, 2009; Tarone et al., 2010), a protein transporting iodine into thyroid follicular cells (Gauthier et al., 2020). Iodine is crucial for the biosynthesis of thyroid hormones (Carvalho and Dupuy, 2017), and production of thyroid hormones decreases in the scenario where thyroidal iodide stores are sufficiently reduced (Greer et al., 2002). Perchlorate is a strong oxidizing anion extensively used in rocket fuels, explosives, and pyrotechnics (NRC, 2005; Blount et al., 2006; Leung et al., 2014; Lisco et al., 2020), and can also form naturally in the atmosphere and soil (NRC, 2005; Trumpolt et al., 2005; Lisco et al., 2020). Perchlorate exposure mainly derives from contaminated drinking water (Murray et al., 2008), food (Kirk et al., 2005; Sanchez et al., 2005; Sanchez et al., 2009), and manufacturing (Braverman et al., 2005). Ingestion of nitrate primarily originates from green leafy vegetables (Mervish et al., 2016), such as spinach (Sanchez et al., 2005; Sanchez et al., 2009), and food additives (Mervish et al., 2016). Thiocyanate is a metabolite of cyanide, which mostly comes from cigarettes for smokers and diet for non-smokers (Tarone et al., 2010; Chandler and Day, 2012; Liu et al., 2017). Three anions, whose exposure levels could be estimated with urine samples (Blount et al., 2007; Lau et al., 2013; Liu et al., 2017), were detected in nearly all urine specimens in the National Health and Nutrition Examination Survey (NHANES) 2001–2002 (Blount et al., 2006).

Many animal and human studies had been conducted to examine the association between three anions and thyroid function (Lamm et al., 1999; Lawrence et al., 2000; Siglin et al., 2000; York et al., 2001; Greer et al., 2002; Braverman et al., 2005; Blount et al., 2006; Braverman et al., 2006; Cao et al., 2010; Mendez and Eftim, 2012; McMullen et al., 2017; Serrano-Nascimento et al., 2018). Siglin et al. (Siglin et al., 2000) administered ammonium perchlorate to rats through drinking water for 14 or 90 days, and observed changes in thyroid hormones and TSH in all groups and changes in thyroid gland weight and histopathology in the 10 mg/kg-day group. Moreover, oral doses of perchlorate ranging from 0.007 to 0.5 mg/kg-day were administered to volunteers in several clinical studies, and no significant changes in pituitary and thyroid hormones were observed (Lawrence et al., 2000; Lawrence et al., 2001; Greer et al., 2002; Braverman et al., 2006) (Table S1). A huge body of cross-sectional studies, including several worker studies, had also been conducted to investigate the associations of perchlorate, nitrate, and thiocyanate exposure with thyroid function, and mixed results were yielded (Table S1). In addition, estimating the health effects of multi-pollutant mixtures has increasingly been a concern in environmental epidemiology (Bobb et al., 2015; Bobb et al., 2018). Perchlorate equivalent concentration (PEC) was developed to estimate the levels of co-exposure of three anions based on the relative potencies of IUI, which were ascertained in vitro (Tonacchera et al., 2004), and no significant associations between PEC and FT4 and TSH were observed in two previous studies (Bruce et al., 2013; Mortensen et al., 2016). Nevertheless, another study in US pregnant women revealed the positive association of the weighted sum of three anions with TSH (Horton et al., 2015).

In the current cross-sectional study, we aimed to investigate the associations of urinary perchlorate, nitrate, thiocyanate, and their co-occurrence with central thyroid hormones sensitivity in US general adults.

2. Materials and methods

2.1. Study population

NHANES is a nationally representative program of surveys examining approximately 5,000 non-institutional civilians in the United States each year. Health interviews and physical examinations were performed in respondents' homes and mobile examination centers (MECs), respectively. The details about survey operations could be accessed online (CDC, 2020). NHANES was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and had obtained informed consents from participants.

We used data from NHANES 2007–2008, 2009–2010 and 2011–2012 cycles. A total of 16,903 participants with medical examination data were preliminarily left after 12,650 participants aged lower than 20 years or with current pregnancy were excluded. 1620 participants with thyroid disease or use of some prescription medications (e.g., thyroxine, methimazole, and propylthiouracil) were further excluded. Afterwards, 7598 participants with complete data on serum FT4, TSH, urinary perchlorate, nitrate, thiocyanate, and creatinine (used to adjust for urine dilution) were identified. Totally, 7598 participants were included in the formal analysis, and the process of sampling was shown in Fig. S1.

2.2. Urinary perchlorate, nitrate, and thiocyanate measurement

Urine samples were shipped to the National Center for Environmental Health, and analyzed for perchlorate, nitrate, and thiocyanate with ion chromatography tandem mass spectrometry (Valentín-Blasini et al., 2005). Urine specimens for the target analytes measurement were stored frozen (−70 °C) for up to 4 years before analysis, and no changes in urinary levels of three agents were observed in experiments evaluating storage at −70 °C for > 2 years (Blount et al., 2006; CDC, 2006). To separate chemicals in urine samples chromatographically, IonPac AS16 column with sodium hydroxide as eluent was utilized. More details about urinary perchlorate, nitrate, and thiocyanate determination were descripted online (CDC, 2011). The detection limits for urinary perchlorate, nitrate, and thiocyanate were 0.05 ng/mL, 700 ng/mL, and 20 ng/mL, respectively (Valentín-Blasini et al., 2007; CDC, 2011). The limit of detection divided by the square root of 2 was assigned as the corresponding value for the results below the detection limit (CDC, 2011).

2.3. Central thyroid hormones sensitivity assessment

Serum specimens used for thyroid function tests were processed, stored, and shipped to University of Washington, Seattle, WA. The methods of FT4 and TSH measurement were described elsewhere (CDC, 2015).

Central sensitivity to thyroid hormones was assessed by the Parametric Thyroid Feedback Quantile-based Index (PTFQI), which measured the magnitude of pituitary inhibition by FT4 and was previ-

ously described by Laclaustra et al. (Laclaustra et al., 2019). Briefly, PTFQI was calculated by FT4 (pmol/L) and TSH (mIU/L) with the standard normal cumulative distribution function as below:

$$PTFQI = \Phi\left(\frac{FT4 - \mu_{FT4}}{\sigma_{FT4}}\right) - \left(1 - \Phi\left(\frac{\ln TSH - \mu_{\ln TSH}}{\sigma_{\ln TSH}}\right)\right) \quad (1)$$

$$FT4 \sim N\left(10.075,\ 2.155^2\right) \quad (2)$$

$$\ln TSH \sim N\left(0.4654,\ 0.7744^2\right) \quad (3)$$

PTFQI ranged from −1 to 1, and indicated higher central thyroid hormones sensitivity (higher TSH response to FT4) as value decreased (Laclaustra et al., 2019).

2.4. Covariates assessment

Demographic, socioeconomic, lifestyle and dietary, and prescription medication information were obtained with questionnaires. Race/ethnicity was categorized into non-Hispanic white, non-Hispanic black, Mexican American, and others. Smoking status and alcohol consumption were both grouped into never, former, and current according to the classifications recommended by NCHS. Physical activity level was classified as never, moderate, and vigorous according to replies of respondents to the items related to daily, recreational, and sedentary activities in a typical week. Dietary information was obtained with 24-h dietary recall interviews by trained interviewers, and total energy intake was calculated with the automated multiple pass method. The prescription medication information during a one-month period prior to survey date was obtained with the computer-assisted personal interviewing system and matched to the drug database. Some mediations, including β-blockers, furosemide, glucocorticoids, androgens (for male) and estrogens (for female), were considered as potential confounders (Blount et al., 2006). Anthropometric measurements were collected by trained health technicians, and body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Urinary iodine was measured with Inductively Coupled Plasma Dynamic Reaction Cell Mass Spectroscopy (ICP-DRC-MS), the principle and details of which were described online (CDC, 2009). Serum albumin was measured with chemiluminescence, and C-reaction protein (CRP) was quantified with latex-enhanced nephelometry. Serum thyroid peroxidase antibodies (TPOAbs) and thyroglobulin antibodies (TgAbs) were measured with sequential two-step immunoenzymatic "sandwich" assays (CDC, 2015). BMI, urinary iodine, serum CRP, serum TPOAbs and TgAbs were log-transformed to alleviate their skewed distribution and modeled as covariates.

2.5. Statistical analysis

Participants were categorized according to the quartiles of log-transformed urinary perchlorate, nitrate and thiocyanate. Continuous variables were expressed with weighted means and standard errors (SEs), and categorical variables were expressed with numbers and weighted proportions. Geometric means of urinary perchlorate, nitrate, thiocyanate, and iodine according to population characteristics were also calculated. Moreover, we estimated total daily perchlorate dose with method by Blount et al. (Blount et al., 2007), to compare the perchlorate exposure level in this study with those from previous clinical and worker studies (Lamm et al., 1999; Lawrence et al., 2000; Lawrence et al., 2001; Greer et al., 2002; Braverman et al., 2005; Braverman et al., 2006). Pair-wise Spearman correlation coefficients were calculated to reveal the correlations among urinary perchlorate, nitrate, and thiocyanate. The ordinary least-squares (OLS) regression model was performed to investigate the associations of urinary perchlorate, nitrate, and thiocyanate with FT4, TSH, and PTFQI. Considering the complex, multistage and probability sampling design of NHANES, sampling design parameters and sampling weights were applied, according to the NHANES analytic tutorials (CDC, 2019). The least-square means differences (LSMDs) and SEs of FT4, TSH, and PTFQI according to quartiles of urinary perchlorate, nitrate, and thiocyanate, compared with the lowest quartile, was calculated. Confounders, including age (continuous), sex (male, female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, others), smoking status (never, former, current), alcohol drinking status (never, former, current), physical activity (never, moderate, vigorous), medication usage (yes, no), BMI (continuous), CRP (continuous), serum albumin (continuous), total energy intake (continuous), and urinary iodine (continuous), were adjusted in the multivariate models. Urinary creatinine (continuous) was also adjusted in the model to correct for urine dilution. Additionally, urinary perchlorate, nitrate, and thiocyanate were mutually adjusted in models. The *P*-value for linear trend was calculated by introducing medians of quartiles as continuous variables into the model. Considering the critical role of iodine in thyroid health, we further performed stratified analyses by urinary iodine (< 100 μg/L, ≥ 100 μg/L) to investigate whether this confounder modified the associations of urinary perchlorate, nitrate, and thiocyanate with FT4, TSH, and PTFQI, according to the definition of sufficient iodine intake recommended by World Health Organization (WHO, 2007). Moreover, stratified analyses by serum cotinine, the biomarker of tobacco smoking, were conducted to examine whether the effect size may differ between categories of cotinine (< 0.015 ng/mL, 0.015–10 ng/mL, ≥ 10 ng/mL), in accordance with previous publications (Pirkle et al., 2006; Steinmaus et al., 2007; Asfar et al., 2019). Stratified analyses by age (< 45 years, ≥ 45 years) and sex (male, female) were also conducted. Effect modification was assessed by introducing a multiplicative term between specific stratification factor and urinary analyte as continuous variables into the multivariate models. Additionally, we performed multivariate restricted cubic spline (RCS) regression models with 3 knots at the 5th, 50th, and 95th percentiles of the distributions of log-transformed three anions, to evaluate the potential nonlinear relationships between three goitrogenic anions and thyroid function biomarkers.

Considering the common mechanisms of IUI of three anions, PEC was calculated to evaluate the co-exposure of three anions based on the relative potencies of IUI of perchlorate, nitrate, and thiocyanate (Tonacchera et al., 2004). The equation used to generate PEC, which had been ascertained by Tonacchera et al. (Tonacchera et al., 2004) and Bruce et al. (Bruce et al., 2013), was

$$PEC = \left[ClO_4^-\right] + \frac{\left[SCN^-\right]}{17.6} + \frac{\left[NO_3^-\right]}{150} \quad (4)$$

and individual contribution of three anions to PEC was evaluated with the equation mentioned elsewhere (Corey et al., 2017). Associations of urinary PEC with FT4, TSH, and PTFQI were investigated with the methods mentioned above. Furthermore, we performed another two statistical methods, including weighted quantile sum (WQS) regression and Bayesian kernel machine regression (BKMR), to investigate the associations of three anions with FT4, TSH, and PTFQI.

WQS regression, a statistical model developed for high-dimensional datasets (Carrico et al., 2015; Czarnota et al., 2015), was applied in the current study. A weighted index indicative of co-exposure of three anions was constructed, and regressed with outcome variables, with the assumption of same directions of associations between three anions and outcomes. The regression model of WQS regression was

$$g(\mu) = \beta_0 + \beta_1\left(\sum_{i=1}^{c} w_i q_i\right) + z^{'}\varphi \quad (5)$$

$$WQS = \sum_{i=1}^{c} w_i q_i \quad (6)$$

where *g* represented the link function (linear, here), μ was the mean linked to the predictor variables, β_0 was the intercept, β_1 was the regression coefficient of the WQS of three anions, *c* represented the

number of the components (three, here), z' and φ indicated the vectors of covariates and their regression coefficients (Carrico et al., 2015). Urinary perchlorate, nitrate, and thiocyanate were scored into quartiles and denoted by q_i ($q_i = 0$, 1, 2, and 3 indicated the 1st, 2nd, 3rd, and 4th quartile, respectively). The empirical weight w_i, ranging from 0 to 1, represented the weight for the i^{th} anion, and all weights summed to 1. Moreover, the weights can help identify important components (Carrico et al., 2015). Data were randomly split into two sets, and weights were estimated in the training set, and then tested for statistical significance in the validation set (Carrico et al., 2015). To increase the sensitivity of identifying important predictors, bootstrap sampling was applied (Carrico et al., 2015). In our study, we set the number of bootstrap samples as 1000, and 40% data as training set. We constructed the multivariate models with the assumptions that all three anions were inversely associated with outcomes. In addition, we applied negative constraints in the optimization function for the weight estimation.

Moreover, BKMR, a recently developed machine learning method to investigate the health effects of mixtures, was also applied in our study. The kernel machine regression model (Bobb et al., 2018) for continuous outcomes could be expressed as

$$Y_i = h(z_{i1}, \cdots, z_{iM}) + \boldsymbol{x}_i^{'}\beta + \epsilon_i \quad (7)$$

where Y_i represented the outcome variable for the i^{th} individual, z_{iM} represented the M^{th} component, h was the exposure–response function, $\boldsymbol{x}_i^{'}$ denoted the vector of covariates, and $\epsilon_i \sim N(0, \sigma^2)$. Notably, in BKMR, the h function allows for nonlinearity exposure–response relationships and interactions among mixtures (Bobb et al., 2015; Bobb et al., 2018). We plotted the univariate exposure–response function of each anion, fixing other two anions at their medians (Valeri et al., 2017; Bobb et al., 2015), to verify the results observed in the single-goitrogen OLS regression model. Associations between co-occurrence of three anions and outcomes were examined by calculating the changes of response variables, comparing the values of all predictors at varying percentiles to their medians (Bobb et al., 2015). Contribution of individual anion to the response variable was estimated by investigating the association of an interquartile range (IQR) increase in each anion with outcome, with other anions fixed at the 25th, 50th, and 75th percentiles (Bobb et al., 2015; Hu et al., 2021). The relative importance of each anion to the outcome variable was also estimated with posterior inclusion probability (PIP) (Bobb et al., 2015; Bobb et al., 2018). Moreover, interactions among three goitrogens were assessed by visualizing the bivariate exposure–response functions for two goitrogens, with the other goitrogen fixed at the 50th percentile (Bobb et al., 2015; Hu et al., 2021). There is no evidence of interactions when the slopes of lines are parallel. Above covariates were also adjusted in BKMR models.

Several secondary analyses were conducted to evaluate the robustness of our results. First, extreme values (defined as $<$ 1st percentile or $>$ 99th percentile) of urinary perchlorate, nitrate, thiocyanate, and creatinine were excluded to examine whether our results were sensitive to influential observations. Second, we divided the urinary analytes measurements by creatinine to adjust for urine dilution rather than directly adjusted urinary creatinine in models. Because skeletal muscle, where excreted creatinine is produced (Bulka et al., 2017), is the major target tissue of thyroid hormone signaling, and muscle weakness is frequently observed in patients with thyroid function disorders (Salvatore et al., 2014), urinary creatinine might be a collider (the descendent of goitrogens exposure and thyroid function) (Fig. S2) and introduce a distorted association (Greenland, 2003). Hence, we further applied the recently developed method known as covariate-adjusted standardization (O'Brien et al., 2016). Following the method described previously (Bulka et al., 2017), we first constructed a multivariate linear regression model of log-transformed urinary creatinine with variables known to have impacts on urine dilution, including age, sex, race/ethnicity, BMI (Bulka et al., 2017), and FT4 (Iglesias and Díez, 2009), in 8456 non-pregnant adults (Table S2). Then, we standardized urinary chemicals concentrations by multiplying analytes concentrations by the ratio of fitted to observed creatinine (O'Brien et al., 2016). Moreover, we excluded serum CRP and BMI from the multivariate-adjustment model under assumptions that CRP mediated and BMI collided the associations, according to previous publications (Blount et al., 2006; Schreinemachers et al., 2015; Amouzegar et al., 2018; Zhu et al., 2019). Finally, we introduced serum TPOAbs and TgAbs as covariates into multivariate models to examine whether two antibodies may affect the documented associations.

We used SAS version 9.4 software (SAS Institute, Cary, NC) and R 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria) for statistical analysis. We conducted RCS regression model with R package "rms" (version 6.2–0), WQS regression with R package "gWQS" (version 3.0.4), and BKMR model with R package "bkmr" (version 0.2.0), which could be accessed from the Comprehensive R Archive Network (CRAN) online. All tests were bilateral and *P*-values below 0.05 were regarded as statistical significance.

3. Results

3.1. Characteristics of study population

The current cross-sectional study comprised 7598 US non-pregnant adults (weighted mean age 45.9 years), including 4058 men (weighted proportion 52.9%) and 3540 women (weighted proportion 47.1%). The weighted mean values of urinary perchlorate, nitrate, thiocyanate, and PEC were 5.48 μg/L, 57.59 mg/L, 2.65 mg/L, and 539.8 μg/L, respectively. Characteristics of study population according to quartiles of urinary perchlorate, nitrate, and thiocyanate were shown in Table 1. For perchlorate, participants with higher urinary levels were more likely to be men (Table 1). Participants with higher urinary and thiocyanate measurements were younger and more likely to be males and current smokers (Table 1). The geometric mean of urinary iodine was 143.36 μg/L (Table S3), and nearly 33% of the participants had excreted iodine $<$ 100 μg/L (Table S4). Moreover, participants with higher PEC were younger, more likely to be male and current smoking individuals and had higher daily energy intake (Table S4). The weighted mean value of total daily perchlorate dose was 0.10 μg/kg-d. The Spearman correlation coefficients among urinary perchlorate, nitrate, and thiocyanate ranged from 0.22 to 0.55 (all $P < 0.001$). Perchlorate, nitrate, and thiocyanate contributed an average of 0.8%, 79.0%, and 19.6% of PEC, respectively.

3.2. Associations of urinary perchlorate, nitrate and thiocyanate with serum thyroxine, thyroid stimulating hormone, and central thyroid hormones sensitivity

The LSMDs and SEs of serum FT4, TSH, and PTFQI were displayed in Table 2. Comparing extreme quartiles, serum FT4 was 0.3324 pmol/L (LSMD ± SE: −0.3324 ± 0.1201 pmol/L, $P < 0.01$) lower for perchlorate and 0.2044 pmol/L (LSMD ± SE: −0.2044 ± 0.0959 pmol/L, $P < 0.05$) lower for thiocyanate. Compared with the lowest quartile, serum TSH was 0.2048 mIU/L (LSMD ± SE: −0.2048 ± 0.0978 mIU/L, $P < 0.05$) lower for participants in the highest thiocyanate quartile. On average, PTFQI decreased by 0.0516 (LSMD ± SE: −0.0516 ± 0.0185, $P < 0.01$) between the highest and lowest perchlorate quartile. The LSMD of PTFQI between the highest and lowest thiocyanate quartile was −0.0793 (LSMD ± SE: −0.0793 ± 0.0205, $P < 0.001$). Above results were also observed in restricted cubic splines (Fig. S3).

Urinary iodine modified the inverse association of urinary thiocyanate with TSH, and a significant inverse association between urinary thiocyanate and serum TSH was observed among participants with low excreted iodine (*P*-interaction = 0.04) (Table S5). Similar effect modification was observed in the inverse association of urinary perchlorate with PTFQI (*P*-interaction = 0.004). Moreover, urinary nitrate was inversely associated with PTFQI in the high iodine excretion group, whereas null association was observed among participants with low

Table 1
Characteristics of study population according to quartiles of urinary perchlorate, nitrate and thiocyanate.[a]

	Perchlorate				Nitrate				Thiocyanate			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Age, years	45.54 (0.56)	46.93 (0.54)	46.10 (0.53)	44.98 (0.51)	49.21 (0.54)	47.32 (0.51)	44.51 (0.58)	42.84 (0.44)	49.21 (0.60)	47.84 (0.65)	45.00 (0.56)	42.37 (0.42)
Men, n (%)	845 (42.95)	1003 (51.80)	1099 (58.00)	1111 (58.67)	817 (40.26)	1021 (53.26)	1113 (57.97)	1107 (59.18)	845 (40.89)	983 (50.15)	1067 (56.89)	1163 (60.83)
Race/ethnicity, n (%)												
Non-Hispanic white	820 (68.14)	858 (67.88)	859 (68.81)	831 (67.33)	890 (71.62)	827 (67.21)	813 (66.02)	838 (67.45)	677 (59.35)	792 (66.33)	897 (71.54)	1002 (73.02)
Non-Hispanic black	434 (11.85)	418 (12.08)	372 (10.32)	348 (10.33)	367 (9.61)	425 (12.34)	420 (12.19)	360 (10.44)	309 (9.18)	330 (8.91)	420 (11.53)	513 (14.32)
Mexican American	243 (6.57)	299 (8.52)	343 (9.10	364 (9.76	300 (7.85)	326 (8.96)	322 (9.49)	301 (7.68)	419 (11.75)	364 (10.36)	303 (7.96)	163 (4.73)
Others	396 (13.43)	327 (11.52)	331 (11.77)	355 (12.58)	339 (10.92)	323 (11.48)	346 (12.30)	401 (14.42)	493 (19.72)	415 (14.40)	279 (8.97)	222 (7.93)
Smoking status, n (%)												
Never	1018 (51.84)	986 (52.77)	978 (51.69)	1045 (56.41)	1085 (55.50)	1017 (53.78)	1006 (54.05)	919 (49.63)	1293 (69.42)	1182 (62.99)	1146 (62.28)	406 (22.28)
Former	414 (22.05)	470 (23.42)	522 (26.80)	462 (24.76)	499 (26.17)	508 (24.88)	469 (24.55)	392 (21.70)	542 (27.79)	580 (29.93)	510 (26.82)	236 (13.84)
Current	460 (26.09)	444 (23.72)	405 (21.51)	388 (18.76)	311 (18.32)	373 (21.22)	426 (21.40)	587 (28.61)	62 (2.76)	136 (7.02)	242 (10.84)	1257 (63.84)
Drinking status, n (%)												
Never	251 (10.20)	233 (8.81)	223 (9.00)	223 (9.54)	291 (11.44)	236 (9.78)	224 (9.17)	189 (7.72)	352 (14.54)	277 (11.77)	197 (8.19)	114 (4.70)
Former	340 (16.04)	355 (16.05)	295 (12.24)	244 (15.77)	378 (16.71)	373 (17.21)	314 (13.95)	269 (12.57)	388 (17.08)	318 (14.11)	314 (14.31)	314 (14.99)
Current	1159 (67.65)	1179 (68.10)	1240 (71.06)	1159 (66.22)	1096 (66.11)	1149 (66.87)	1231 (69.85)	1261 (70.01)	993 (60.15)	1161 (66.79)	1257 (71.43)	1326 (72.91)
Physical activity, n (%)												
Never	699 (30.01)	685 (28.23)	629 (24.38)	577 (24.56)	751 (29.24)	674 (29.21)	609 (26.22)	556 (22.86)	767 (31.52)	630 (25.86)	578 (24.22)	615 (26.40)
Moderate	590 (33.13)	561 (31.97)	565 (30.01)	582 (31.28)	605 (35.67)	599 (31.19)	573 (31.25)	521 (28.54)	575 (33.10)	611 (33.45)	611 (33.18)	501 (27.13)
Vigorous	604 (36.86)	656 (39.79)	711 (45.61)	739 (44.16)	540 (35.09)	628 (39.60)	719 (42.53)	823 (48.60)	556 (35.38)	660 (40.69)	710 (42.60)	784 (46.47)
Medication usage[b], n (%)	32 (1.81)	17 (1.32)	14 (0.64)	11 (0.79)	26 (1.69)	25 (1.34)	14 (0.99)	9 (0.60)	32 (2.33)	16 (1.02)	7 (0.34)	19 (1.10)
BMI, kg/m^2	27.43 (0.14)	28.62 (0.16)	28.64 (0.19)	29.01 (0.22)	27.68 (0.14)	28.51 (0.20)	29.07 (0.24)	28.39 (0.23)	27.15 (0.22)	28.47 (0.20)	29.50 (0.23)	28.31 (0.12)
Serum CRP, mg/dL	0.40 (0.02)	0.36 (0.02)	0.36 (0.02)	0.36 (0.02)	0.37 (0.02)	0.39 (0.02)	0.36 (0.01)	0.36 (0.02)	0.35 (0.02)	0.36 (0.03)	0.35 (0.02)	0.41 (0.02)
Serum albumin, g/dL	4.32 (0.01)	4.28 (0.01)	4.30 (0.01)	4.29 (0.01)	4.29 (0.01)	4.28 (0.01)	4.30 (0.01)	4.31 (0.01)	4.28 (0.01)	4.31 (0.01)	4.31 (0.01)	4.29 (0.01)
Urinary perchlorate, μg/L	1.18 (0.01)	2.66 (0.01)	4.68 (0.02)	13.41 (0.51)	2.16 (0.06)	4.24 (0.15)	6.03 (0.27)	9.15 (0.49)	3.70 (0.22)	5.16 (0.24)	6.62 (0.30)	6.06 (0.38)
Urinary nitrate, mg/L	30.08 (0.97)	46.25 (1.08)	66.37 (1.90)	87.48 (2.28)	16.84 (0.21)	35.84 (0.18)	56.55 (0.18)	115.83 (2.51)	33.64 (1.02)	53.73 (2.04)	66.22 (1.73)	71.53 (1.45)
Urinary thiocyanate, mg/L	1.80 (0.09)	2.64 (0.13)	2.89 (0.11)	3.26 (0.21)	1.16 (0.06)	2.09 (0.08)	2.84 (0.11)	4.33 (0.24)	0.32 (0.00)	0.83 (0.01)	1.76 (0.01)	7.02 (0.22)
Urinary creatinine, mg/dL	67.27 (2.27)	108.98 (2.82)	140.40 (2.70)	163.32 (2.56)	52.10 (1.14)	99.02 (1.61)	142.67 (2.01)	179.95 (3.03)	77.75 (2.33)	110.32 (2.20)	140.29 (2.20)	142.27 (2.55)
Urinary iodine, μg/L	146.30 (23.13)	179.91 (9.36)	332.32 (36.78)	339.52 (15.74)	156.11 (18.37)	213.02 (10.08)	330.38 (43.97)	293.19 (12.55)	172.89 (13.47)	278.60 (42.88)	277.70 (16.87)	257.81 (12.42)
Serum FT4, pmol/L	10.39 (0.07)	10.32 (0.08)	10.18 (0.09)	10.04 (0.09)	10.36 (0.08)	10.28 (0.08)	10.13 (0.08)	10.16 (0.08)	10.42 (0.09)	10.35 (0.07)	10.10 (0.07)	10.10 (0.08)
Serum TSH, mIU/L	2.02 (0.09)	1.87 (0.04)	1.98 (0.10)	1.91 (0.05)	2.03 (0.06)	2.00 (0.08)	1.99 (0.09)	1.78 (0.04)	2.01 (0.04)	1.95 (0.05)	2.06 (0.11)	1.78 (0.08)
Serum TPOAbs, IU/mL	14.54 (3.08)	15.40 (2.15)	17.80 (1.82)	18.17 (2.12)	15.41 (2.36)	16.51 (2.94)	16.62 (2.05)	17.32 (2.27)	15.63 (2.08)	16.55 (1.77)	17.52 (2.36)	16.07 (2.89)
Serum TgAbs, IU/mL	8.74 (2.37)	7.92 (1.88)	6.86 (2.37)	8.83 (1.60)	11.51 (2.91)	4.76 (1.07)	9.17 (1.09)	6.92 (2.18)	12.64 (3.82)	8.89 (2.36)	6.78 (2.11)	5.03 (1.87)
Total energy intake, kcal	2085.46 (30.54)	2233.45 (29.47)	2281.74 (31.30)	2315.05 (37.98)	2074.78 (40.08)	2194.59 (29.01)	2324.45 (24.82)	2309.92 (35.15)	1959.33 (27.49)	2205.45 (32.04)	2261.60 (41.32)	2430.85 (35.95)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FT4, free thyroxine; TgAbs, thyroglobulin antibodies; TPOAbs, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

[a] Continuous variables were expressed as weighted means and SEs, and categorical variables were expressed as numbers and weighted percentages. The sums of percentages may not reach 100%, owing to the rounding of decimals and missing values.

[b] Including beta-blockers, furosemide, glucocorticoids, androgens (male), estrogens (female).

Table 2
Associations of urinary perchlorate, nitrate, thiocyanate with serum free thyroxine, thyroid stimulating hormone, and central thyroid hormones sensitivity.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-trend
Perchlorate					
No. of observations	1893	1902	1905	1898	
Range (μg/L)	≤ 1.90	1.91–3.45	3.46–6.20	≥ 6.21	
FT4 (pmol/L)	0.0000 (reference)	−0.0690 ± 0.0771	−0.2339 ± 0.1019*	−0.3324 ± 0.1201**	0.006
TSH (mIU/L)	0.0000 (reference)	−0.1048 ± 0.0934	0.0594 ± 0.1646	−0.0250 ± 0.1228	0.88
PTFQI	0.0000 (reference)	−0.0234 ± 0.0165	−0.0253 ± 0.0136	−0.0516 ± 0.0185**	0.004
Nitrate					
No. of observations	1896	1901	1901	1900	
Range (mg/L)	≤ 26.70	26.80–45.10	45.20–70.20	≥ 70.30	
FT4 (pmol/L)	0.0000 (reference)	0.0551 ± 0.0934	−0.0581 ± 0.1022	0.0682 ± 0.1102	0.74
TSH (mIU/L)	0.0000 (reference)	−0.0589 ± 0.0555	−0.0217 ± 0.0984	−0.2950 ± 0.1621	0.08
PTFQI	0.0000 (reference)	−0.0009 ± 0.0163	−0.0275 ± 0.0143	−0.0295 ± 0.0223	0.11
Thiocyanate					
No. of observations	1898	1901	1899	1900	
Range (mg/L)	≤ 0.54	0.54–1.15	1.16–2.68	≥ 2.69	
FT4 (pmol/L)	0.0000 (reference)	0.0468 ± 0.0927	−0.1344 ± 0.0825	−0.2044 ± 0.0959*	0.009
TSH (mIU/L)	0.0000 (reference)	−0.0713 ± 0.0663	0.0502 ± 0.1170	−0.2048 ± 0.0978*	0.07
PTFQI	0.0000 (reference)	−0.0144 ± 0.0176	−0.0313 ± 0.0159	−0.0793 ± 0.0205***	< 0.001

Least-square mean ± standard error was estimated using ordinary least-squares regression model, adjusting for urinary creatinine (mg/dL, continuous), age (years, continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, others), sex (male, female), smoking (never, former, current), alcohol drinking status (never, former, current), physical activity (never, moderate, vigorous), log-transformed body mass index (kg/m^2, continuous), mediation usage (yes, no), serum albumin (g/L, continuous), total energy intake (kcal, continuous), log-transformed C-reactive protein (mg/dL, continuous), log-transformed urinary iodine (μg/L, continuous), log-transformed urinary perchlorate (μg/L, continuous), nitrate (mg/L, continuous) and thiocyanate (mg/L, continuous) (mutual adjustment).
Abbreviations: FT4, free thyroxine; TSH, thyroid stimulating hormone; PTFQI, Parametric Thyroid Feedback Quantile-based Index.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

iodine excretion (*P*-interaction = 0.02). No evidence of effect modification of serum cotinine in the associations of three agents with FT4, TSH, and PTFQI (all *P*-interaction > 0.05) was revealed (Table S5). We observed significant inverse associations of urinary perchlorate with FT4 and PTFQI in high cotinine group. Moreover, the inverse association of urinary thiocyanate with PTFQI was observed across subgroups defined by serum cotinine. Neither sex nor age modified the inverse associations of urinary perchlorate or thiocyanate with FT4 and PTFQI (all *P*-interaction > 0.05) (Table S5). We simultaneously observed significant inverse associations of urinary perchlorate and thiocyanate with FT4 in men. Urinary perchlorate was inversely associated with FT4 in those aged ≥ 45 years, whereas thiocyanate was inversely associated with FT4 in those aged < 45 years. The inverse association of urinary thiocyanate with PTFQI persisted across subgroups defined by sex and age.

3.3. Co-exposure of three goitrogens and serum thyroxine, thyroid stimulating hormone, and central thyroid hormones sensitivity

After adjusting for all covariates, compared with those in the lowest quartile, participants in the highest PEC quartile had significantly decreased levels of serum FT4 (LSMD ± SE: −0.2337 ± 0.0714 pmol/L, $P < 0.01$) (Table 3). Moreover, PTFQI decreased by 0.0862 between the highest and lowest PEC quartile (LSMD ± SE: −0.0862 ± 0.0188, $P < 0.001$).

WQS index, indicative of co-exposure of three goitrogens, was inversely associated with FT4 [WQS β: −0.279, 95% confidence interval (CI): −0.372, −0.186] and PTFQI (WQS β: −0.051, 95% CI: −0.068,

Table 4
Associations of weighted quantile sum (WQS) of urinary perchlorate, nitrate and thiocyanate with serum free thyroxine, thyroid stimulating hormone, and central thyroid hormones sensitivity.

Outcomes	β-coefficient	95% CI	*P*-value
FT4 (pmol/L)	−0.279	(-0.372, −0.186)	< 0.001
TSH (mIU/L)	−0.064	(-0.181, 0.054)	0.29
PTFQI	−0.051	(-0.068, −0.034)	< 0.001

Estimates were obtained in WQS regression model, adjusting for urinary creatinine (mg/dL, continuous), age (years, continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, others), sex (male, female), smoking (never, former, current), alcohol drinking status (never, former, current), physical activity (never, moderate, vigorous), log-transformed body mass index (kg/m^2, continuous), mediation usage (yes, no), serum albumin (g/L, continuous), total energy intake (kcal, continuous), log-transformed C-reactive protein (mg/dL, continuous), log-transformed urinary iodine (μg/L, continuous).
Abbreviation: FT4, free thyroxine; TSH, thyroid stimulating hormone; PTFQI, Parametric Thyroid Feedback Quantile-based Index.

Table 3
Associations of perchlorate equivalent concentration with serum free thyroxine, thyroid stimulating hormone, and central thyroid hormones sensitivity.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-trend
No. of observations	1899	1900	1900	1899	
Range (μg/L)	≤ 243.59	243.71–410.81	410.81–658.57	≥ 658.71	
FT4 (pmol/L)	0.0000 (reference)	−0.0655 ± 0.0696	−0.1648 ± 0.0915	−0.2337 ± 0.0714**	0.003
TSH (mIU/L)	0.0000 (reference)	−0.0989 ± 0.0825	0.0859 ± 0.0927	−0.3109 ± 0.1692	0.05
PTFQI	0.0000 (reference)	−0.0293 ± 0.0143*	−0.0539 ± 0.0186**	−0.0862 ± 0.0188***	< 0.001

Least-square mean ± standard error was estimated using ordinary least-squares regression model, adjusting for urinary creatinine (mg/dL, continuous), age (years, continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, others), sex (male, female), smoking (never, former, current), alcohol drinking status (never, former, current), physical activity (never, moderate, vigorous), log-transformed body mass index (kg/m^2, continuous), mediation usage (yes, no), serum albumin (g/L, continuous), total energy intake (kcal, continuous), log-transformed C-reactive protein (mg/dL, continuous), log-transformed urinary iodine (μg/L, continuous).
Abbreviations: FT4, free thyroxine; TSH, thyroid stimulating hormone; PTFQI, Parametric Thyroid Feedback Quantile-based Index.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

−0.034), but not TSH (WQS β: −0.064, 95% CI: −0.181, 0.054) (Table 4). Contributions of three goitrogens to the WQS index were depicted in Fig. S4, and thiocyanate had the largest weights for both PTFQI (0.54) and FT4 (0.51).

The univariate exposure–response functions were shown in Figs. 1-3A, and the directions were roughly consistent with results observed in single-goitrogen OLS regression model. Fixing other two anions at medians, perchlorate was inversely associated with FT4 and PTFQI. Similar trends of exposure–response functions of thiocyanate were also observed. Co-exposure of three anions was inversely associated with FT4 and PTFQI, but not TSH, and both FT4 and PTFQI significantly decreased when three anions were at or above their 60th percentiles compared to their median values (Figs. 1-3B). Contributions of three anions to outcomes were reckoned by estimating the change of the response variables when single anion increased from its 75th percentile to 25th percentile, with other two anions fixed at their 25th, 50th, and 75th percentiles. As displayed in Figs. 1-3C, the inverse associations of co-occurrence of three anions with FT4 and PTFQI were mainly attributed to thiocyanate. An IQR increase in thiocyanate was associated with significantly decreased FT4 and PTFQI when nitrate and perchlorate were fixed at their quartiles, while no significant alternations in FT4 and PTFQI were observed when compared nitrate or perchlorate at 75th percentile with 25th percentile and fixed other two anions at their quartiles. In the mixture, thiocyanate was the most important anion for the inverse associations with FT4 and PTFQI with the PIP of 1. In addition, changes of FT4 and PTFQI comparing specific anions at 75th percentile with 25th percentile varied when the remaining anions increased from 25th to 75th percentiles, indicating potential interactions among three anions. The bivariate exposure–response functions for goitrogens were graphically shown in Figs. 1-3D, further elucidating the potential interactions among three anions. As depicted in Fig. 1**D**, slope of the inverse association between urinary perchlorate and FT4 tended to be steeper at higher thiocyanate levels, prompting the potential interaction between perchlorate and thiocyanate on FT4. Moreover, slopes of all lines were unparalleled in Fig. 3**D**, indicating the interactions among three anions on PTFQI.

3.4. Secondary analyses

After excluding outliers of urinary perchlorate, nitrate, thiocyanate,

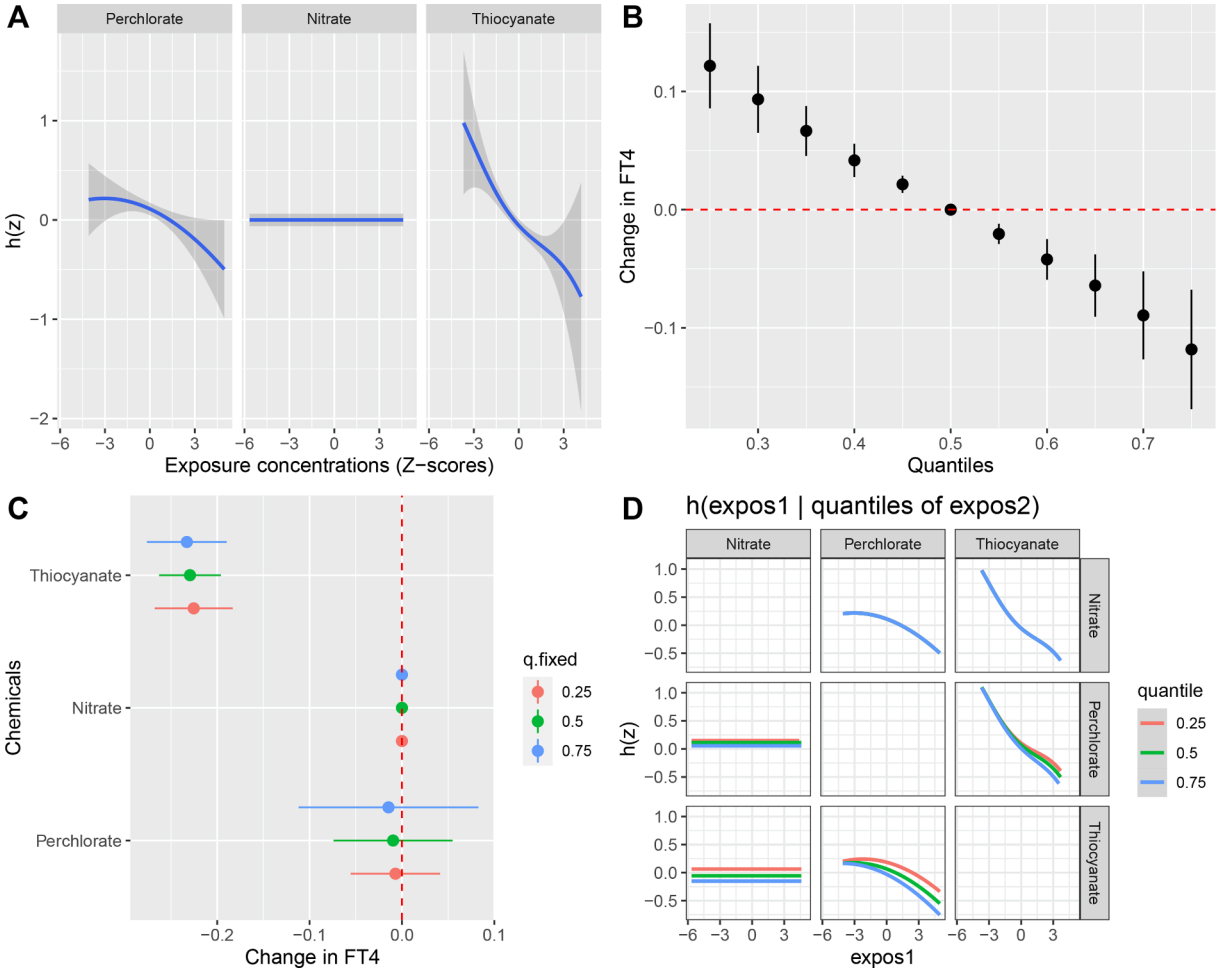

Fig. 1. Association of co-exposure of perchlorate, nitrate, and thiocyanate with FT4 by BKMR model[a]. (A) Univariate exposure–response functions and 95% confidence intervals for each anion with other anions fixed at their median values. (B) Overall effect of the mixture (estimates and 95% confidence intervals). Change in FT4 when three anions were set at varying percentiles compared to the median values was plotted. (C) Single goitrogen association (estimates and 95% confidence intervals). Change in FT4 comparing each anion at 75th percentile with 25th percentile, with other two anions fixed at 25th, 50th, and 75th percentiles, was plotted. (D) Bivariate exposure–response functions for perchlorate, nitrate, and thiocyanate when another anion was fixed at varying (25th, 50th, 75th) percentiles and other anion was fixed at the median. [a] Model was adjusted for urinary creatinine (mg/dL, continuous), age (years, continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, others), sex (male, female), smoking (never, former, current), alcohol drinking status (never, former, current), physical activity (never, moderate, vigorous), log-transformed body mass index (kg/m^2, continuous), mediation usage (yes or no), serum albumin (g/L, continuous), total energy intake (kcal, continuous), log-transformed C-reactive protein (mg/dL, continuous), log-transformed urinary iodine (μg/L, continuous). Abbreviations: BKMR, Bayesian kernel machine regression; FT4, free thyroxine.

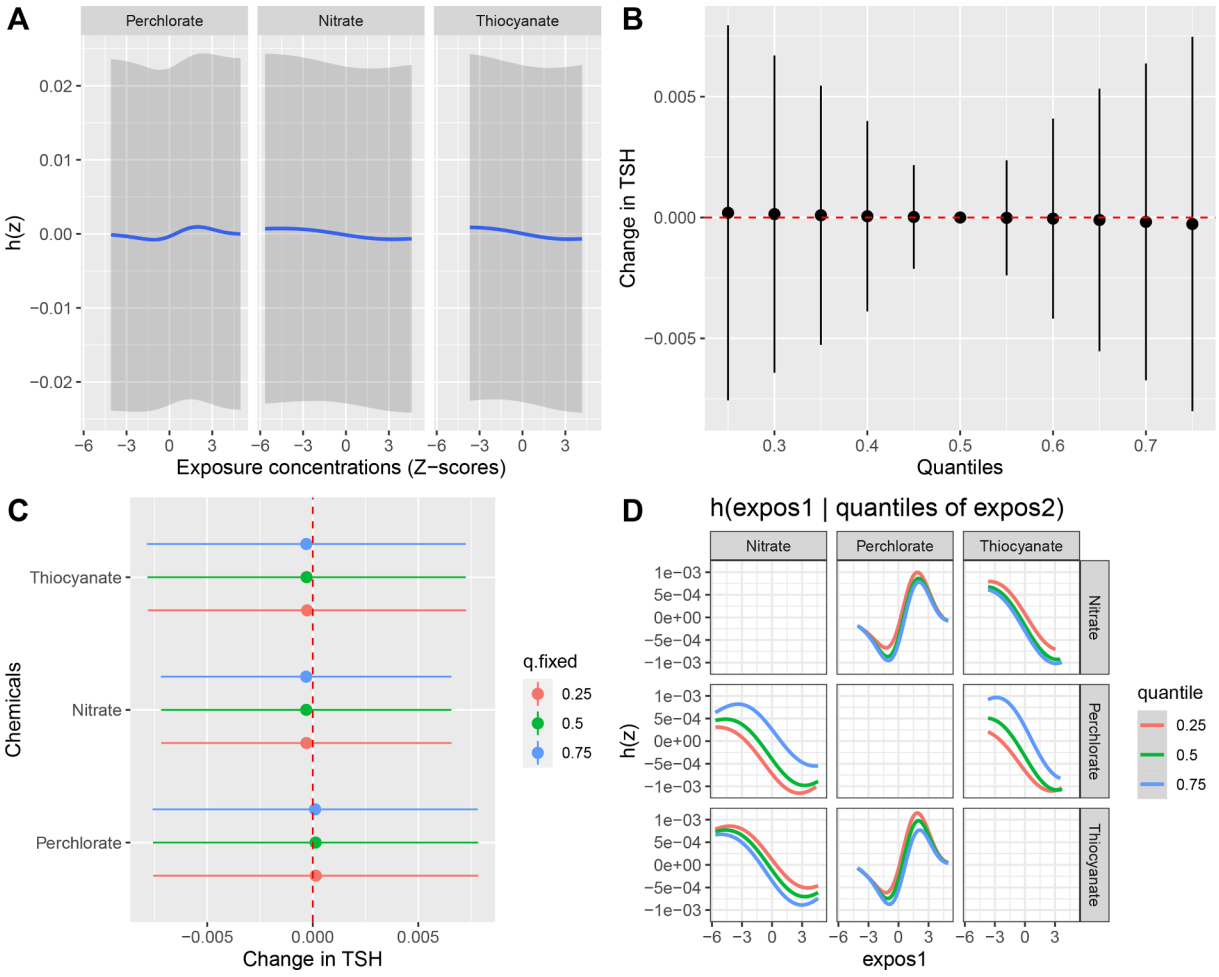

Fig. 2. Association of co-exposure of perchlorate, nitrate, and thiocyanate with TSH by BKMR model[a]. (A) Univariate exposure–response functions and 95% confidence intervals for each anion with other anions fixed at their median values. (B) Overall effect of the mixture (estimates and 95% confidence intervals). Change in TSH when three anions were set at varying percentiles compared to the median values was plotted. (C) Single goitrogen association (estimates and 95% confidence intervals). Change in TSH comparing each anion at 75th percentile with 25th percentile, with other two anions fixed at 25th, 50th, and 75th percentiles, was plotted. (D) Bivariate exposure–response functions for perchlorate, nitrate, and thiocyanate when another anion was fixed at varying (25th, 50th, 75th) percentiles and other anion was fixed at the median. [a] Model was adjusted for urinary creatinine (mg/dL, continuous), age (years, continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, others), sex (male, female), smoking (never, former, current), alcohol drinking status (never, former, current), physical activity (never, moderate, vigorous), log-transformed body mass index (kg/m^2, continuous), mediation usage (yes or no), serum albumin (g/L, continuous), total energy intake (kcal, continuous), log-transformed C-reactive protein (mg/dL, continuous), log-transformed urinary iodine (μg/L, continuous). Abbreviations: BKMR, Bayesian kernel machine regression; TSH, thyroid stimulating hormone.

and creatinine, the inverse associations of PEC and WQS index with FT4 and PTFQI persisted (Tables S6-7). Comparing extreme PEC quartiles, serum FT4 was 0.2281 pmol/L (LSMD ± SE: −0.2281 ± 0.0750 pmol/L, $P < 0.01$) lower and PTFQI was 0.0818 (LSMD ± SE: −0.0818 ± 0.0214, $P < 0.001$) lower (Table S6). The regression coefficients of WQS index with FT4 and PTFQI were −0.235 (95% CI: −0.330, −0.141) and −0.048 (95% CI: −0.066, −0.030), respectively (Table S7). Moreover, inverse associations of co-occurrence of three anions with FT4 and PTFQI were consistently demonstrated in BKMR model (Figs. S5-7). FT4 and PTFQI both significantly decreased when three anions were set at their 60th percentiles or above compared to the median values.

However, the associations of PEC with FT4 and PTFQI were sensitive to diverse urine dilution adjustment methods (Tables S8-9). Conventional creatinine standardization method resulted in null associations of PEC with FT4 and PTFQI (Table S8), whereas the inverse associations of PEC with FT4 and PTFQI were consistently observed in the covariates-adjusted standardization model (Table S9). It was notable that the inverse associations of co-occurrence of three anions with FT4 and PTFQI persisted in WQS regression and BKMR model regardless of urine dilution adjustment models (Tables S10-11, Figs. S8-13).

Excluding serum CRP and BMI from adjustment models distorted neither the inverse associations of PEC and WQS index with FT4 nor PTFQI (Tables S12-13). Moreover, inverse associations of three anions with FT4 and PTFQI were consistently observed in the truncated multivariate-adjustment BKMR model (Figs. S14-16).

After introducing serum TPOAbs and TgAbs as covariates into multivariate models, the inverse associations of PEC with FT4 and PTFQI persisted (Table S14). Surprisingly, compared with the lowest quartile, the highest PEC quartile was associated with significant decreased serum TSH levels. However, the inverse associations of concurrent exposure of three anions with FT4 and PTFQI, but not TSH, were observed in both WQS regression and BKMR models (Table S15, Figs. S17-19).

4. Discussion

In this US population-based cross-sectional study, we investigated the associations of urinary perchlorate, nitrate, thiocyanate, and their co-occurrence with central thyroid hormones sensitivity in general adults. In single-goitrogen model, inverse associations of urinary

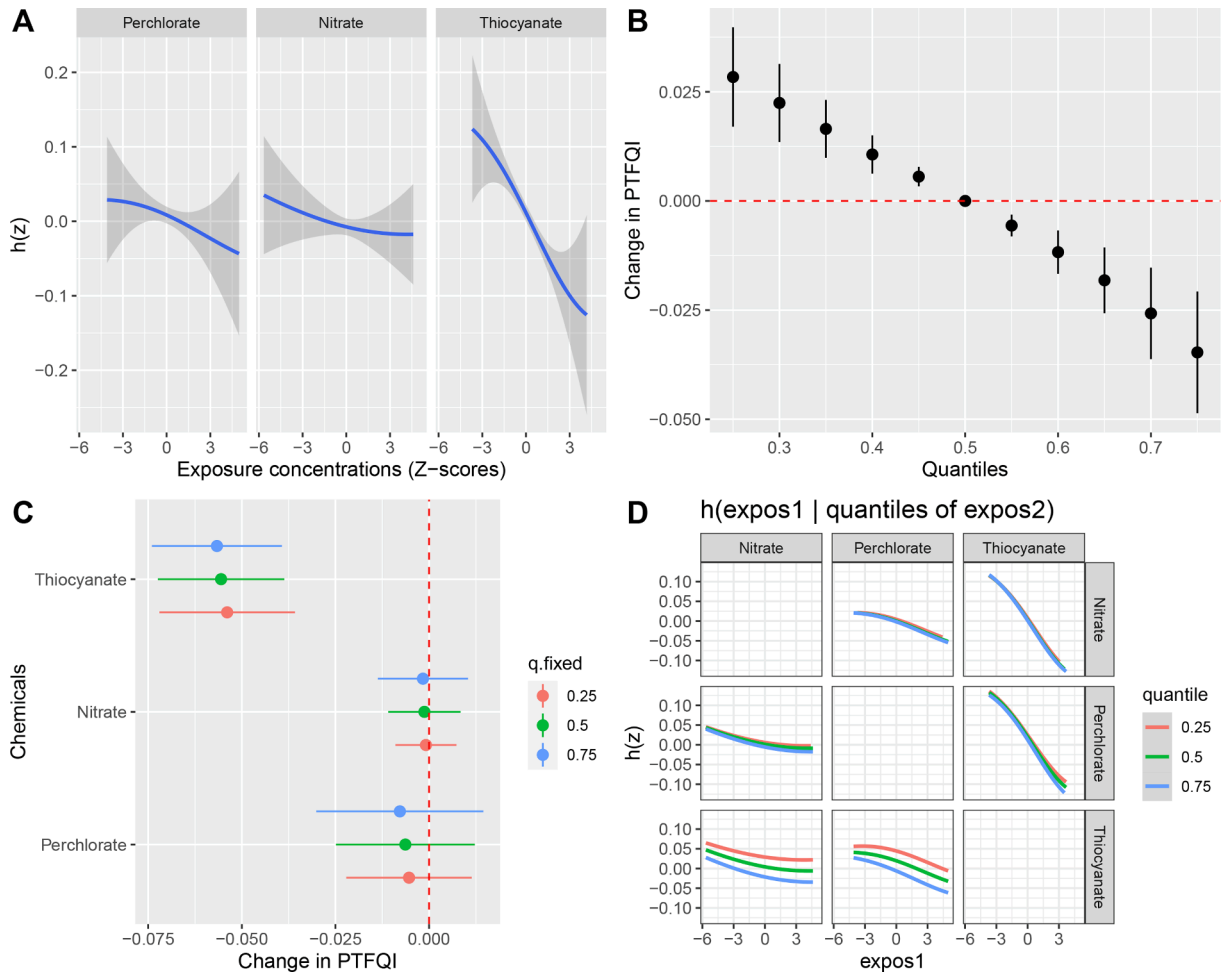

Fig. 3. Association of co-exposure of perchlorate, nitrate, and thiocyanate with PTFQI by BKMR model[a]. (A) Univariate exposure–response functions and 95% confidence intervals for each anion with other anions fixed at their median values. (B) Overall effect of the mixture (estimates and 95% confidence intervals). Change in PTFQI when three anions were set at varying percentiles compared to the median values was plotted. (C) Single goitrogen association (estimates and 95% confidence intervals). Change in PTFQI comparing each anion at 75th percentile with 25th percentile, with other two anions fixed at 25th, 50th, and 75th percentiles, was plotted. (D) Bivariate exposure–response functions for perchlorate, nitrate, and thiocyanate when another anion was fixed at varying (25th, 50th, 75th) percentiles and other anion was fixed at the median. [a] Model was adjusted for urinary creatinine (mg/dL, continuous), age (years, continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, others), sex (male, female), smoking (never, former, current), alcohol drinking status (never, former, current), physical activity (never, moderate, vigorous), log-transformed body mass index (kg/m^2, continuous), mediation usage (yes or no), serum albumin (g/L, continuous), total energy intake (kcal, continuous), log-transformed C-reactive protein (mg/dL, continuous), log-transformed urinary iodine (μg/L, continuous). Abbreviations: BKMR, Bayesian kernel machine regression; PTFQI, Parametric Thyroid Feedback Quantile-based Index.

perchlorate and thiocyanate with PTFQI were observed. We applied three statistical models to investigate the association of co-occurrence of three anions with PTFQI, and observed consistent results. PEC, a weighted index calculated with relative potencies of IUI of three anions, was inversely associated with PTFQI. Inverse association between weighted quantile sum of three anions and PTFQI was also observed. Moreover, in BKMR model, PTFQI significantly decreased when the levels of three anions were at or above their 60th percentiles compared to the median values.

4.1. *Single goitrogens and thyroid function*

The current cross-sectional study represents the first to investigate the associations of urinary perchlorate, nitrate, thiocyanate, and their co-occurrence with central thyroid hormones sensitivity. Considering the important role of thyroid hormones in energy metabolism (Chidakel et al., 2005; Brent, 2012), much concern has been raised about the associations between thyroid hormones and metabolic disorders (e.g., diabetes). Nonetheless, previous studies on thyroid hormones and diabetes yielded mixed results (Gronich et al., 2015; Ittermann et al., 2018), and both hyperthyroidism and hypothyroidism were suggested to be associated with an increased risk of diabetes (Gronich et al., 2015; Ittermann et al., 2018). Laclaustra et al. (Laclaustra et al., 2019) prompted that the contradictory findings might be explained by a mild acquired resistance to thyroid hormone, and observed a positive association between impaired sensitivity to thyroid hormones with risk of diabetes. Recently, TFQI, a composite index estimated based on the interaction between FT4 and TSH, has been applied to estimate central sensitivity to thyroid hormones and gained much attention (Laclaustra et al., 2019; Nie et al., 2020; Liu et al., 2021; Mehran et al., 2021). Positive associations of TFQI with diabetes, metabolic syndrome, and diabetes-related and total mortality were observed (Laclaustra et al., 2019; Alonso et al., 2021; Mehran et al., 2021). Moreover, Mehran et al. (Mehran et al., 2021) suggested that the new TFQI index seemed to be the indicator of reduced sensitivity to thyroid hormones most suitable to associate its population variations with diabetes and hypertension in euthyroid subjects.

Our results were in line with the limited evidence, which revealed the inverse association of urinary perchlorate with FT4 in general population (Mendez and Eftim, 2012; McMullen et al., 2017). Much concern

has been raised about the effect of perchlorate exposure on thyroid function over decades, and serval clinical studies had been conducted in euthyroid subjects (Lawrence et al., 2000; Lawrence et al., 2001; Greer et al., 2002; Braverman et al., 2006; Bruce et al., 2018). These clinical studies reported no effect of a range of perchlorate doses (0.007–0.5 mg/kg-day) on thyroid and pituitary hormones (Table S16). Moreover, several occupational studies had investigated the association between chronic perchlorate exposure and thyroid function, and reported no effects of perchlorate on pituitary and thyroid hormones (Lamm et al., 1999; Braverman et al., 2005). No differences in thyroid parameters were found in 14 perchlorate workers with a mean absorbed dose up to 34 mg/d (Lamm et al., 1999), and Braverman et al. reported no adverse changes in thyroid hormones with doses up to an estimated 0.167 mg/kg-d (Braverman et al., 2005). The mean urinary perchlorate level in the current study was 5.48 μg/L, corresponding to a mean dose of 0.10 μg/kg-d. Based on the clinical study by Greer et al. (Greer et al., 2002), the National Research Council study committee proposed a reference dose of 0.7 μg/kg based on a No Observed Effect Level (NOEL) for IUI (NRC, 2005). The estimated daily perchlorate dose in this study is much lower than the NOEL for IUI of 7 μg/kg-d, suggesting that perchlorate was unlikely to operate via the known mechanism of action (MOA) (Pleus and Corey, 2018). IUI must be significantly decreased and sustained for months or longer to remarkably reduce thyroidal iodine stores and produce thyroid hormone changes (Greer et al., 2002; Pleus and Corey, 2018). Whether low environmental levels of perchlorate may operate via another MOA is unknown, and needs further investigation (Pleus and Corey, 2018). In addition, compared with clinical and occupational studies, epidemiologic studies yielded mixed results (Table S1). The inconsistency may be explained by iodine sufficiency in the population, population characteristics (e.g., general adults and pregnant women), and study design (e.g., timing of sampling) (Pleus and Corey, 2018).

Notably, Mendez et al. (Mendez and Eftim, 2012) and McMullen et al. (McMullen et al., 2017) observed no significant associations of urinary thiocyanate with FT4 and TSH in general population, inconsistent with our results. However, sample sizes were small and different populations (adolescents aged 12–20 years were included) were included in these studies (Mendez and Eftim, 2012; McMullen et al., 2017). McMullen et al. (McMullen et al., 2017) found that participants aged 12–21 had significantly lower levels of urinary thiocyanate compared to those aged 22–49. National Survey on Drug Use and Health estimates suggested that adults had higher rates of current use of a tobacco product compared to adolescents (Institute of Medicine, 2015). In the current study, smokers had much higher urinary thiocyanate measurements than non-smokers, consistent with previous evidence (Buratti et al., 1997; Jain, 2013). A cross-sectional sample of 2027 females from NHANES 2003–2008 reported that urinary thiocyanate levels among smokers were approximately five times higher than non-smokers (Jain, 2013). Moreover, a publication in 99 healthy male white-collar workers found that urinary thiocyanate was correlated with urinary cotinine ($r = 0.86$, $P < 0.001$, n = 99), a well-known biomarker for tobacco smoking (Buratti et al., 1997). The association between tobacco smoking and thyroid function had gained much attention during past decades (Hegedüs et al., 1985; Brix et al., 2000; Vestergaard, 2002). A pair-matched case-control study in Denmark, an area with borderline iodine deficiency, suggested that smoking is associated with an increased risk of suffering clinically overt thyroid disease (Brix et al., 2000). Thiocyanate generated from cigarette smoking can help explain the association between smoking and thyroid diseases (Erdogan, 2003; Steinmaus et al., 2007). Nonetheless, compared with perchlorate, which had been announced by US Environmental Protection Agency as a regulated contaminant (EPA, 2017), thiocyanate is not independently regulated (McMullen et al., 2017). Further studies are warranted to replicate our findings and have a better understanding of the association between low-level environmental thiocyanate exposure and thyroid function, and thiocyanate may need more aggressive regulation.

In addition, we observed null associations of urinary nitrate with FT4 and TSH in US general adults. Nevertheless, a previous cross-sectional study in Netherlands suggested that higher nitrate exposure levels were associated with lower serum TSH measurements (van Maanen et al., 1994). Notably, nitrate concentrations of drinking water were applied to estimate the nitrate exposure levels in that study (van Maanen et al., 1994), probably introducing imprecise assessment and misclassification of nitrate exposure. Besides, some important confounders, such as iodine and other NIS inhibitors, were not adjusted. Further studies are warranted to investigate the association between environmental nitrate exposure and thyroid function in general population.

4.2. Co-exposure of goitrogens and thyroid function

Humans are exposed to three iodine inhibiting anions from various environments and foods (Zhu et al., 2019), and estimating the health effects of the mixture has increasingly been of interest (Bruce et al., 2013; Horton et al., 2015; Mortensen et al., 2016). However, much remains to be learned about the association between co-exposure of three anions and thyroid function in general population. Previous evidence, although limited, revealed no significant associations of PEC with FT4 and TSH in general population (Bruce et al., 2013), inconsistent with our results. However, the observed no significant associations of PEC with FT4 and TSH by Bruce et al. (Bruce et al., 2013) should be interpreted cautiously since the confusion introduced by conventional creatinine standardization. Our results highlighted the pitfalls inherent in dividing urinary analytes levels by creatinine, the performance of which had been challenged over a long period (Christensen et al., 2014; Hoet et al., 2016; O'Brien et al., 2016). Previous evidence had pointed out the poor performance of traditional creatinine standardization in the scenario where some covariates (e.g., BMI) can affect creatinine (O'Brien et al., 2016). In simulation studies, covariate adjustment (creatinine as a covariate in the model) and covariate-adjusted standardization performed well in the above scenario (O'Brien et al., 2016). Further investigations should take the priorities of urine dilution adjustment methods into account, and a directed acyclic graph as well as multiple urine dilution adjustment methods are recommended, if the measurement error is a unneglectable concern.

Biological understanding of three anions is necessitated when the association of the mixture with thyroid function is to be examined. It is acknowledged that three agents inhibit iodine uptake at NIS, and several in vivo and in vitro publications had examined the relative potencies of three anions to cause IUI in the past decades (Table S17) (Wyngaarden et al., 1953; Alexander and Wolff, 1966; Greer et al., 1966; Tonacchera et al., 2004; De Groef et al., 2006). The relative IUI potency of perchlorate was validated to be much greater than those of nitrate and thiocyanate (Table S17) (Wyngaarden et al., 1953; Alexander and Wolff, 1966; Greer et al., 1966; Tonacchera et al., 2004), and the relative IUI protencies of several goitrogens were summarized as $TcO_4^- \geq ClO_4^- > ReO_4^- > SCN^- > BF_4^- > I^- > NO_2^- > Br^- > Cl^-$ by Wolff (Wolff, 1998). Tonacchera et al. (Tonacchera et al., 2004) observed that perchlorate, nitrate and thiocyanate acted on the NIS in a simple additive fashion and the relative molar potency of perchlorate to inhibit radioactive iodine uptake was 15 and 240 times that of thiocyanate and nitrate, and established the PEC formula. In our study, the average contributions to NIS inhibition were estimated to be 0.8% for perchlorate, 79.0% for nitrate, and 19.6% for thiocyanate, which is similar to what others reported (Tarone et al., 2010; Bruce et al., 2013). Apart from PEC, we applied two statistical methods to investigate the association of co-exposure of three anions with thyroid function, and validate the results based on PEC in the current study. Inverse associations of co-exposure of three anions with PTFQI and FT4, where thiocyanate had the largest contribution, were consistently observed in WQS regression and BKMR models.

Previous studies typically investigated the associations between concurrent exposure of three anions and thyroid parameters with linear regression models (Bruce et al., 2013; Horton et al., 2015; Mortensen

et al., 2016). In this study, we applied multiple statistical models that allow for both linear and non-linear exposure–response relationships, and observed consistent results. Another important concern is the potential interactions among chemicals. In vitro data suggested that perchlorate, nitrate, and thiocyanate had addictive effects on inhibiting NIS (Tonacchera et al., 2004). A previous study constructed a two-way interaction model, and reported that the regression coefficient of perchlorate with T4 was higher in the upper thiocyanate tertile than lower tertile among 362 US women with urinary iodine < 100 μg/L (Steinmaus et al., 2007). BKMR allows a flexible exposure–response function of mixtures and their interactions (Bobb et al., 2015), and was preferred to investigate the interactions among three anions in the current study. Using bivariate exposure–response functions, we provided a clue that perchlorate and thiocyanate may interact in affecting FT4 levels. Whether the absence of significant association between urinary nitrate and thyroxine and clear interactions between nitrate and other two anions may be attributed to differences between in vivo and in vitro is unknown and needs further investigation. Regardless, previous evidence as well as our findings suggested that these anions sharing common MOA may interact in affecting thyroid function.

Overall, considering the ubiquitous exposure of three anions and their potential interactions, further studies or risk assessments should have an exposure-wise perspective.

4.3. Modification of iodine status and tobacco smoking

Women with low excreted iodine, among whom the strongest inverse association between urinary perchlorate and serum T4 was observed, had been identified as susceptible population to perchlorate exposure (Blount et al., 2006). In our study, urinary perchlorate was inversely associated with FT4 across subgroups defined by urinary iodine, and the inverse association was much stronger in low iodine excretion group. Moreover, the interaction between perchlorate and iodine was marginally significant. To date, little was known about whether the association between thiocyanate exposure and thyroid function may vary across strata defined by excreted iodine in general population. An inverse association between urinary thiocyanate and serum TSH was observed among general adults with low excreted iodine in the current study, and evidence of effect modification of iodine was revealed. Although suggestive, the observed effect modification of excreted iodine in our study should be interpreted cautiously since spot urine samples were applied to determine iodine levels. Urinary iodine levels can have marked within-individual variability over time (Steinmaus et al., 2007; Zimmermann et al., 2008), hence, single measurement of urinary iodine may cause misclassification and hardly reflect the sufficiency or insufficiency of individual iodine intake (Zimmermann et al., 2008).

Interestingly, urinary perchlorate was inversely associated with PTFQI in participants with urinary iodine < 100 μg/L, and a significant interaction between urinary perchlorate and excreted iodine was observed. There is growing evidence that iodine has impacts on hypothalamus-pituitary-thyroid HPT axis other than enables production of thyroid hormones (Li et al., 2012; Lavado-Autric et al., 2013; Calil-Silveira et al., 2016). Lavado-Autric et al. (Lavado-Autric et al., 2013) observed an increased type 2 deiodinase (DIO2) activity in the pituitary of low-iodine diet rats. Pituitary triiodothyronine (T3) levels, which are determined by DIO2 activity (Kaplan, 1984; Li et al., 2012), regulate the gene expression and secretion of TSH (Li et al., 2012).

Tobacco smoking is recognized as an iodine-independent risk factor for thyroid diseases (Wiersinga, 2013; Kim et al., 2019). To date, evidence of interaction among smoking and three anions on thyroid function remain scant. A previous cross-sectional study in US women with urinary iodine levels < 100 μg/L found that the regression coefficient between perchlorate and T4 was greater in women with high cotinine measurements (Steinmaus et al., 2007). Cotinine, the metabolite of nicotine, has a half-life of 15–20 h in plasma (García-Esquinas et al., 2018), and had been applied as a biomarker f or recent smoking (Benowitz et al., 2009). Compared with respondents' replies to questionnaires, misclassification introduced by biased reporting or recall could be avoided with the sensitive biomarker. No evidence of effect modification of serum cotinine was observed in US general adults in our study. It should be noted that Steinmaus et al. (Steinmaus et al., 2007) found no clear evidence of interaction between urinary perchlorate and cotinine on serum T4 in men or in women with urinary iodine levels > 100 μg/L. Compared with males, females may have a much higher risk of goiter due to their increased susceptibility to autoimmune thyroid disease or increased demands on the thyroid during pregnancy (Blount et al., 2006). Further studies with sex, excreted iodine, and tobacco smoking considered are warranted to identify the subpopulations that may be more susceptible to environmental exposure to three anions.

4.4. Strengths and limitations

The current study had several strengths. First, analyses were performed in a large and nationally representative sample from three NHANES cycles. Second, our study applied multiple statistical models, including the traditional OLS regression and two recently developed machine learning methods, to examine the associations of concurrent exposure of three anions with FT4, TSH, and central thyroid hormones sensitivity, and consistent results were observed.

However, the limitations of our study should not be neglected. First, we examined the associations of three goitrogens and their co-occurrence with central sensitivity to thyroid hormones among US adults with a cross-sectional design. Hence, our results should be interpreted cautiously, due to the limitations of causal inference and generalization of our results to other populations worldwide. Second, spot urine samples were used to determine the concentrations of three anions and iodine, and probably resulted in measurement error and misclassification, owning to variable hydration of participants and temporal variability. Urinary iodine levels can have marked within-individual variability over time (Steinmaus et al., 2007). Single measurement of perchlorate can hardly reflect the long-term exposure level since the relatively short half-life (Greer et al., 2002; Steinmaus et al., 2007). However, it was burdensome to collect 24-h urine samples in large-scale surveys, such as NHANES, and several urine dilution adjustment methods were performed to evaluate the robustness of our results. Third, within-person fluctuations in serum TSH, which are caused by internal and external factors (e.g., pulsatile secretion, circadian rhythm, season, and ageing) (van der Spoel et al., 2021), could not be captured with NHANES single measurement of hormones. Serum TSH concentration reaches peak and nadir at approximately 23 p.m. and 16 p.m., respectively, and the peak concentration is almost twice the nadir concentration (Fisher, 1996). Hence, further longitudinal studies with repeated measurements of three anions and iodine in urine samples and pituitary and thyroid hormones are expected to have a better understanding of the causal associations of long-term, low-dose three goitrogens exposure with thyroid function, and validate our results.

Moreover, despite confounders based on a priori knowledge from the literature were sufficiently controlled in models, residual confounding could not be eliminated. For example, tobacco smoking, the common cause of thiocyanate exposure and thyroid dysfunction (Bartalena et al., 1995), is an unneglectable confounder in the field of thiocyanate exposure and thyroid function. Although we have adjusted smoking in models, multiple mechanisms of toxicity aroused by smoking (Utiger, 1995) may lead to residual confounding, and complicate the investigation of thiocyanate and thyroid function (Chandler and Day, 2012).

Additionally, the limitations of the composite index should be acknowledged. First, the new PTFQI index failed to define central thyroid hormones sensitivity from the physiological perspective, although it is established based on the interaction between TSH and FT4 (Laclaustra et al., 2019) and has been applied in a growing body of epidemiologic studies (Laclaustra et al., 2019; Juiz-Valiña et al., 2020; Nie et al., 2020; Alonso et al., 2021; Liu et al., 2021; Mehran et al., 2021). Second, PTFQI

merely manifests the magnitude of central thyroid hormones sensitivity (Laclaustra et al., 2019), however, assessment of peripheral sensitivity to thyroid hormones is sophisticated and probably requires gene sequencing (Refetoff, 1994). More importantly, the role of central thyroid hormones sensitivity in the pathogenesis of thyroid diseases remains unclear. The complexity of the parameter definition and limited clinical investigations make our results hard to interpret for clinicians, and further studies are anticipated to elucidate the impacts of central sensitivity to thyroid hormones on the pathogenesis, treatment, and prognosis of thyroid diseases.

5. Conclusions

Urinary perchlorate and thiocyanate were positively associated with central thyroid hormones sensitivity in US general adults. Using three statistical models, we consistently observed a positive association of co-occurrence of perchlorate, nitrate, and thiocyanate with central sensitivity to thyroid hormones. These results were merely correlative, and further studies with experimental design are warranted to validate our results and elucidate the underlying causative mechanistic links. Significant inverse associations of urinary perchlorate, thiocyanate, and co-occurrence of three anions with serum FT4 were also observed. The observed significant associations of co-exposure of three anions with serum FT4 and PTFQI were primarily attributed to thiocyanate. Further studies should have an exposure-wise perspective, and thiocyanate should be of more concern. The estimated perchlorate dose in this study was much lower than the NOEL recognized to cause IUI. Whether there exists alternative MOA of perchlorate remains unclear and needs further investigation. Although suggestive and worth further exploration, our results should be interpreted with caution due to the cross-sectional and single-measure study design. Further longitudinal epidemiologic studies with a repeated-measures study design, which can allow for within-individual variability, are warranted to validate our results, and have a better understanding of the causal associations of long-term, low-dose three goitrogens exposure with thyroid function.

CRediT authorship contribution statement

Lei King: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft. **Yue Huang:** Validation, Data curation, Investigation, Writing – review & editing. **Tao Li:** Methodology, Validation, Data curation, Investigation, Writing – review & editing. **Qiang Wang:** Validation, Data curation, Investigation. **Wanyi Li:** Data curation, Investigation. **Zhilei Shan:** Methodology, Writing – review & editing. **Jiawei Yin:** Methodology, Writing – review & editing. **Liangkai Chen:** Methodology, Writing – review & editing. **Pei Wang:** Data curation, Investigation. **Changchang Dun:** Data curation, Investigation. **Litao Zhuang:** Data curation, Investigation. **Xiaolin Peng:** Conceptualization, Supervision, Project administration, Writing – review & editing. **Liegang Liu:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

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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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author (lgliu@mails.tjmu.edu.cn).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107249.

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