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CLINICAL STUDY

The hidden danger: prolonged exposure to inorganic contaminants and kidney health in adolescents

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ABSTRACT

Research on the impact of prolonged exposure to inorganic contaminants, such as perchlorate, nitrate, and thiocyanate (PNT), on the kidney health of individuals in the 12~19 age range is lacking. We analyzed data from the United States National Health and Nutrition Examination Survey (NHANES) over the period 2005–2016 to investigate the linear relationship between chronic kidney disease (CKD)-related parameters and PNT exposure levels, and to explore population heterogeneity from multiple aspects. Weighted multiple regression analysis estimated the independent associations between water or urine exposure indicators and CKD-related parameters. We utilized stratified subgroup analysis and smooth linear fitting as supplements. Lower estimated glomerular filtration rate (eGFR) (non- or new-creatinine (CR)-adjusted), albumin-to-creatinine ratio (ACR), and blood urea nitrogen (BUN) were associated with urine PNT exposure. Water exposure may not be the primary source of PNT exposure. Females had a stronger negative association between nitrate and eGFR after non- or new-CR adjustment. With the most demographic heterogeneity, perchlorate affected eGFR, ACR, and BUN. Our findings associated urinary PNT exposure with altered renal parameters (eGFR, ACR, BUN) in adolescents aged 12-19, suggesting potential environmental health implications that warrant further investigation.

IMPACT STATEMENT

This study observed associations between urinary PNT levels and altered renal parameters (eGFR, ACR, BUN) in adolescents aged 12–19. Tap water was identified as a minor exposure source, suggesting that other routes may contribute significantly to PNT intake. These findings provide valuable evidence for future environmental health policies regarding PNT exposure.

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1. Introduction

Chronic Kidney Disease (CKD) is a serious and increasingly prevalent medical condition worldwide, posing significant challenges to both clinical and public health systems [1]. Children and adolescents with CKD represent a particularly vulnerable population, facing a high risk of progressing to end-stage kidney disease, which is associated with increased hospitalization rates and mortality [2]. For children aged 0 to 14 requiring dialysis, the remaining life expectancy is only about 20 years [3]. Traditional risk factors for CKD progression in this population include hypertension, obesity, diabetes, and disorders of divalent mineral metabolism [4–7]. However, emerging evidence suggests that environmental contaminants, such as perchlorate, nitrate, and thiocyanate (PNT), may also play a significant role in the development and progression of CKD.

PNT are ubiquitous environmental inorganic contaminants. Widely used in military and industrial applications, such as solid fuel propellants, pyrotechnics, and electroplating solutions, perchlorate can contaminate food and water supplies, posing human health risks [8,9]. 1998 the U.S. EPA added perchlorate to the Drinking Water Contaminant Candidate List due to its widespread environmental presence [10]. A study by Huber et al. combining data from the National Health and Nutrition Examination Survey (NHANES) and the Unregulated Contaminant Monitoring Rule (UCMR1), found that 23.7% of perchlorate exposure in the general population was attributable to contaminated tap water and food [11].

Nitrate, another common environmental contaminant, originates from biological nitrogen fixation, agricultural fertilizers, and processed meat preservatives. It is naturally present in water and green plants, with high

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concentrations in leafy greens such as kale and radishes, as well as in dairy products [12]. Thiocyanate, a biomarker of cigarette smoke exposure, is also associated with industrial processes, including gold mining and coal gasification [13,14]. Urinary levels of PNT are frequently used as biomarkers to assess exposure levels in epidemiological studies [15,16].

The health risks associated with PNT exposure are diverse and well-documented. A growing body of research indicates that these contaminants may inversely affect liver function [17], disrupt thyroid activity [15], and even contribute to cancer development [18] and obesity [9]. For instance, a cross-sectional study by Guo et al. suggested a negative association between perchlorate levels in drinking water and the weight and height of children [19]. Additionally, PNT disrupts the endocrine system by competitively inhibiting iodide uptake, affecting thyroid function. Experimental studies have shown that perchlorate can increase insulin production and electrical activity in pancreatic beta cells by modulating calcium channel activity, similar to the effects of BAY K8644 [20]. Furthermore, perchlorate exposure has been linked to oxidative stress in liver cells [17], highlighting its potential for systemic toxicity.

Despite these findings, the impact of PNT exposure on kidney health, particularly in children and adolescents, remains poorly understood. While some studies suggest potential protective effects of PNT on renal function, such as improved estimated glomerular filtration rate (eGFR) and reduced urinary albumin-to-creatinine ratio (ACR), others report adverse outcomes, including thyroid dysfunction and metabolic disturbances [15,17,18]. A notable study analyzing data from 13,373 U.S. adults found that elevated nitrate and thiocyanate levels were associated with improved renal function markers, such as increased eGFR and decreased ACR. However, the study's cross-sectional nature limits causal inference [19]. These conflicting findings underscore the need for further research to clarify the mechanisms and overall health impacts of PNT exposure, particularly in vulnerable populations such as adolescents.

Adolescents are uniquely susceptible to environmental pollutants due to their ongoing physiological development and the potential for long-term health consequences. However, research on the effects of PNT exposure on renal development and function in this age group is limited. To address this critical gap, we conducted a cross-sectional study using data from the NHANES to examine the association between urinary PNT levels and renal function markers, including eGFR, ACR, and blood urea nitrogen (BUN), in adolescents aged 12–19. We hypothesize that prolonged exposure to PNT inversely affects renal function in this population, as measured by reduced eGFR, elevated ACR, and increased BUN. By focusing on this vulnerable group, our study aims to provide new insights into the potential risks of PNT exposure and inform public health strategies for mitigating these risks.

2. Materials and methods

2.1. Study participants

The cross-sectional analysis of NHANES data, which collects information on the health and nutrition statuses of a nationally representative sample of non-institutionalized Americans (Protocol #2005-06, Protocol #2011-17), was approved by the National Center for Health Statistics Ethics Review Board. Every procedure followed the guidelines set out in the Declaration of Helsinki.

The people who were assessed for PNT in spot urine samples or for perchlorate and nitrate in home tap water samples were identified (n=4,963) out of all the people aged 12 to 19 who ever took part in the US NHANES between 2005 and 2016 (n=8,886). Next, those who lacked information on their BUN (n=0), ACR (n=18), or eGFR (n=534) were excluded. Finally, exclude participants without available data of covariates (n=818): age by year (n=0); age by month (n=8); sex (n=0); race (n=0); family poverty income ratio (PIR) (n=289); education level (n=0); body mass index (BMI) (n=2); taken prescription medicine (n=1); systolic blood pressure (BP)/diastolic BP (n=130); glycohemoglobin/fasting blood glucose (n=9); leisure time physical activity (LTPA) (n=289); daily protein intake (n=87); uric acid (n=1); triglycerides (n=2); cholesterol (n=0), leaving a final sample of 3,593 participants chosen for the primary analyses. Figure 1 displays the specifics of the research population's inclusion and exclusion.

2.2. Measurement of chronic kidney disease

CKD was assessed by two main variables: eGFR (mL/min/1.73 m^2) and ACR (mg/g). The most recent modified version of the Schwartz equation was used to compute the eGFR: eGFR = 0.413*[height (cm)/serum creatinine (mg/dL) [21], whereby the data on serum creatinine and standing height were sourced from the Standard Biochemistry Profile & Hormones module and the Body Measures module, respectively. Trained Mobile Examination Center (MEC) health technicians gathered the body measurement data. The DxC800 modular chemistry side measures creatinine levels in serum, plasma, or urine using the Jaffe rate technique (kinetic alkaline picrate). An isotope dilution mass spectrometry reference technique may be used to track the creatinine calibration. BUN was included as a supplementary metabolic parameter to provide additional context on nitrogen homeostasis.

2.3. Quantification of chemicals in urine and home tap water

Human urine samples may have their nitrate, perchlorate, and thiocyanate levels quantitatively assessed using this method, which combines ion chromatography with electrospray tandem mass spectrometry. An IonPac AS16 column with sodium hydroxide as an eluent sorts the particles. Negative ions are made by an electrospray contact and sent to the mass spectrometer from the column eluent. Relative

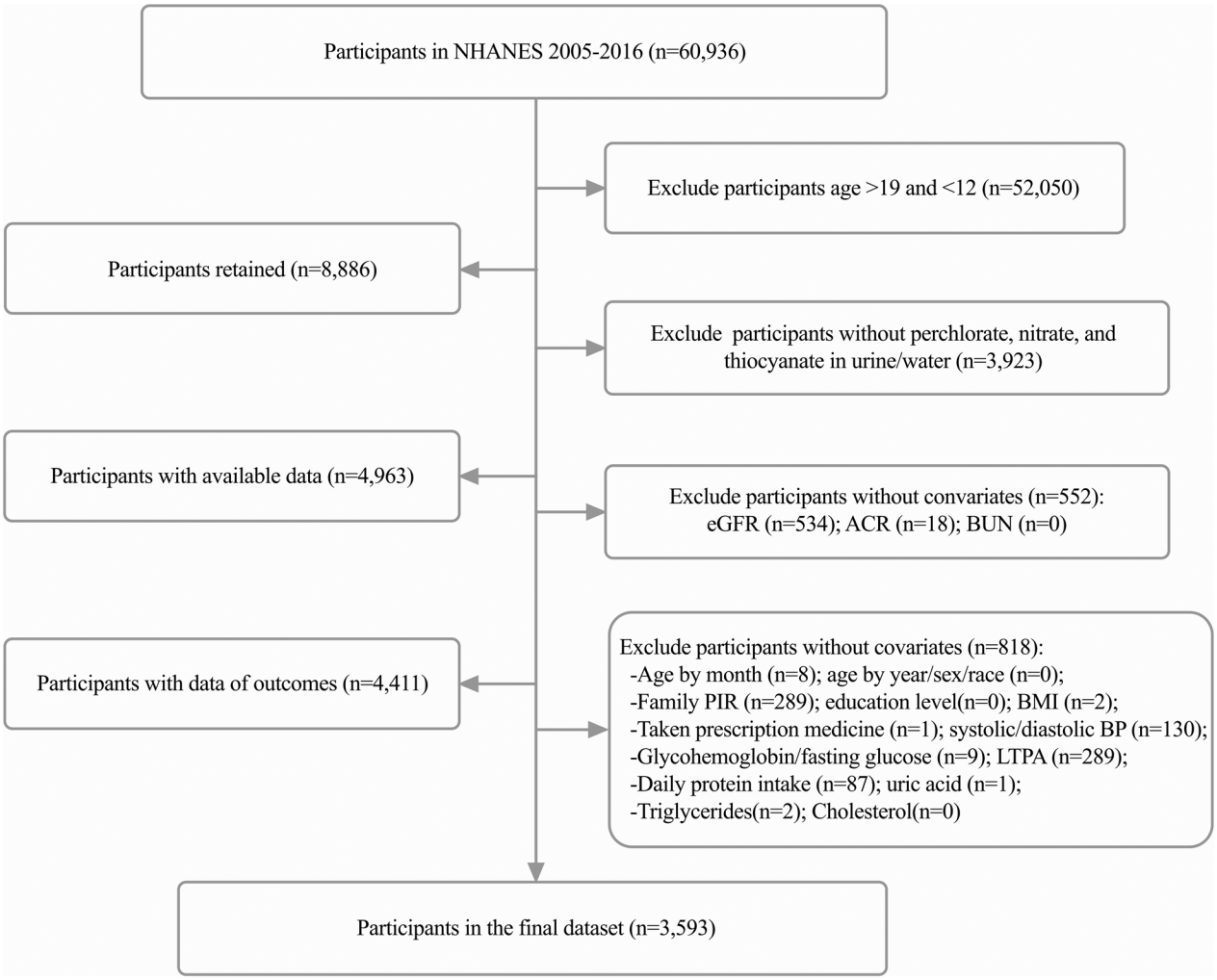

Figure 1. The inclusion and exclusion details of the study population.

response factors—the ratio of the native analyte to the stable isotope-labeled internal standard—and standard concentrations are used to compute the concentrations of individual analytes. Lower detection limits for urinary PNT were 0.05, 700, and 20 ng/mL, respectively. If the result is below the limit, the variable value is the detection limit divided by the square root of two.

Only data from 2005 to 2006 on household tap water perchlorate and nitrate amounts were available. The IonPac AS20 column uses sodium hydroxide eluent for chromatographic separation. An electrospray interface generates and sends negative ions from the column eluent to the mass spectrometer. The data set's analytes had stable detection limits. The variable "URD___LC" specifies whether the result was below the detection limit. Quality assurance and quality control techniques are outlined on the NHANES website.

2.4. Covariates

Age, sex, race, family PIR, education, BMI, prescription drug use, BP, diabetes, LTPA in the last week, daily protein consumption, uric acid, triglycerides, and cholesterol were examined as possible correlates of eGFR, ACR, and BUN. All factors except "age" were categorical in this research.

Poverty criteria from the Department of Health and Human Services determine the family PIR. The measure has three levels: "mild" (Family PIR <1.99), "moderate" (1.99 ≤ Family PIR ≤ 3.49), and "severe" (Family PIR > 3.49). According to participant age, all educational information was taken from "Education Level - Children/Youth 6-19". Adult BMI categories vary from those used for children and adolescents, with "underweight" (BMI 5th percentile), "normal weight" (BMI 5th to 85th percentiles), "overweight" (BMI 85th to 95th percentiles), and "obese" (BMI 95th percentile) being the most common [22]. The question "In the past month, have you used or taken medication for which a prescription is needed?" defines "taken prescription medicine". Those over 16 replied for themselves, while those under 16 and those who could not answer *via* proxies did so. The clinical practice guideline classifies BP data as normal, high, Stage 1, and Stage 2 [23]. Individuals with HbA1c ≥6.5% and fasting glucose ≥126mg/dL were classified as diabetic, whereas those with 5.7% to 6.4% and fasting glucose 100 ~ 125mg/dL were considered high risk (pre-diabetes). The prior week's LTPA measures

exercise intensity. The definition of "active" is 420 min or more each week, according to the note on this metric in NHANES. For the model's confounders adjustment, daily protein consumption, uric acid, triglycerides, and cholesterol were dichotomous variables split by medians.

2.5. Statistical analyses

R-project and EmpowerStats were used for all statistical analyses, with a significance threshold of $p < 0.05$ and two-tailed testing. This research followed the CDC data analysis criteria. The NHANES survey design is complex and prone to non-response; therefore, we employed sample weights to evaluate the data. Specifically, WTSPC2YR weights were utilized to analyze water perchlorate and nitrate contents.

In this research, urinary creatinine concentration was linked to the primary outcomes. Traditional creatinine adjustment (traditional-CR-adjustment) and a new method for covariate-adjusted creatinine standardization (new-CR-adjustment) were used separately to adjust urine dilution on urine PNT data [19,24]. This formula was used for traditional creatinine adjustment: PNT-traditional = UC/Ucr, where UC represents the measured urinary PNT concentration (ng/mL) and Ucr represents the observed urinary creatinine concentration. The covariate-adjusted creatinine standardization was performed using the following formula [25,26]: PNT-new = UC/(Ucr/Ucr-fit). Given the unique physiological characteristics of adolescent populations, we employed both non-creatinine-adjusted and creatinine-adjusted models for eGFR assessment. This dual approach accounts for potential confounding effects of muscle mass development during puberty, which is particularly important when analyzing sex-specific differences.

We constructed a multivariate linear regression model, regressing the ln-transformed creatinine concentration as the dependent variable on factors such as age, sex, race, BMI, and eGFR that are known to influence urine dilution. Ucr and Ucr-fit represent observed urinary creatinine levels and fitted creatinine values obtained from this model. UC represents the measured urinary PNT concentration (ng/mL). Then, indicators on all exposure factors were natural logarithmic (ln) transformed, including ln (PNT), ln (PNT-traditional), and ln (PNT-new). PNT exposures in water were also ln-transformed, including ln (perchlorate) and ln (nitrate), before multivariable analysis to better approximate normal distribution.

Continuous variables are means and SD, while categorical variables are frequencies or percentages. We dichotomized continuous variables for clinical interpretability and alignment with epidemiological standards. To mitigate bias and power loss, we performed sensitivity analyses with constant variables, confirming consistent results, and used biologically meaningful thresholds supported by the literature. Median, 25th, and 75th percentiles of eGFR, ACR, and BUN were computed based on participant characteristics. Weighted means (continuous variables), percentages (categorical variables), and baseline characteristic standard errors were analyzed using sample weights. After adjusting for relevant confounders, weighted multiple regression analysis determined the independent connection between water or urine exposure indicators and CKD-related indicators, represented by β values and 95% confidence intervals. Visualization is complemented by smooth linear fitting. Three quantitative models assessed possible associations: Model 1 did not include any covariates for adjustment; Model 2 was adjusted for age, sex, race, and BMI. In Model 3, eGFR was adjusted for: age, sex, race, education level, BP, diabetes, LTPA, daily protein intake (gm/kg), and uric acid; ACR was adjusted for: age, sex, BMI, BP, diabetes, daily protein intake (gm/kg), uric acid; BUN was adjusted for: age, sex, race, family PIR, education level, LTPA, daily protein intake (gm/kg), uric acid. Covariates were selected *via* backward elimination. Starting with all potential confounders (e.g., age, sex, race, BMI), variables were sequentially removed based on significance ($p > 0.10$) and model fit (Akaike Information Criterion, AIC). The process continued until only significant covariates remained, ensuring a parsimonious model while minimizing overfitting.

Subgroup analysis of nonlinear interactions was described using weighted generalized additive models and smooth curve fitting. The data were stratified to examine relevant differences by age, sex, race, family PIR, education level, and BMI. Ln likelihood ratio tests were used to determine the statistical significance of urine PNT-covariate interactions on eGFR, ACR, and BUN.

To address potential biases, we conducted a variance inflation factor (VIF) analysis, confirming no significant multicollinearity (VIF < 5). Sensitivity analyses excluded participants with extreme values (e.g., eGFR < 15 mL/min/1.73 m^2) or comorbidities (e.g., diabetes, hypertension) to evaluate robustness. The sample size was determined based on NHANES data availability, ensuring sufficient statistical power. A post-hoc power analysis using G*Power (version 3.1) indicated that our final sample of 3,593 participants exceeded the required size ($n = 1{,}500$) to detect a medium effect size (Cohen's $f^2 = 0.15$) with 80% power at $\alpha = 0.05$. The complex survey design, including stratification, clustering, and weighting, was accounted for to ensure generalizability.

3. Results

3.1. Characteristics of the study population

Table 1 shows participant demographics and kidney function. eGFR, ACR, and BUN medians (25th–75th percentiles) were 93.93 (82.36–106.62) mL*min^{-1}*1.73m^{-2}, 7.81 (4.82–15.28) mg/g, and 10.00 (8.0–12.0) mg/dL. The cross-sectional research comprised 3,593 individuals, with a mean age of 15.45 ± 0.05 years, and 51.74% were males. The largest proportion was non-Hispanic White (61.27%). Over half (51.13%) have a "High school" education. The percentage of individuals with a "normal" BMI (61.53%) was higher than the total of underweight (3.31%), overweight (16.47%), and obese (18.69%). 70.79% did not use prescription medication in the final month of the study. The majority (84.14%) had normal

Table 1. Demographic characteristics and kidney function state of the participants ($n = 3593$).

	Values ($N = 3,593$)	eGFR ($mL*min^{-1}*1.73m^{-2}$)	*P* values	ACR (mg/g)	*P* values	BUN (mg/dL)	*P* values
Age (years)	15.45 ± 0.05	93.93 (82.36, 106.62)		7.81 (4.82, 15.28)		10.00 (8.00, 12.00)	
Sex			<0.001		<0.001		<0.001
Male	1,856 (51.74)	89.18 (78.91, 102.11)		6.43 (4.22, 11.70)		11.00 (9.00, 13.00)	
Female	1,737 (48.26)	98.18 (87.41, 111.24)		9.61 (5.93, 21.44)		9.00 (8.00, 11.05)	
Race			<0.001		<0.001		<0.001
Mexican American	959 (12.45)	101.24 (88.16, 115.31)		8.10 (4.91, 14.56)		10.00 (8.00, 12.00)	
Other Hispanic	294 (5.62)	99.54 (86.08, 113.27)		7.33 (5.08, 15.34)		10.00 (8.00, 12.00)	
Non-Hispanic White	1,056 (61.27)	93.04 (82.02, 105.06)		7.98 (4.94, 15.74)		10.00 (9.00, 13.00)	
Non-Hispanic Black	996 (13.50)	89.57 (77.74, 102.76)		6.47 (3.98, 12.75)		9.00 (7.00, 11.00)	
Other Race	288 (12.45)	94.21 (81.89, 105.64)		7.95 (4.65, 15.57)		11.00 (9.00, 13.00)	
Family PIR			0.053		0.558		<0.001
Mild (Family PIR <1.99)	2,006 (41.68)	94.34 (82.50, 108.89)		7.50 (4.83, 14.40)		10.00 (8.00, 12.00)	
Moderate (1.99 ≤ Family PIR ≤ 3.49)	758 (23.17)	94.69 (82.55, 106.38)		8.12 (4.87, 15.89)		10.00 (8.00, 12.00)	
Severe (PIR > 3.49)	829 (35.15)	92.68 (81.88, 103.98)		7,92 (4.70, 15.80)		11.00 (9.00, 13.00)	
Education levels			<0.001		<0.001		0.002
Less than high school	1,537 (41.59)	102.84 (91.73, 114.68)		8.56 (5.54, 16.59)		10.00 (8.00, 12.00)	
High school	1,792 (51.13)	88.19 (78.93, 99.04)		7.19 (4.53, 14.53)		10.00 (8.00, 13.00)	
Higher than high school	237 (6.64)	82.04 (74.27, 94.20)		7.02 (3.81, 13.39)		10.00 (8.00, 13.00)	
Other	27 (0.63)	93.83 (84.19, 106.09)		8.92 (4.16, 28.79)		8.00 (7.00, 11.00)	
BMI (kg/m^2)	23.75 ± 0.15		0.148		<0.001		0.103
Underweight (<5%)	104 (3.31)	94.29 (81.73, 109.36)		11.69 (6.93, 38.06)		11.00 (9.00, 14.00)	
Normal (5%-85%)	2,127 (61.53)	93.18 (81.45, 105.49)		8.55 (5.09, 17.70)		10.00 (8.00, 12.00)	
Overweight (85%-95%)	599 (16.47)	94.58 (82.60, 107.27)		6.54 (4.48, 13.60)		10.00 (8.00, 12.00)	
Obese (≥95%)	763 (18.69)	95.37 (83.74, 108.78)		6.15 (4.22, 10.31)		10.00 (8.00, 12.00)	
Taken prescription medicine			0.791		0.735		0.832
Yes	821 (29.21)	93.93 (81.69, 106.04)		7.92 (4.91, 15.53)		10.00 (8.00, 12.00)	
No	2,772 (70.79)	93.96 (82.55, 106.78)		7.68 (4.79, 14.96)		10.00 (8.00, 12.00)	
Blood pressure			<0.001		<0.001		0.861
Normal BP	2,970 (84.14)	94.87 (82.73, 107.38)		7.99 (4.93, 15.50)		10.00 (8.00, 12.00)	
Elevated BP	411 (10.32)	91.52 (80.76, 104.64)		5.80 (4.06, 12.33)		10.00 (8.00, 12.00)	
Stage 1 HTN	181 (4.86)	86.26 (75.21, 95.78)		7.56 (5.00, 18.58)		10.00 (8.00, 13.00)	
Stage 2 HTN	31 (0.67)	82.73 (76.57, 91.27)		5.86 (3.75, 6.86)		9.13 (6.25, 14.00)	
Diabetes			0.001		0.003		0.632
Yes	25 (0.81)	95.48 (88.90, 125.53)		12.34 (5.13, 24.25)		12.00 (6.80, 12.96)	
High risk	554 (13.57)	96.43 (85.21, 112.49)		6.99 (4.62, 11.66)		10.00 (8.00, 13.00)	
No	3,014 (85.62)	93.34 (81.88, 105.62)		7.92 (4.84, 15.79)		10.00 (8.00, 12.00)	
LTPA			<0.001		0.903		<0.001
Non-active (<420min/week)	1,819 (48.30)	95.50 (84.41, 108.95)		7.83 (4.94, 15.04)		10.00 (8.00, 12.00)	
Active (≥420min/week)	1,774 (51.70)	92.11 (80.46, 104.25)		7.80 (4.72, 15.28)		11.00 (9.00, 13.00)	
Daily Protein Intake (gm/kg)	1.16 (0.77, 1.60)		0.012		0.011		<0.001
Below median	1,802 (47.98)	94.85 (82.91, 107.42)		7.24 (4.69, 14.83)		10.00 (8.00, 12.00)	
Above median	1,791 (52.02)	92.63 (80.87, 105.49)		8.23 (4.91, 15.44)		11.00 (9.00, 13.00)	
Uric acid (mg/dL)	5.00 (4.20, 5.80)		<0.001		<0.001		<0.001
Below median	1735 (46.19)	100.02 (88.48, 112.66)		9.33 (5.74, 18.73)		9.54 (8.00, 12.00)	
Above median	1,858 (53.81)	88.49 (78.76, 100.67)		6.75 (4.35, 13.04)		11.00 (9.00, 13.00)	
Triglycerides (mg/dL)	81.00 (56.00, 120.00)		0.190		0.604		0.064
Below median	1,788 (44.76)	94.64 (82.70, 106.69)		7.93 (4.81, 15.35)		10.00 (8.00, 12.00)	
Above median	1,805 (55.24)	93.18 (81.89, 106.60)		7.66 (4.82, 15.16)		10.00 (8.00, 12.00)	
Cholesterol (mg/dL)	157.00 (139.00, 176.00)		0.363		0.738		0.567
Below median	1,761 (49.45)	94.58 (82.86, 106.59)		7,68 (4,71, 15.05)		10.00 (8.00, 12.00)	
Above median	1,832 (50.55)	93.28 (81.30, 106.64)		7.92 (4.88, 15.30)		10.00 (8.00, 12.00)	

Family PIR, family income-to-poverty ratio; *BMI*, body mass index; *BP*, blood pressure; *LTPA*, leisure-time physical activity; *eGFR*, estimated glomerular filtration rate; *ACR*, albumin creatinine ratio; *BUN*, blood urea nitrogen. Continuous variables were expressed as mean ± standard deviation, and the weighted linear regression model calculated the P value. The categorical variables were expressed as frequencies (percentages), and a weighted chi-square test calculated the P value. $p < 0.05$ was considered statistically significant.

BP, and 85.62% had normal blood glucose. The median (25th–75th percentile) values for daily protein consumption, uric acid, triglycerides, and cholesterol were 1.16 (0.77, 1.60) g/kg, 5.00 (4.20, 5.80) mg/dl, 81.00 (56.00, 120.00), and 157.00 (139.00, 176.00). All renal function-related measures—"taken prescription medicine", "triglycerides", and "cholesterol"—did not vary across groups.

3.2. Relationship between PNT and kidney function

Table 2 presents a multiple linear regression analysis of urine PNT exposure and CKD, including eGFR, ACR, and BUN. Smooth linear fitting complements visualization (Figures 2–4).

Perchlorate and nitrate were consistently inversely linked with eGFR across all linear models, regardless of whether

Table 2. Association between urinary PNT (ln-transformed) and eGFR, ACR, and BUN.

			Model 1 β (95% CI)	*P* values	Model 2 β (95% CI)	*P* values	Model 3 β (95% CI)	*P* values
eGFR	*non-CR-adjusted*	*Perchlorate*	−2.369 (-3.518, −1.220)	<0.001	−2.148 (-3.210, −1.085)	<0.001	−1.882 (-2.888, −0.876)	<0.001
		Nitrate	−2.418 (-3.800, −1.035)	<0.001	−2.241 (-3.467, −1.014)	<0.001	−1.585 (-2.655, −0.515)	0.004
		Thiocyanate	−2.050 (-3.102, −0.998)	<0.001	−0.268 (-1.2.09, 0.673)	0.573	−0.028 (-0.953, 0.898)	0.953
	Traditional-CR-adjusted	*Perchlorate*	3.681 (2.204, 5.159)	<0.001	2.147 (0.869, 3.424)	0.001	1.441 (0.155, 2.728)	0.029
		Nitrate	12.622 (10.360, 14.883)	<0.001	8.829 (6.911, 10.747)	<0.001	7.610 (5.860, 9.359)	<0.001
		Thiocyanate	2.316 (1.292, 3.339)	<0.001	3.298 (2.427, 4.169)	<0.001	2.838 (1.914, 3.762)	<0.001
	New-CR-adjusted	*Perchlorate*	−3.391 (-4.787, −1.995)	<0.001	−3.158 (-4.485, −1.831)	<0.001	−3.339 (-4.692, −1.986)	<0.001
		Nitrate	−5.361 (-7.491, −3.230)	<0.001	−5.270 (-7.152, −3.387)	<0.001	−4.989 (-6.768, −3.210)	<0.001
		Thiocyanate	−2.190 (-3.207, −1.172)	<0.001	−0.089 (-0.988, 0.810)	0.844	−0.212 (-1.166, 0.742)	0.659
ACR	*non-CR-adjusted*	*Perchlorate*	−8.835 (-17.520, −0.151)	0.046	−8.667 (-17.798, 0.464)	0.063	−5.692 (-10.787, −0.597)	0.029
		Nitrate	−9.264 (-20.144, 1.617)	0.094	−8.914 (-20.543, 2.716)	0.131	−5.280 (-11.795, 1.235)	0.111
		Thiocyanate	−6.928 (-12.643, −1.212)	0.018	−4.980 (-10.391, 0.431)	0.071	−2.709 (-7.162, 1.744)	0.230
	Traditional-CR-adjusted	*Perchlorate*	−6.484 (-14.224, 1,257)	0.100	−8.872 (-18.127, 0.384)	0.060	−7.819 (-15.057, −0.580)	0.035
		Nitrate	−4.133 (-17.474, 9.209)	0.540	−9.871 (-26.782, 7.040)	0.249	−9.911 (-24.926, 5.104)	0.193
		Thiocyanate	−3.301 (-6.847, 0.244)	0.068	−2.188 (-5.988, 1.613)	0.256	−2.169 (-5.691, 1.354)	0.224
	New-CR-adjusted	*Perchlorate*	−7,876 (-15.460, −0.291)	0.042	−7.775 (-16.237, 0.687)	0.071	−6.832 (-13.405, −0.259)	0.042
		Nitrate	−7.968 (-21.102, 5.166)	0.231	−7.440 (-23.037, 8.157)	0.346	−7.756 (-21.372, 5.859)	0.260
		Thiocyanate	−4.084 (-7.595, −0.572)	0.023	−1.608 (-5.516, 2.300)	0.416	−1.544 (-5.295, 2.208)	0.415
BUN	*non-CR-adjusted*	*Perchlorate*	0.550 (0,342 0.758)	<0.001	0.487 (0.275, 0.699)	<0.001	0.418 (0.210, 0.627)	<0.001
		Nitrate	0.600 (0.346, 0.854)	<0.001	0.533 (0.279, 0.786)	<0.001	0.474 (0.228, 0.720)	<0.001
		Thiocyanate	0.530 (0.333, 0.726)	<0.001	0.445 (0.251, 0.639)	<0.001	0.439 (0.254, 0.623)	<0.001
	Traditional-CR-adjusted	*Perchlorate*	0.246 (0.045, 0.447)	0.017	0.220 (0.013, 0.427)	0.038	0.192 (-0.020, 0.404)	0.075
		Nitrate	−0.073 (-0,441, 0.295)	0.696	−0.083 (-0.464, 0.298)	0.665	−0.037 (-0.400, 0.327)	0.842
		Thiocyanate	0.229 (0.010, 0.448)	0.041	0.144 (-0.067, 0.355)	0.177	0.192 (-0.001, 0.385)	0.052
	New-CR-adjusted	*Perchlorate*	0.455 (0.240, 0.669)	<0.001	0.359 (0.139, 0.579)	0.002	0.302 (0.081, 0.524)	0.008
		Nitrate	0.470 (0.118, 0.821)	0.009	0.301 (-0.058, 0.661)	0.099	0.274 (-0.078, 0.626)	0.126
		Thiocyanate	0.354 (0.143, 0.565)	0.001	0.243 (0.026, 0.460)	0.029	0.270 (0.073, 0.468)	0.008

Model 1: No covariates were adjusted; *Model 2*: Adjust for age, sex, race, and BMI; *Model 3: eGFR was adjusted for:* age, sex, race, education level, BP, diabetes, LTPA, daily protein intake (gm/kg), uric acid; *ACR was adjusted for:* age, sex, BMI, BP, diabetes, daily protein intake (gm/kg), uric acid; *BUN was adjusted for:* age, sex, race, family PIR, education level, LTPA, daily protein intake (gm/kg), uric acid. *PNT*, perchlorate, nitrate, and thiocyanate; *CR*, creatinine; *eGFR*, estimated glomerular filtration rate; *ACR*, albumin creatinine ratio; *BUN*, blood urea nitrogen. $p < 0.05$ was considered statistically significant.

PNT concentrations were new-CR-adjusted or not (non-CR-adjusted). Thiocyanate is inversely associated with eGFR in Model 1; however, after traditional-CR-adjustment, all models exhibited a consistent positive association ($p < 0.05$). With traditional-CR-adjusted, PNT was positively associated with eGFR (all $p < 0.05$). Take perchlorate as an example (Model 1: $\beta = 3.681$, 95% CI: 2.204-5.159, $p < 0.001$; Model 2: $\beta = 2.147$, 95% CI: 0.869-3.424, $p = 0.001$; Model 3: $\beta = 1.441$, 95% CI: 0.155-2.728, $p = 0.029$), where the β value decreased and the *P* value increased with the addition of more covariates. The connection between nitrate and eGFR in Model 1 exhibited a significant impact ($\beta = 12.622$, 95% CI: 10.360-14.883, $p < 0.001$) after using traditional-CR-adjustment.

The connection between ACR and urine PNT exposure was less than eGFR, notably in Model 2, where no associations were detected (all $p > 0.05$). Nitrate was not linked with

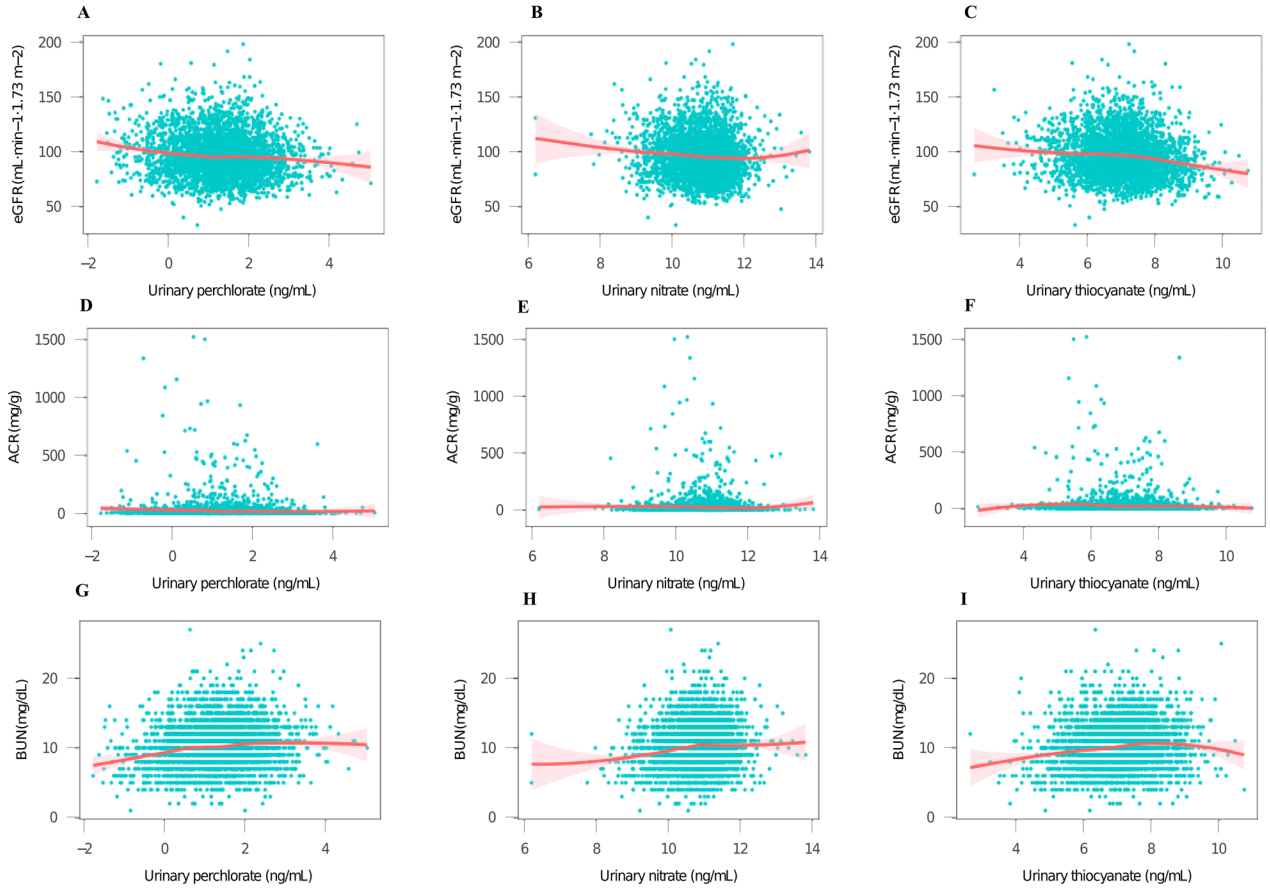

Figure 2. Linear fitting of the relationship between PNT and renal function when non-CR-adjustment was applied.

ACR in all models, whether corrected for urine creatinine concentration or not (all $p > 0.05$). Perchlorate, thiocyanate, and ACR had a negative association in multiple linear regression. In Model 1, thiocyanate was inversely associated with ACR, both non-CR-adjusted (β = −6.928, 95% CI: −12.643–1.212, $p < 0.05$) and new-CR-adjusted (β = −4.084, 95% CI: −7.595–0.572, $p < 0.05$). In Models 1 and 3, perchlorate was consistently inversely associated with ACR, regardless of adjustment ($p < 0.05$). inversely

While associations were observed with established renal function markers (eGFR and ACR), PNT exposure also correlated with BUN levels, a secondary metabolic parameter. Non-CR-adjusted PNT exposure in urine was positively linked with BUN in all models ($p < 0.001$). In Model 3, perchlorate was positively linked with BUN, except when corrected for traditional-CR ($\beta = 0.192$, 95% CI: −0.020-0.404, $p > 0.05$). Nitrate is strongly associated with BUN in non-CR-adjusted models, but only in Model 1 with new-CR adjustment ($\beta = 0.470$, 95% CI: 0.118-0.009, $p < 0.05$). Thiocyanate was positively associated with BUN in non-CR-adjusted and new-CR-adjusted models, but only in Model 1 with traditional-CR-adjustment ($\beta = 0.229$, 95% CI: 0.010-0.448, $p < 0.05$).

Multiple linear regression analysis reveals that household tap water perchlorate and nitrate exposure is associated with CKD, as indicated by eGFR, ACR, and BUN, in Supplementary Table 1. The linear association was not significant ($p > 0.05$).

3.3. Stratified results using demographic characteristics

Model 1 subgroup analysis of urine PNT exposure and eGFR, ACR, and BUN was performed to investigate group differences. The subgroup analysis results, along with the corresponding smooth linear fitting lines, are presented in Supplementary Tables 2–7, stratified by sex (Supplementary Figures 1–3), age (Supplementary Figures 4–6), race (Supplementary Figures 7–9), BMI (Supplementary Figures 10–12), family PIR (Supplementary Figures 13–15), and education levels (Supplementary Figures 16–18).

Supplementary Table 2 reveals a stronger negative association between nitrate and eGFR in females compared to males, both non-CR-adjusted ($p < 0.05$) and new-CR-adjusted ($p < 0.05$). However, no association was found in males ($p > 0.05$). The positive association between nitrate and eGFR was stronger in males ($\beta = 16.974$, 95% CI: 13.969-19.980, $p < 0.001$) than in females ($\beta = 8.579$.95% CI: 5.882-11.276, $p < 0.001$) (P for interaction < 0.001). Biologic sex differences in ACR and BUN were insignificant (all P values > 0.05). Interaction analyses revealed significant effect modification by sex, with stronger associations observed in females ($p < 0.05$). Sensitivity analyses confirmed our results' robustness, as excluding participants with extreme values or comorbidities did not substantially alter the observed associations.

All participants were separated into two age groups: group 1 (12–15 years old) and group 2 (16-19 years old) in

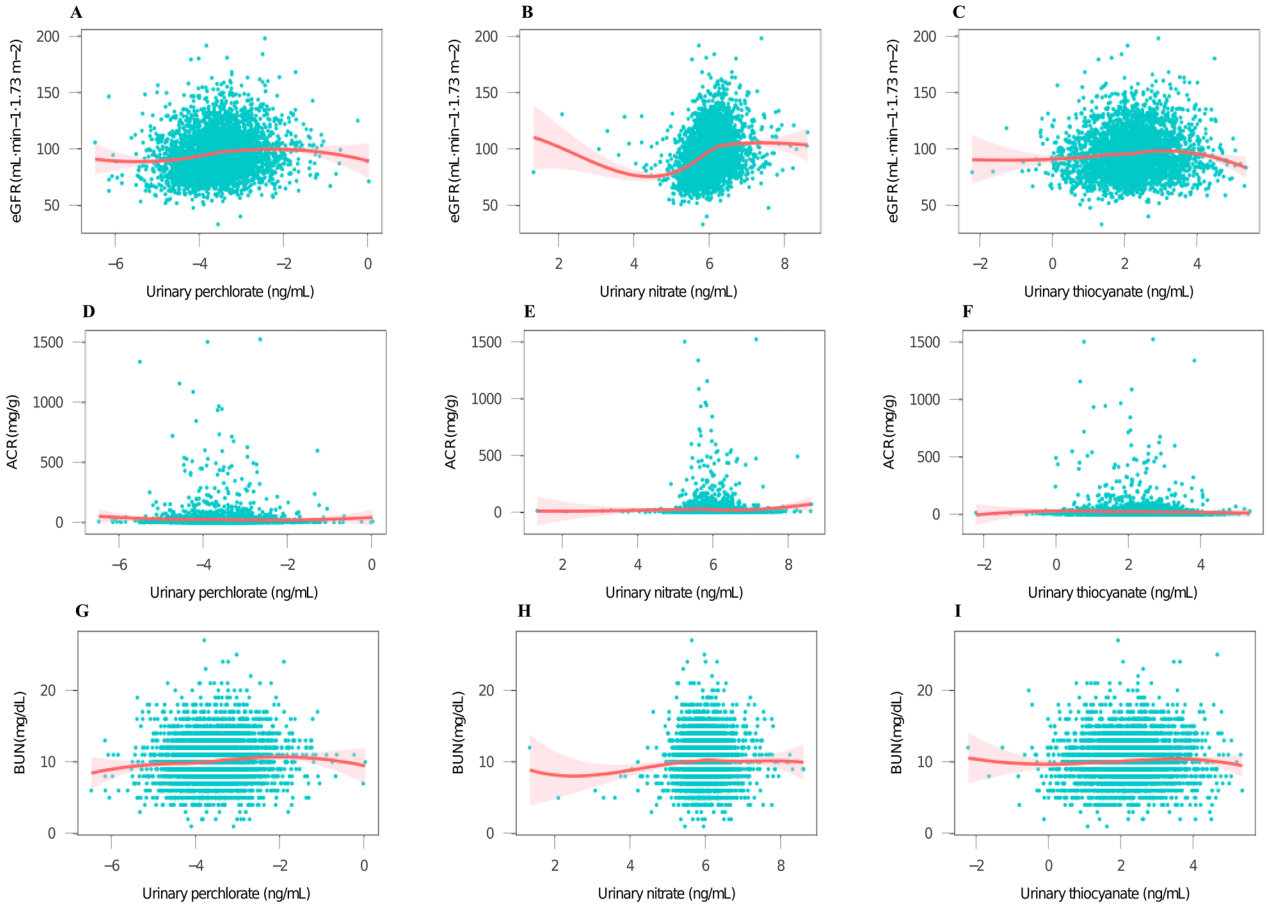

Figure 3. Linear fitting of the relationship between PNT and renal function when traditional-CR-adjustment was applied.

subgroup analyses (Supplementary Table 3, Supplementary Figures 4–6). Group 1 showed a stronger positive association between thiocyanate and eGFR compared to group 2 as adjusted by Traditional-CR ($\beta = 4.686$, 95% CI: 3.180-6.191, $p < 0.001$) (P for interaction < 0.05). Perchlorate was negatively associated with eGFR in group 1 ($\beta = -4.051$, 95% CI: −5.986–2.117, $p < 0.001$) and positively associated with BUN in group 2 ($\beta = 0.571$, 95% CI: 0.284-0.857, $p < 0.001$) after new-CR-adjustment. Interestingly, only group1 showed a negative association between thiocyanate and ACR after new-CR-adjustment ($\beta = -7.274$, 95% CI: −13.878–0.669, $p < 0.05$), with a larger effect value than in multiple linear regression Model 1 ($\beta = -4.084$, 95% CI: −7.595–0.572, $p < 0.05$). After new-CR-adjustment, only group 2 showed a significant association between nitrate and BUN ($\beta = 0.917$, 95% CI: 0.407-1.426, $p < 0.001$) (P for interaction < 0.05).

BUN stratified by race (Supplementary Table 4) and BMI (Supplementary Table 5) showed no statistically significant changes (all P values for interaction > 0.05) across all concentration correction outcomes. The same was true for ACR stratified by household PIR (Supplementary Table 6), education level (Supplementary Table 7), and BMI. The findings are generally applicable to demographically diverse participant groups. Perchlorate had the most population heterogeneity among the three contaminants in all subgroup studies.

4. Discussion

This study is the first cross-sectional investigation to evaluate the association between PNT exposure and CKD markers in adolescents aged 12–19. Our analysis revealed significant associations between urinary PNT levels and reduced renal function, as indicated by lower eGFR, higher ACR, and elevated BUN. These findings suggest that PNT exposure may inversely affect adolescent kidney health, independent of traditional risk factors. It is important to note that while BUN elevations were observed, these findings should be interpreted cautiously. As a nonspecific marker influenced by renal and extrarenal factors (including dietary protein intake and hydration status), BUN serves primarily as a supplementary indicator rather than a diagnostic criterion for CKD [27]. Our inclusion of BUN was intended to provide a more comprehensive assessment of nitrogen metabolism while recognizing eGFR and ACR as the definitive markers of renal function in this study.

Our findings contribute to the growing body of literature on the health effects of PNT by explicitly focusing on adolescents, a population that has been underrepresented in environmental health research. While prior studies have explored the broader implications of PNT exposure, our study is among the first to demonstrate an association between PNT exposure and deteriorated renal function markers in this age

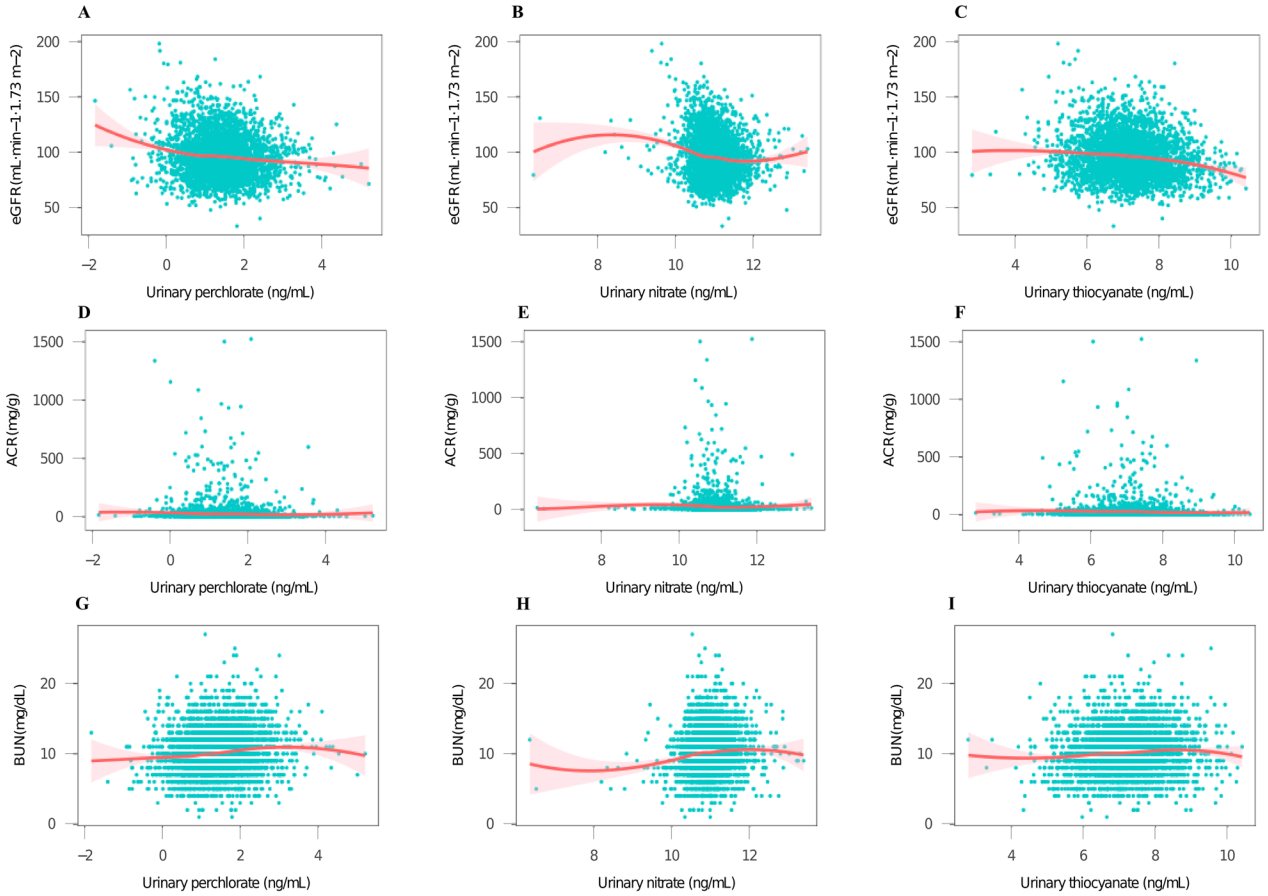

Figure 4. Linear fitting of the relationship between PNT and renal function when the new-CR-adjustment was applied.

group. For example, Li et al. reported similar associations between PNT exposure and renal function in U.S. adults, though the effects varied by exposure levels [28]. Our results also highlight that tap water may not be the primary source of PNT exposure, emphasizing the need to consider alternative exposure pathways in future research and policy interventions.

Our study also identified demographic heterogeneity in the effects of PNT exposure. Females exhibited a stronger negative association between nitrate and eGFR, while thiocyanate and ACR were negatively associated in the 12–15 age group but positively associated in the 16–19 age group. These findings align with a study in China, which found that children aged 6–11 were more vulnerable to perchlorate than older individuals [29]. The divergent eGFR associations between analytical models reflect important physiological considerations in adolescents. The modified associations under creatinine adjustment likely stem from puberty-related muscle mass development, particularly in females, where creatinine production rates change significantly during growth spurts [30]. However, the associations between PNT exposure and renal function markers were consistent across PIR, education level, and BMI, underscoring the robustness of our findings.

Globally, CKD prevalence has risen by 23.9% since 1990, reaching 9.1% in 2017, with approximately 19 million cases occurring in children and adolescents [31,32]. Despite this significant burden, the causes of CKD in younger populations remain understudied due to limited data and unreliable diagnostic methods [33]. Our findings highlight the role of environmental stressors, such as PNT exposure, as modifiable risk factors for renal immaturity, kidney function loss, and CKD development.

Studies have shown that PNT affects people's health, especially the heart and hormone systems. Perchlorate inhibits thyroid iodide absorption and thyroid function. Thyroid problems may hinder children's somatic growth [34]. Most research on perchlorate and child development employs indirect inference, evaluating its effects on thyroid hormone levels through physiological studies. This research also seeks to inspire the study of endocrine and renal function, which is currently being planned.

Thus far, direct population epidemiological research on children and adolescents has been inadequate. In a retrospective cross-sectional study by Guo et al. perchlorate in home tap water was found to inversely correlate with children's height and weight [19,35]. Jiang et al. discovered that children and adolescents exposed to thiocyanates were more likely to be overweight or obese, and to have central obesity, whereas perchlorate exposure was negatively related [36].

The biological mechanisms underlying these associations are complex. Perchlorate, nitrate, and thiocyanate interfere with thyroid function and oxidative stress pathways, possibly indirectly impacting kidney health [37,38]. Perchlorate competitively inhibits iodide uptake by the thyroid, which may

disrupt hormonal regulation of renal function [37,39]. Nitrate and thiocyanate may contribute to oxidative stress and inflammation, both of which are implicated in the pathogenesis of CKD [40,41]. Furthermore, the interactions between these contaminants as co-exposures could amplify their individual effects, though further research is needed to elucidate these mechanisms.

While our study benefits from a large, nationally representative sample, several limitations should be noted. First, the cross-sectional design limits our ability to infer causality, and reverse causation (e.g., kidney conditions affecting PNT excretion) cannot be ruled out. Future longitudinal studies are needed to establish temporal relationships and clarify causality. Second, although NHANES data are rigorously collected, reliance on self-reported measures may introduce bias. We mitigated this by using standardized protocols and adjusting for potential confounders. Third, while eGFR is a widely used marker of renal function, it has limitations in adolescents due to its dependence on muscle mass and creatinine production. Future studies should incorporate additional biomarkers, such as cystatin C or urinary protein levels, to provide a more comprehensive assessment of kidney health. Besides, while we reported BUN values as an additional metabolic parameter, we acknowledge its limited specificity as a standalone marker of renal function in epidemiological studies. Finally, the limited availability of water PNT contamination data in the NHANES database may reduce the precision of our findings.

Despite these limitations, our findings have important implications for public health. The global burden of CKD underscores the need for targeted interventions to reduce environmental exposures, particularly in vulnerable populations like adolescents. Our results suggest monitoring perchlorate levels in environmental media, evaluating exposure doses, and implementing timely control measures are crucial for mitigating health risks [40]. Additionally, our study highlights the need for further research to explore the biological mechanisms underlying PNT-induced renal dysfunction and identify effective prevention and intervention strategies.

5. Conclusion

In conclusion, urinary PNT exposure was associated with altered renal parameters (eGFR, ACR, and BUN) in adolescents aged 12–19. These findings underscore the potential importance of monitoring inorganic pollutants, which may influence kidney health in this vulnerable population. While tap water appeared to be a minor contributor to PNT exposure in our study, further research is needed to clarify exposure sources and the biological mechanisms underlying these observed relationships.

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Ethical approval

The National Center has reviewed NHANES for the Health Statistics Research Ethics Review Board. All adult participants provided written informed consent, and participants under 18 were required to obtain permission from their parents or guardians.

Author contributions

All authors contributed to the study conception and design. Professor Mingyi Zhao and Professor Qingnan He provided constructive comments and guidance throughout the study. Xiaoran Xue and Zaiqiu Zhang prepared the materials, collected the data, and performed the analysis. Marady Hun and Min Wen contributed to the preparation of the original draft. Marady Hun helped with drawing the charts. Xiaoran Xue wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data supporting this study's findings are available in the National Health and Nutrition Examination Survey at https://www.cdc.gov/nchs/nhanes/index.htm. These data were derived from the following public domain resources: NHANES Questionnaires, Datasets, and Related Documentation.

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