Environmental Science and Pollution Research (2023) 30:7605–7616
https://doi.org/10.1007/s11356-022-22637-1

RESEARCH ARTICLE

Exposures to volatile organic compounds, serum vitamin D, and kidney function: association and interaction assessment in the US adult population

Wei Liu[1,2] · Shuting Cao[1,2] · Jixuan Ma[1,2] · Da Shi[3] · Linling Yu[1,2] · Zi Ye[1,2] · Meng Yang[4] · Bin Wang[1,2] · Weihong Chen[1,2]

Received: 28 April 2022 / Accepted: 17 August 2022 / Published online: 31 August 2022

Abstract

The relationships of exposures to volatile organic compounds (VOCs) with vitamin D and kidney function remain unclear. Our analyses included 6070 adults from 2003 to 2010 survey cycles of the National Health and Nutrition Examination Survey to explore associations of six VOCs with serum vitamin D, albumin-to-creatinine ratio (ACR), and estimated glomerular filtration rate (eGFR). The results suggested that dibromochloromethane was positively associated with ACR, and chloroform was inversely associated with ACR. U-shaped associations of toluene, m-/p-xylene, bromodichloromethane, and 1,4-dichlorobenzene with ACR were observed. Toluene, m-/p-xylene, and 1,4-dichlorobenzene were associated with eGFR in U-shaped manners, while bromodichloromethane and chloroform were inversely associated with eGFR. Elevation in 1,4-dichlorobenzene was associated with decrease in vitamin D, while chloroform and m-/p-xylene were in U-shaped associations with vitamin D. VOCs mixture was U-shaped associated with ACR, inversely associated with eGFR, and inversely associated with vitamin D. Vitamin D was in a U-shaped association with ACR. Vitamin D significantly interacted with VOCs on the two kidney parameters. In the US adult population, exposures to VOCs were associated with kidney function and serum vitamin D level decline, and the serum vitamin D may have interaction effects with VOCs exposures on kidney function.

Keywords Volatile organic compound · Vitamin D · Kidney function

Responsible Editor: Lotfi Aleya

Meng Yang, Bin Wang, and Weihong Chen contributed equally to this article and should be considered co-corresponding authors.

✉ Meng Yang
zhugecaoming1019@126.com

✉ Bin Wang
gentwong@163.com

✉ Weihong Chen
wchen@mails.tjmu.edu.cn

[1] Department of Occupational & Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China

[2] Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China

[3] Food and Human Nutritional Science, Faculty of Agriculture and Food Science, University of Manitoba, Winnipeg, Manitoba, Canada

[4] Wuhan Children's Hospital (Wuhan Maternal and Child Health Care Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430016, Hubei, China

Introduction

Healthy kidney function is the cornerstone of metabolism and the guarantee of the body's environment homeostasis. Nowadays, kidney diseases (KDs) affect more than 10% of the population worldwide and account for the third-largest increase in global deaths (Mortality and global health estimates: Causes of death 2016; Jha et al. 2013). Widespread attention has been attracted by the enlarging size of the KDs population over the last decades (Murphy et al. 2016). Albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) are two main kidney measures of kidney function that are widely used in defining and staging chronic kidney diseases (CKDs) (Levey et al. 2015). Accumulating evidence has suggested that exposure to some environmental and occupational pollutants may impair kidney health (Blake et al. 2018; Kang et al. 2019; Sanders et al. 2019) manifested as abnormal renal function and even KDs.

Volatile organic compounds (VOCs), a large group of chemicals, are ubiquitous in the living environment. For example, benzene, toluene, ethylbenzene, xylene, and styrene, collectively referred to as BTEXS, are common pollutants ubiquitous in the living environment, especially in the indoor environment (Chambers et al. 2011; Xu et al. 2019). Chlorobenzenes are halogenated aromatic hydrocarbons primarily used in chemical synthesis processes, such as the manufacturing of dyes, pesticides, and deodorizers (Wei and Zhu 2016). Disinfection by-products, including bromoform, chloroform, bromodichloromethane, and dibromochloromethane, are formed when chlorine reacts with organic compounds in drinking water and recreational water bodies (Grellier et al. 2010). Inhalation and ingestion (drinking water) are the two most common routes of above-mentioned VOC exposure for the general population (Chambers et al. 2011; Grellier et al. 2010; Wei and Zhu 2016).

Although emissions of many VOCs have declined in recent years, VOCs indoor concentrations typically exceed outdoor levels by 2–5 times (Su et al. 2011). VOCs may still pose a significant health threat given the increasing amount of time humans spend indoors with urbanization development. Some VOCs, such as BTEXS (Shi et al. 2013) and chlorobenzene (den Besten et al. 1991), are paradigmatic nephrotoxicants that have been studied in mice and rats. However, there are few studies that have explored the relationships between VOCs exposures and impaired renal function in the general population. A cross-sectional study performed in the Canadian Health Measures Survey suggested blood BTEXS levels were associated with a significant decrease in serum creatinine, suggesting an increased risk of renal hyperfiltration (Cakmak et al. 2020). Another environment-wide association study of CKD suggested that four VOCs were associated with kidney injury such as albuminuria and reduced eGFR, but other seven VOCs were associated with lower risks of one or more manifestations of CKD (Lee et al. 2020). In general, the association of exposure to single VOC with kidney health remains inconclusive, and the impact of exposure to VOCs as a mixture on kidney health has not been explored in the general population.

Vitamin D is a fat-soluble essential nutrient, which plays a central role in calcium and phosphate metabolisms. Humans acquire vitamin D from diet and sunlight-induced cutaneous synthesis (Holick 2007). In addition to inadequate intake due to unhealthy lifestyle, disease status, and diet, exposures to some environmental pollutants may also be associated with vitamin D deficiency (Johns et al. 2016, 2017). However, no study has ever evaluated the relationships between VOCs exposures and vitamin D level. Vitamin D deficiency is common in CKDs and may promote the development and progression of CKDs (Ravani et al. 2009). Evaluating associations of VOCs exposures with vitamin D and kidney function will be helpful to understand the potential mechanism underlying the associations of VOCs exposures with kidney function decline and provide new potential for improving kidney health.

According to clues from previous research, we hypothesized that VOCs exposures may impair kidney function, and there may be interaction effects between VOCs exposures and vitamin D on kidney function. To fill this research gap, in the present study, we investigated associations of blood VOCs with serum vitamin D biomarker and kidney function in a general population-based study of 6070 US adults. Survey-weight regression, restricted cubic spline model, and quantile g-computation were applied in this study to evaluate the associations of blood VOCs with serum vitamin D biomarker and two kidney parameters (ACR and eGFR). The interaction effects between VOCs and vitamin D on the two kidney parameters were also explored.

Material and methods

Study population

The National Health and Nutrition Examination Survey (NHANSE) recruited a representative sample of the US population by using a complex, multistage probability design (Centers for Disease Control and Prevention/National Center for Health Statistics 2017). The NHANSE was conducted periodically at the beginning and became a continuous annual survey released in a 2-year cycle since 1999. Each participant participated in only one cycle and was assigned an ID number that was unique in all cycles. The study protocol was approved by the National Center for Health Statistics Research Ethics Review Board. All participants were well informed and provided written consents.

We included and excluded participants according to previous studies of blood VOCs, serum vitamin D, or kidney function (Cakmak et al. 2020; Johns et al. 2017; Lee et al. 2020). In order to improve statistical power and obtain as reliable data as possible, this study was restricted to the population who participated in the 2003–2010 cycles of the NHANSE. There were 41,156 participants in these year cycles, and a subsample included 6680 adults without missing data on blood VOC levels or kidney function parameters. After excluding individuals without data of essential covariates ($n=366$) or serum vitamin D biomarker ($n=244$), 6070 subjects were finally included into the analyses. There was no significant difference in age, gender, race, or other characteristics between included and excluded participants ($P>0.05$). The flowchart of subject selection is shown in Appendix A Fig. S1.

Determinations of blood VOCs

The quantitative detection of blood VOCs was conducted by utilizing headspace solid-phase micro extraction/gas chromatography/isotope dilution mass spectrometry. A detailed description of the analytical methods and quality control has been described elsewhere (National Center for Health Statistics 2016). In brief, a total of 3 mL blood sample coupled with 40 μL labeled internal standard solution were transferred into a solid-phase microextraction headspace vial, which was immediately crimp-sealed using a Teflon-lined septum and steel/aluminum crimp seal and were tested as soon as possible. All containers used for contacting samples were pre-treated to remove VOCs they contained. For quality control, at least three quality assessment samples were analyzed in each run that included the water blank and two different pools of quality control material at different concentrations. Samples in the run would be re-pretreated and redetected if quality control of the run did not meet the following standards: The spike percent recoveries from blood should be in a range of 75–125%. The relative standard deviations for the quality control samples should be less than 15%. No target compounds should be detected in water blank sample. Calibration curves should achieve a squared coefficient of determination of at least 0.98. Six VOCs, including bromodichloromethane (73.75%), chloroform (91.21%), toluene (93.70%), m-/p-xylene (90.57%), dibromochloromethane (54.84%), and 1,4-dichlorobenzene (54.48%), with > 50% of measurements at or above limits of detection (LODs) were included in the analyses (Appendix A Table S1). Concentrations less than the LODs were assigned LOD divided by square root of 2.

Determinations and calculations of kidney parameters

Kidney function was assessed via ACR and eGFR. Urinary albumin was determined by a fluorescent immunoassay, and creatinine in serum and urine were measured via the Jaffe rate methods (Kang et al. 2021). The ACR was calculated literally as albumin divided by creatinine in urine. The eGFR was calculated via the Modification of Diet in Renal Disease study (MDRD) eGFR equation (Murphy et al. 2016), and the formula is as follows: 175 × standardized serum creatinine ^ (−1.154) × age ^ (−0.203) × 1.212 [if black] × 0.742 [if female].

Serum vitamin D biomarker

Serum 25-hydroxyvitamin D [25(OH)D] as the main form of vitamin D in the human body was measured by radioimmunoassay (RIA; DiaSorin) in 2003–2006. From 2007 to 2010, the serum total 25(OH)D, defined as the sum of $25(OH)D_3$ and $25(OH)D_2$, was measured via a fully validated standardized liquid chromatography-tandem mass spectrometry method. The RIA data was converted to LC–MS/MS-equivalent data through special regression equations and expressed as nmol/L. Concentrations below the LODs were substituted by the values of LODs divided by square root of 2. The details of analytical methods and quality control had been described elsewhere (National Center for Health Statistics 2015).

Covariates

Covariate selection was conducted according to the results of preliminary analysis and previous studies about VOCs exposures, vitamin D, or kidney function (Cakmak et al. 2020; Johns et al. 2017; Lee et al. 2020) as well as the biological and statistical considerations with the change-in-estimate method (Greenland 1989; Tian et al. 2022). Demographic information (including age, gender, race/ethnicity, the ratio of family income to poverty, and educational level) and lifestyle (including drinking and physical activities) were collected via household surveys. Drinking was defined as having alcohol of more than 42 g/day for men or more than 28 g/day for women in the last 12 months. Physical activity was defined as self-reported vigorous or moderate recreational physical activity for at least 10 min per week. Serum cotinine, measured by an isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (Alwis et al. 2015; CDC 2018), is a reliable biomarker of tobacco smoke exposure. Educational level was grouped into less than high school, high school or equivalent, and college or above. The ratio of family income to poverty < 1 was defined as at poverty level. Mediations use was defined as taking relevant mediations such as ACE-inhibitor and angiotensin receptor antagonist in the last 30 days. When the outcome was serum 25(OH)D, 6-month sampling period (a proxy variable for sun exposure), past 30-day vitamin D supplement use, and eGFR (to control the possibility that lower serum vitamin D is the result of poor kidney function rather than

VOCs exposures) were adjusted additionally. Because diet vitamin D intake was not available from the NHANES, we adjusted for vitamin D-rich food intake (including shrimp, milk, mushroom, fish, and eggs) collected by a 24-h diet recall (Milesevic et al. 2018).

Statistical analyses

In continuous models, levels of blood VOCs, kidney parameters, and serum total 25(OH)D were all ln-transformed to improve their normality due to their skew distributions. In categorical models, participants were categorized into four groups according to quartiles of blood VOCs levels with the first quartile as the reference. Pairwise correlations of six blood VOCs levels (not ln-transformed) were evaluated via Spearman's correlation coefficients. All analyses were performed in R software (version 4.1.0), and *P* value less than 0.05 in two-sided test was considered statistically significant.

Single chemical regression

Survey-weight regression was performed to explore potential dose–response relationships of blood VOCs with vitamin D and kidney parameters. Restrict cubic spline regression models with knots at 5th, 50th, and 95th percentiles were also conducted to determine whether there were nonlinear relationships of individual blood VOCs with vitamin D and kidney parameters (*P* for nonlinear < 0.05 suggested nonlinear relationships). Sensitivity analysis was performed by additionally including data of NHANES 2015–2020 (target VOCs data in 2011–2014 was not included for additional analysis, because these data may not be accurately measured due to elevated background VOCs levels that existed in the mobile examination centers as clarified by NHANES (National Center for Health Statistics 2017) and published studies (Ding et al. 2002; Vaughan Watson et al. 2021), forced inclusion of these biased data would bias the scientific results.).

Quantile g-computation

Quantile g-computation is an improved method to analyze the environmental mixture exposure based on weighted quantile sum regression (Keil et al. 2020; Liu et al. 2022). It shares the simplicity of interpretation and computational ease of weighted quantile sum regression regardless of directional homogeneity. In quantile g-computation, multiple chemicals were categorized into preset percentiles and given weights, and an overall effect of all target pollutants (as a whole mixture) on the outcome was estimated. In this study, quantile g-computation was employed to evaluate the overall associations of six blood VOC mixtures with kidney parameters and serum 25(OH)D. Both linear models and nonlinear models were fitted to assess the associations of VOCs mixture with vitamin D and kidney parameters. Akaike information criterion (AIC) and Bayesian information criterion (BIC) (lower AIC and BIC suggest better goodness of model fitting) were employed to compare the goodness of fitting of two models and to identify the best fitted model to interpret the results of the associations between VOC mixtures with vitamin D and kidney parameters. And $P < 0.05$ indicated the significance of the associations (linear or nonlinear). Sensitivity analysis was performed by additionally including data of NHANES 2015–2016 (data of blood toluene was not published in NHANES 2017–2020).

Interactions between VOCs and vitamin D on kidney function

Interaction effects of single blood VOC and VOC mixture with vitamin D on kidney parameters were estimated by adding interaction terms of single blood VOC or VOCs mixture with vitamin D status in the models. Interaction plots (Wang et al. 2022) were used to visualize the interactions of single blood VOC and VOC mixture with serum 25(OH)D on kidney parameters. Compared with simple interaction analysis, the interaction plot can clearly and accurately show the changes in the relationships between VOCs and renal parameters as serum 25(OH)D change.

Results

Descriptive analyses

Basic characteristics of the study population are shown in Table 1. The mean age of study population was 44.84 years old, and the mean of body mass index was 28.50 kg/m^2. There were slightly more females than males (51.28% vs. 48.72%) and more drinkers than non-drinkers (75.57% vs. 24.43%). The majority of participants were non-Hispanic whites (71.11%), and more than half of the participants were physically active (62.39%). The median levels with interquartile ranges of serum 25(OH)D, ACR, and eGFR were 63.10 (48.30, 78.60) nmol/L, 0.08 (0.05, 0.28) mg/g, and 84.17 ml/min/1.73 m^2 (72.94, 97.74), respectively. The median levels of bromodichloromethane, chloroform, toluene, m-/p-xylene, dibromochloromethane, and 1,4-dichlorobenzene were 1.40 pg/mL, 8.90 pg/mL, 0.10 ng/mL, 0.11 ng/mL, 0.63 pg/mL, and 0.09 ng/mL, respectively. Strong correlations (Spearman's correlation coefficients > 0.70) were found between dibromochloromethane and bromodichloromethane and toluene and m-/p-xylene; Appendix A Fig. S2).

Associations between blood VOCs and kidney parameters

Single chemical analyses

The results of survey-weight regression are shown in Fig. 1. After adjustment for potential covariates, ACR was significantly decreased in the other quartiles compared with the first quartile of individual VOCs (except

Table 1 Basic characteristics of study population

Characteristics	Overall
Age	44.84 (0.24)
Gender	
Male	2838 (48.72%)
Female	3232 (51.28%)
Race	
Mexican American	1120 (8.45%)
Other Hispanic	316 (3.79%)
Non-Hispanic White	3192 (71.11%)
Non-Hispanic Black	1184 (10.98%)
Other race — including multi-racial	258 (5.66%)
Body mass index, kg/m^2	28.50 (0.11)
Serum cotinine, ng/mL	0.07 (0.02, 26.70)
Drinking status, %	
Non-drinker	2736 (24.43%)
Drinker	3334 (75.57%)
Physical activity, %	
Inactive	2551 (37.61%)
Active	3519 (62.39%)
Education level	
Less than high school	1282 (16.33%)
High school or equivalent	1572 (39.45%)
College or above	3216 (44.22%)
The ratio of family income to poverty	
< 1	1021 (14.66%)
≥ 1	5049 (85.34%)
Serum 25(OH)D, nmol/L	63.10 (48.30, 78.60)
ACR, mg/g	0.08 (0.05, 0.28)
eGFR, ml/min/1.73 m^2	84.17 (72.94, 97.74)
Blood VOCs	
Bromodichloromethane, pg/mL	1.40 (0.44, 3.23)
Chloroform, pg/mL	8.90 (4.20, 18.00)
Toluene, ng/mL	0.10 (0.06, 0.23)
m-/p-xylene, ng/mL	0.11 (0.07, 0.18)
Dibromochloromethane, pg/mL	0.63 (0.44, 1.70)
1,4-dichlorobenzene, ng/mL	0.09 (0.08, 0.22)

Data were presented as number (weighted percentage), weighted mean (standard error), or weighted median (weighted interquartile range)

VOCs volatile organic compounds, *ACR* albumin-to-creatinine ratio, *eGFR* estimated glomerular filtration rate, *BMI* body mass index, *25(OH)D* 25-hydroxyvitamin D

dibromochloromethane). ACR was inversely and dose-dependently associated with four VOCs (all $P_{trend} < 0.05$) other than 1,4-dichlorobenzene ($P_{trend} = 0.427$) and dibromochloromethane (positively, $P_{trend} = 0.003$). Otherwise, inverse dose–response associations were revealed between eGFR and three VOCs (bromodichloromethane, chloroform, and 1,4-dichlorobenzene, all $P_{trend} < 0.05$).

The results of restricted cubic spline model are shown in Fig. 2. We observed nonlinear relationships of VOCs (except chloroform and dibromochloromethane) with ACR (all P for nonlinear < 0.01). Visible U-shaped associations between four VOCs (bromodichloromethane, inflection point (IP) = 1.483 pg/m; toluene, IP = 0.141 ng/mL; m-/p-xylene, IP = 0.142 ng/mL; and 1,4-dichlorobenzene, IP = 0.491 ng/mL) and ACR were observed. Bromodichloromethane and chloroform were linearly and inversely associated with eGFR (both P for nonlinear > 0.05). eGFR showed U-shaped change with increases of three VOCs (toluene, IP = 0.096 ng/mL; m-/p-xylene, IP = 0.103 ng/mL; and 1,4-dichlorobenzene, IP = 0.513 ng/mL) (all P for nonlinear < 0.05). In sensitivity analysis (Appendix A Fig. S3), the associations between VOCs (except dibromochloromethane) and two kidney parameters were stable after including data of NHANES 2015–2020.

Overall effect assessment of VOCs mixture

As shown in Appendix A Table S2, the AIC and BIC jointly suggested that the nonlinear model of association between VOCs mixture and ACR fitted better than the linear model (AIC: 25923.09 vs. 26618.60; BIC: 26125.10 vs. 26719.61). The linear association rather than nonlinear association between the VOCs mixture and eGFR was better fitted (AIC: 184.26 vs 391.14; BIC: 391.14 vs. 446.72). As shown in Fig. 3, a significant U-shaped association graphically described the effect of VOCs mixture on ACR ($P < 0.001$). The eGFR was significantly and monotonically decreased with the elevation in VOCs mixture ($P = 0.025$). In addition, Appendix A Fig. S4 A-B shows the weight coefficient of each single VOC estimated by quantile g-computation. When the outcome was ACR, bromodichloromethane (0.615), toluene (0.236), and chloroform (0.149) were assigned negative weight coefficients, and dibromochloromethane (0.510), 1,4-dichlorobenzene (0.428), and m-/p-xylene (0.062) were assigned positive weight coefficients. When the outcome was eGFR, bromodichloromethane (0.362), chloroform (0.359), 1,4-dichlorobenzene (0.244), and toluene (0.035) devoted negative contributions to the mixture effect, and dibromochloromethane (0.791) and m-/p-xylene (0.209) were assigned positive weight coefficients. In sensitivity analysis (Appendix A Fig. S5), an inverse rather than U-shaped association was observed between VOCs mixture and ACR after additionally including data of NHANES 2015–2016.

Interactions between blood VOCs and serum 25(OH)D on kidney parameters

Associations between blood VOCs and serum 25(OH)D

As shown in Appendix A Table S3, survey-weight regression revealed significant inverse dose–response associations

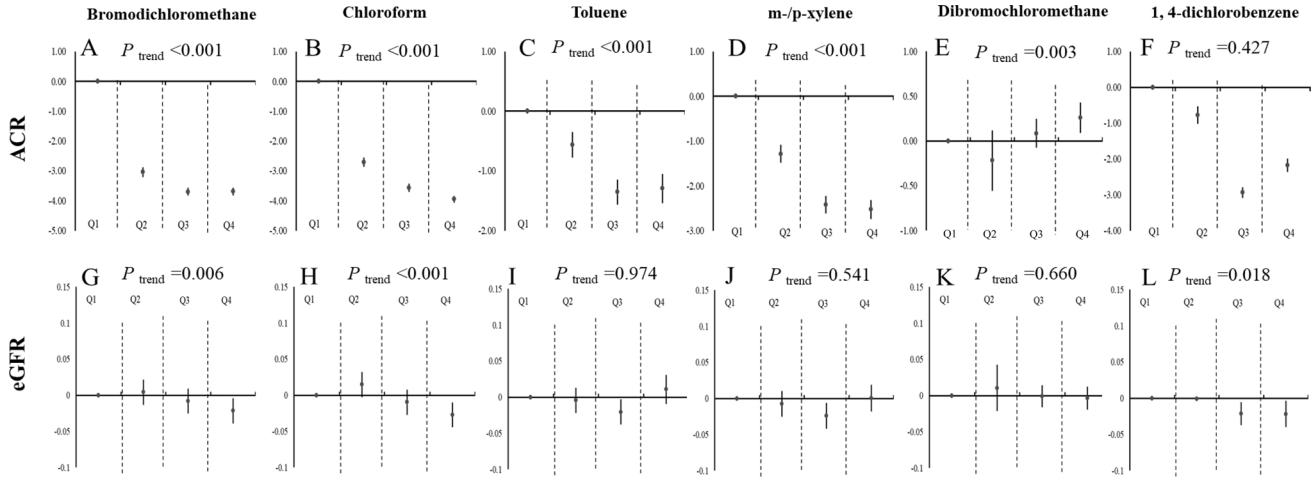

Fig. 1 Associations between blood VOCs and kidney parameters in survey-weight regression. **A** Bromodichloromethane and ACR; **B** Chloroform and ACR; **C** toluene and ACR; **D** m-/p-xylene and ACR; **E** dibromochloromethane and ACR; **F** 1,4-dichlorobenzene and ACR; **G** bromodichloromethane and eGFR; **H** Chloroform and eGFR; **I** toluene and eGFR; **J** m-/p-xylene and eGFR; **K** dibromochloromethane and eGFR; **L** 1,4-dichlorobenzene and eGFR. VOCs, volatile organic compounds; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index. All models were adjusted for age, gender, race, BMI, drinking, serum cotinine, physical activity, educational level, the ratio of family income to poverty, and mediations use

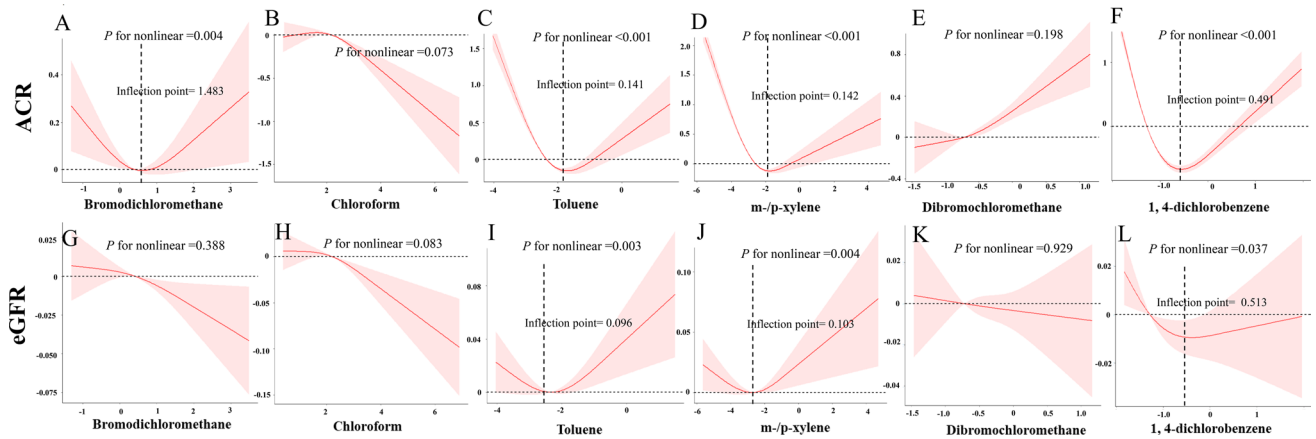

Fig. 2 Associations between blood VOCs and kidney parameters in restricted cubic spline models. **A** Bromodichloromethane and ACR; **B** chloroform and ACR; **C** toluene and ACR; **D** m-/p-xylene and ACR; **E** dibromochloromethane and ACR; **F** 1,4-dichlorobenzene and ACR; **G** bromodichloromethane and eGFR; **H** chloroform and eGFR; **I** toluene and eGFR; **J** m-/p-xylene and eGFR; **K** dibromochloromethane and eGFR; **L** 1,4-dichlorobenzene and eGFR. VOCs, volatile organic compounds; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index. The *X*-axis represents the ln-transformed concentration of blood VOCs. The *Y*-axis represents ln-transformed kidney parameters (ACR/eGFR) levels. Inflection point shows the original concentration of blood VOCs. All models were adjusted for age, gender, race, BMI, drinking, serum cotinine, physical activity, educational level, the ratio of family income to poverty, and mediations use

of bromodichloromethane and 1,4-dichlorobenzene with 25(OH)D (both P trend < 0.05). Moreover, significant U-shaped associations of chloroform (IP = 16.215 pg/mL) and m-/p-xylene (IP = 0.071 ng/mL) with 25(OH)D (all P for nonlinear < 0.05) were detected by restrict cubic spline regressions (Appendix A Fig. S6). VOC mixture was linearly rather than nonlinearly associated with serum 25(OH)D (AIC: 4910.26 vs. 5220.48; BIC: 5334.57 vs. 5950.49, Appendix A Table S2). The serum 25(OH)D level was significantly and monotonically decreased with the elevation of VOCs mixture ($P < 0.001$, Appendix A Fig. S7), and the weight coefficients are shown in Appendix A Fig. S4-C. 1,4-dichlorobenzene (0.745) had the greatest proportional negative contribution to the mixture effect, followed by bromodichloromethane (0.149), toluene (0.079), and chloroform (0.027). m-/p-xylene (0.622) and dibromochloromethane

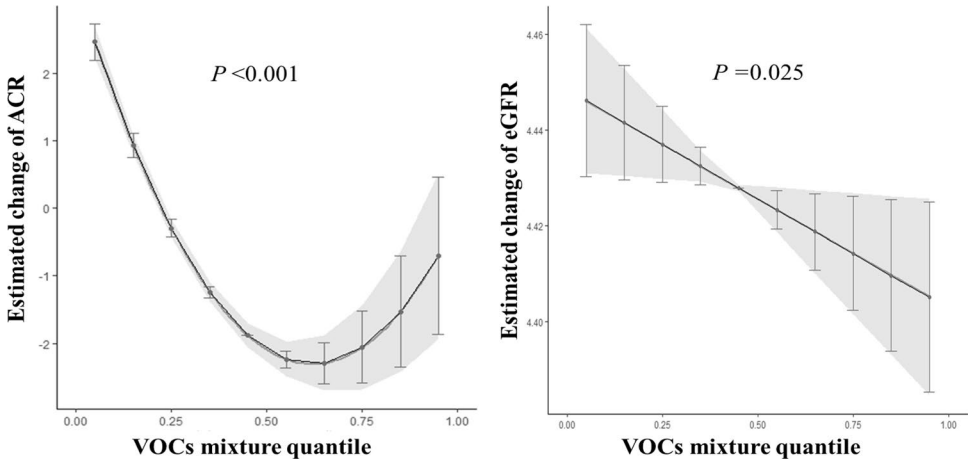

Fig. 3 Associations of blood VOCs mixture with kidney parameters in quantile g-computation. VOCs, volatile organic compounds; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index. All models were adjusted for age, gender, race, BMI, drinking, serum cotinine, physical activity, educational level, the ratio of family income to poverty, and mediations use

(0.378) were negatively weighted in the mixture with serum 25(OH)D.

Associations between vitamin D and kidney parameters

The ACR showed significant elevation in the fourth quartile of vitamin D compared with the first quartile, but it did not change in a monotonous trend across quartiles of vitamin D ($P_{trend} > 0.05$). We did not observe significant association between vitamin D and eGFR ($P > 0.05$ and $P_{trend} > 0.05$) (Appendix A Table S4). The results from restrict cubic spline suggested the association of vitamin D with ACR was nonlinear (P for nonlinear < 0.05), and ACR changed in a U-shaped manner (IP = 44.791 nmol/L) with increasing vitamin D level (Appendix A Fig. S8).

Interaction effect

Figure 4 visualizes how serum 25(OH)D level modifies associations between blood VOCs and kidney parameters. The ACR level was significantly decreased with elevated levels of three VOCs (chloroform, toluene, and 1,4-dichlorobenzene) and VOC mixture at higher serum 25(OH)D level, and the negative effects of the above three VOCs and m-/p-xylene on ACR were strengthened with an increase in serum 25(OH)D level. VOC mixture was positively associated with ACR at lower serum 25(OH)D level, but this effect was weakened and turned negative with an increase in serum 25(OH)D level. The positive effect of dibromochloromethane on ACR was slightly strengthened with the elevation of serum 25(OH)D level. Significant interaction effects of three VOCs (chloroform, toluene, and 1,4-dichlorobenzene) and VOC mixture with serum vitamin D on ACR were observed ($P_{interaction} < 0.05$). Four VOCs (bromodichloromethane, chloroform, m-/p-xylene, and 1,4-dichlorobenzene) were inversely associated with eGFR at lower serum 25(OH)D level, but the effects of these VOCs on eGFR were weakened with an increase in serum 25(OH)D level. Toluene, m-/p-xylene, and VOC mixture were positively associated with eGFR at higher serum 25(OH)D level. The protective effects of the two VOCs and VOCs mixture on eGFR were strengthened with increase in serum 25(OH)D level. Significant interaction effects of all VOCs (except dibromochloromethane) and VOCs mixture with serum vitamin D on eGFR were observed ($P_{interaction} < 0.05$).

Discussion

In the US adult population, four blood VOCs, including bromodichloromethane, toluene, m-/p-xylene, and 1,4-dichlorobenzene, were associated with ACR in a U-shaped manner. Chloroform was linearly and inversely associated with ACR, and dibromochloromethane was linearly and positively associated with ACR. Bromodichloromethane and chloroform were linearly and inversely associated with eGFR, while toluene, m/p-x, and 1,4-dichlorobenzene were in U-shaped associations with eGFR. 1,4-dichlorobenzene was inversely associated with serum 25(OH)D, while chloroform and m-/p-xylene were in U-shaped associations with serum 25(OH)D. Overall, results from quantile g-computation showed that VOC as a mixture was in a U-shaped association with ACR and inversely associated with eGFR and serum 25(OH)D. Serum 25(OH)D showed a U-shaped association with ACR. Associations of three VOCs (chloroform, toluene, and 1,4-dichlorobenzene) and VOCs mixture with ACR were significantly inverse at higher level of 25(OH)D and were strengthened with increasing level of 25(OH)D. Inverse associations of VOCs (except dibromochloromethane) and VOC mixture with eGFR were weakened and even turned to be positive with increasing level of serum 25(OH)D.

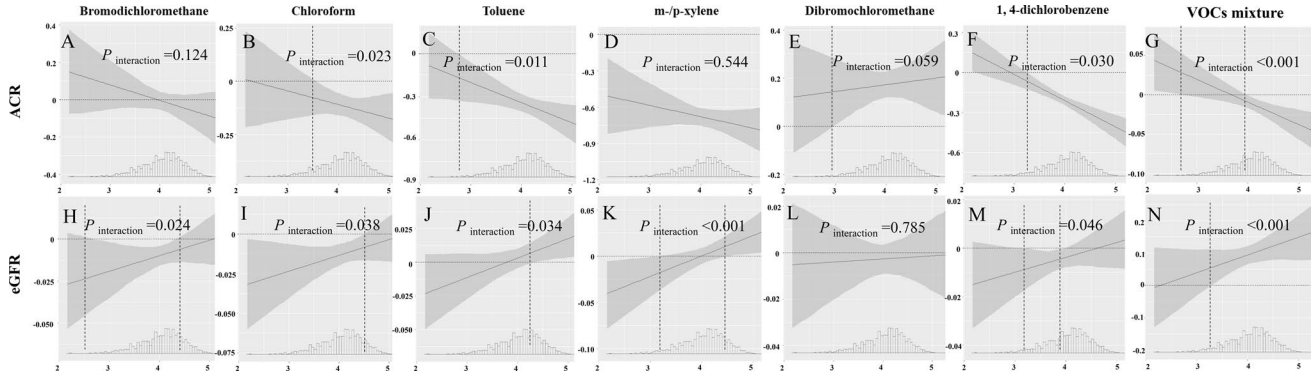

Fig. 4 Regression estimates (with 95% confidence interval) of blood VOCs on kidney parameters with the changes in serum 25(OH)D. **A** Bromodichloromethane and ACR; **B** chloroform and ACR; **C** toluene and ACR; **D** m-/p-xylene and ACR; **E** dibromochloromethane and ACR; **F** 1,4-dichlorobenzene and ACR; **G** VOCs mixture and ACR **H** bromodichloromethane and eGFR; **I** chloroform and eGFR; **J** toluene and eGFR; **K** m-/p-xylene and eGFR; **L** dibromochloromethane and eGFR; **M** 1,4-dichlorobenzene and eGFR; **N** VOCs mixture and eGFR. VOCs, volatile organic compounds; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D. The *X*-axis represents the ln-transformed concentration of serum 25(OH)D. Bar plots on the *X*-axis represent the number of participants with corresponding level of serum 25(OH)D. The dashed vertical line represents the serum 25(OH)D concentration where the 95% confidence interval of the regression estimates of VOCs do not include zero. All models were adjusted for age, gender, race, BMI, drinking, serum cotinine, physical activity, educational level, the ratio of family income to poverty, and mediations use

The impact of occupational and acute exposures to VOCs on kidney health has been reported (Gonzalez-Yebra et al. 2006; Hsiao et al. 2009; Singh et al. 2016). An investigation of insect repellent factories suggested that blood urea nitrogen was significantly higher in workers with on-site exposure to 1,4-DCB compared with non-exposed workers (Hsiao et al. 2009). However, only two epidemiological studies have explored the relationships between exposures to relatively low levels of VOCs and kidney function in the general population (Gonzalez-Yebra et al. 2006). However, only two epidemiological studies have explored the relationships between exposures to relatively low levels of VOCs and kidney function in the general population (Cakmak et al. 2020; Lee et al. 2020). Compared with the above-mentioned two population-based studies that explored the associations of some individual VOCs with CKD and serum creatinine, we assessed the associations of six VOCs as individual compounds and as a whole mixture with two kidney parameters, which improved the evidence of and helped to understand the nature of multiple VOC exposure–associated early kidney injury.

Renal function impairment resulting from exposures to some VOCs, including bromodichloromethane, chloroform, and dibromochloromethane, has been suggested by accumulating animal and cell studies. Significant increases in serum creatinine and blood urea nitrogen could be observed in rats dosed with 150 mg/kg/day oral exposure of bromodichloromethane after 6 days (Thornton-Manning et al. 1994). Mixture exposure of disinfection by-products also resulted in DNA hypomethylation in the kidneys of the mice and rats (Tao et al. 2005). Repeated exposures to bromodichloromethane and chloroform, two potent kidney cytotoxicants, could also induce renal tubular degeneration, necrosis, and degeneration disorders in varied animal models (Butterworth and Bogdanffy 1999; Torti et al. 2001), and mitochondrion is a potential toxic target of the two disinfection by-products (Chen et al. 2019).

Intriguingly, nonlinear U-shaped association between VOCs mixture and ACR was observed in the present study, and three VOCs (toluene, m/p-x, and 1,4-dichlorobenzene) were also in U-shaped associations with eGFR. The associations between VOC exposures and kidney function found in our study were in line with those observed by Sabit et al. (Cakmak et al. 2020), but the potential mechanism remains inconclusive. An explanation of these findings is that VOCs may cause myotoxicity in the form of muscle atrophy, leading to decreases in creatinine levels (Kaukiainen et al. 2004). In addition, VOC exposure-induced glomerular hyperfiltration may explain these U-shaped relationships. Glomerular hyperfiltration is a phenomenon caused by damage of the glomerular filtration barrier, which is characterized by an abnormal rise in eGFR and precedes albuminuria clinically (Bjornstad et al. 2015; Helal et al. 2012). It is worth more effort to explore the possible mechanism underlying these U-shaped associations, considering the potential implications for the nephrology community. We also observed that the associations of different VOCs, especially benzene derivatives and disinfection by-products, with renal function did not show a good agreement. This may be because the physical and chemical properties of different VOCs are different. Compared with the benzene series, disinfection by-products tend to have stronger oxidation and are more likely to induce oxidative damage in the body, which may further lead to renal function injury (Coppolino et al. 2018; Liu et al. 2021).

Among six VOCs, one chlorinated VOC (1,4-dichlorobenzene) was inversely associated with vitamin D, and two chlorinated VOCs (bromodichloromethane and chloroform) were significantly and inversely associated with vitamin D at a lower dose. These results were in line with previous study findings that chlorinated compounds, such as $CdCl_2$, CCl_4, and polychlorinated biphenyls, were found to cause vitamin D deficiency (Brzoska and Moniuszko-Jakoniuk 2005; Nussler et al. 2014; Routti et al. 2008). One possible mechanism underlying vitamin D level decline associated with VOC exposures is that VOCs may trigger depression of cytochrome P450, dysregulation of thyroid hormone, and disturbance of calcium homeostasis (Mousavi et al. 2019). Another possible explanation could be that VOCs may impair kidney function and then inhibit the synthesis and reabsorption of vitamin D and calcium, given the important interdependence between kidney health and vitamin D (Kumar et al. 2012). In addition, VOC-associated vitamin D decline may also be due in part to the lack of sunlight exposure from spending more time indoors, where levels of VOCs are usually higher than outdoors (Su et al. 2011). In general, further animal and perspective cohort studies are needed to validate the associations of VOCs with vitamin D and explore underlying mechanism.

The mutually improved relationship between proper vitamin D status and healthy kidney function has been demonstrated to some extent. In the NHANES III, serum vitamin D biomarkers were significantly lower in participants with a severe decrease in eGFR compared with normal renal function groups (Chonchol and Scragg 2007). As illustrated by Hilpert et al. (2002) and Shimada et al. (2004), the increase of fibroblast growth factor-23 and the decrease of eGFR in kidney injury induced a dose-dependent decrease in 1-α-hydroxylase that are important for maintaining vitamin D status. Conversely, supplementation of vitamin D in CKD patients has performed well in inhibiting disease progression and improving metabolism in many clinical trials (Al-Badr and Martin 2008; Batacchi et al. 2017). Harmonious vitamin D status can inhibit transforming growth factor-β signal transduction and reduce the production of proinflammatory cytokines in kidney through activation of vitamin D receptor (Li 2010), which is of great significance in antiproteinuric, antifibrotic, and anti-inflammatory activities. Du and colleagues also demonstrated that activation of vitamin D receptors could protect kidney health by suppressing renal tubular cell apoptosis (Du et al. 2019). Although there is considerable evidence suggesting that vitamin D is effective for protecting kidney function, controversy over the use of vitamin D supplementation still exists (Jean et al. 2017). Remarkably, vitamin D overload may cause hypercalcemia with subsequent long-term kidney injury (Minisola et al. 2015; Pludowski et al. 2018). The U-shaped association between serum vitamin D and ACR may also be a reminder of such risk.

The protective effect of vitamin D on renal tubular cells may largely explain why vitamin D was observed to alter the effects of VOCs on kidney parameters (Du et al. 2019). In addition to its direct protective effect on the kidney, harmonious vitamin D status may also reduce the risk of hypertension, which is important for maintaining healthy kidney function (Jean et al. 2017). Moreover, vitamin D plays an important role in maintaining the hepatic level of cytochrome P450 (Mousavi et al. 2019), whose detoxification of environmental pollutants may inhibit the effects of VOCs on renal function. The interaction effects between VOCs and vitamin D on kidney function observed in this study provide clues for the mechanism and intervention of VOC-associated renal function. However, the current results of our study cannot fully explain this interaction, nor is it sufficient to support the supplementation of vitamin D to counter the effects of VOCs on renal function, especially considering the side effects of excessive vitamin D supplementation. Further intervention experiments are needed to confirm the results of this study and give a complete picture of the mechanism.

This large nationally representative population-based study provided unique epidemiological evidence for the associations of VOC exposures with kidney function and vitamin D. Not only were the associations between individual VOCs and kidney parameters explored by survey-weight regression and restricted cubic spline models, but also the effect of VOC mixture on kidney function was analyzed by quantile g-computation. Moreover, the potential role of vitamin D was revealed epidemiologically through interaction analyses. The results of our study put positive implications on the risk assessment of VOCs and the pathogenesis of KDs, but several limitations need to be taken into account when interpreting the results. First, cross-sectional design precludes the causal inference, especially since there was the possibility that vitamin D deficiency is simply a complication of poor renal function, although we have adjusted eGFR in the models with serum vitamin D as the outcome. Second, although U-shaped associations between several VOCs and kidney parameters were observed, the evidence on the mechanism of VOCs exposures and renal function was insufficient. Third, other potential confounders, such as some diseases status and genetic susceptibility probably associated with vitamin D status or kidney function, were not considered, although we have tried to adjust many potential confounders.

Conclusion

In single chemical analyses, blood toluene, m-/p-xylene, and 1, 4-dichlorobenzene were U-shaped associated with two kidney parameters. Bromodichloromethane was U-shaped associated with ACR, but inversely associated with eGFR. Chloroform was inversely associated with two kidney

parameters, and dibromochloromethane was positively associated with ACR. Six blood VOCs (as a mixture) in Quantile g-computation showed a U-shaped association with ACR, an inverse association with eGFR, and an inverse association with serum vitamin D. Exposures to six VOCs were associated with kidney function injury and vitamin D level decline among US adults. Meanwhile, vitamin D level may interactively alter the associations of VOC exposures with kidney function. Further prospective cohort studies, intervention studies, and mechanism studies are needed to confirm our findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-022-22637-1.

Author contribution Wei Liu: conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft, writing — review and editing, and visualization

Shuting Cao: methodology, investigation, and writing — review and editing

Jixuan Ma: methodology, investigation, and writing — review and editing

Da Shi: methodology, investigation, and writing — review and editing

Linling Yu: validation, investigation, and writing — review and editing

Zi Ye: software, data curation, and writing — review and editing

Meng Yang: conceptualization, investigation, resources, data curation, writing — review and editing, and supervision

Bin Wang: conceptualization, investigation, resources, data curation, writing — review and editing, and supervision

Weihong Chen: conceptualization, investigation, resources, data curation, writing — review and editing, and supervision

Data availability The datasets generated during and/or analyzed during the current study are available from Weihong Chen (wchen@mails.tjmu.edu.cn) and Bin Wang (gentwong@163.com) on reasonable request.

Declarations

Ethics approval and consent to participate The study protocol was approved by the National Center for Health Statistics Research Ethics Review Board. All participants were well informed and provided consents. A proof/certificate of approval is available at: https://www.cdc.gov/nchs/nhanes/irba98.htm

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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