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Original Article

The associations between volatile organic compounds exposure and urine flow rate in US adults: NHANES 2011-2020

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Abstract: Objective: Metabolites of volatile organic compounds (mVOCs) have attracted considerable attention in contemporary research. The urine flow rate (UFR) serves as an objective metric for a full evaluation of bladder function. This research aimed to investigate the correlation between mVOCs and UFR. Methods: We examined mVOCs and UFR data from the National Health and Nutrition Examination Survey (NHANES) between 2011 and 2020. The mVOCs measurements were subjected to log transformation to achieve normal distribution. We used weighted multivariate linear regression models to evaluate the association between mVOCs andUFR. The relationship between mVOCs mixture and UFR was assessed using three different analytical models: Bayesian kernel machine regression (BKMR), weighted quantile sum (WQS), and quantile g-computation (Qgcomp). An analysis stratified by gender was also conducted. Results: The research had 3,370 participants, of whom 1,703 (51%) were male. Multivariate linear regression revealed a negative correlation between increased mVOCs and UFR across all research cohorts (all $P < 0.001$). The BKMR model displayed a notable negative correlation, identifying N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMA) and Phenylglyoxylic acid (PGA) as possibly important chemicals. The WQS model exhibited a negative connection with UFR across the total cohort and its male and female subgroups, with all *P* values being less than 0.05. The findings of the Qgcomp model aligned with those of the WQS model. Conclusions: Our data indicate a substantial negative connection between exposure to urinary mVOCs and UFR among US adults, with no notable gender differences seen.

Keywords: Metabolites of volatile organic compounds, urine flow rate, NHANES, cross-sectional study, public health

Introduction

The typical process of urination is closely associated with the urethral sphincter, bladder neck, and detrusor muscle. Voiding dysfunction, often classified into obstructive and underactive symptoms, is a common problem impacting the elderly in aging populations. The 2023 Japan Community Health Survey (JaCS 2023) indicates that males with lower urinary tract symptoms (LUTS) demonstrate inferior health status [1]. The urodynamic examination, regarded as the gold standard for diagnosing LUTS, encompasses the measurement of urine flow rate (UFR). This non-invasive technique evaluates the volume of urine expelled per unit time during natural urination, thereby reflecting detrusor muscle strength, bladder outlet resistance, and indirectly, the health and functionality of the bladder [2, 3].

Volatile organic compounds (VOCs) are carbon compounds characterized by low molecular weight, allowing them to easily vaporize at ambient temperatures and pressures [4]. They are widespread in the atmosphere, with origins in both natural and anthropogenic activities, including industrial and vehicular emissions [5, 6]. In contrast to other pollutants found in food or certain professional settings, VOCs predominantly occur in the atmosphere, rendering them more accessible to the general populace.

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The human body can inadvertently absorb VOCs via inhalation, ingestion, and dermal contact. Prolonged exposure to low concentrations of VOCs may negatively impact the endocrine system [7], respiratory system [8], neurological system [9], and urinary system [10]. Although VOCs may be identified in biological specimens including blood, urine, breath, saliva, and sweat [11, 12], achieving accurate findings can be difficult. Multiple factors contribute to its complexity. Biologically, VOCs in biological samples exist at very low concentrations, frequently in the parts-per-billion (ppb) or parts-per-trillion (ppt) range. Their identification and quantification are exceedingly difficult, necessitating highly sensitive analytical methods. Furthermore, biological samples are intricate matrices with a diverse assortment of components, including proteins, lipids, carbohydrates, and other metabolites. These coexisting compounds can disrupt the analysis of VOCs, resulting in false positives or negatives and hindering the precise identification and quantification of the target VOCs. Urinary metabolites of VOCs (mVOCs) exhibit a prolonged physiological half-life relative to their blood counterparts, persisting in the body for an extended period. The non-invasive characteristics of urine sampling make mVOCs an especially significant biomarker for evaluating prolonged exposure to VOCs [13].

Despite the growing evidence connecting mVOCs to bladder cancer [14] and the risk of overactive bladder [15], the field lacks sufficient studies on how mVOCs exposure affect UFR. Although Chiu et al. [16] revealed the association between muscle strength and UFR based on the National Health and Nutrition Examination Survey (NHANES) database, no studies have systematically evaluated the combined effects of mVOCs mixtures on UFR. Given that VOCs and their metabolites have been associated with neurotoxicity [23, 26] and systemic oxidative stress [30] - both of which can impair neurological control of the bladder and detrusor muscle function - we hypothesize that exposure to mVOCs may negatively impact UFR. This study aims to fill this critical research gap by systematically evaluating the relationship between individual and mixed mVOCs exposure and UFR in a nationally representative population.

This study is the first to integrate multi-model analyses [Bayesian kernel machine regression (BKMR), weighted quantile sum (WQS), and quantile g-computation (Qgcomp)] aiming to uncover the dose-response relationship between mVOCs exposure and UFR and identify key driver compounds, thereby addressing the research gap in this field. This cross-sectional study sought to investigate UFR relationships with particular mVOCs or their mixtures while identifying the most influential chemical compounds through data from an American population survey.

Methods and materials

Study population

We obtained data from five NHANES survey cycles (2011-2020), which initially included 45,462 participants. The inclusion criteria for our analysis were: (1) adult participants (age ≥ 20 years); (2) availability of valid UFR measurement data; and (3) availability of urinary mVOCs measurement data. Participants were excluded if they had: (1) missing data on key covariates (e.g., age, gender, BMI, smoking status); (2) a history of urinary tract infection or surgery that could severely affect urination; or (3) extreme UFR values (defined as the top and bottom 1%) considered physiologically implausible or indicative of measurement error. After applying these criteria, 3,370 participants were included in the final analysis. The participant selection flowchart is illustrated in Figure S1.

Measurements of mVOCs

We examined urinary mVOCs by using ultra-performance liquid chromatography in conjunction with electrospray tandem mass spectrometry (UPLC-ESI/MSMS) [13]. The chromatographic separation was performed on an Acquity UPLC® HSS T3 (1.8 μm*2.1 mm*150 mm, Waters Inc.) using a binary mobile phase system consisting of 15 mM ammonium acetate and acetonitrile. Quantification of target analytes was achieved by establishing calibration curves through comparison of the relative response factors, calculated as the peak area ratio of native analytes to their corresponding stable isotope-labeled internal standards, against predefined concentration gradients of certified reference standards. As per NHANES guidelines, mVOCs concentrations were reported in ng/mL, with values beneath the lower limit of detection (LLOD) being imputed as LLOD

divided by the square root of two. For detailed methodologies and additional information, one can consult the NHANES website.

Across the five NHANES survey cycles, 25 types of urinary mVOCs were identified. However, 11 metabolites were removed from the analysis because their values exceeded detection limits in more than 10% of participants or contained numerous censored measurements. Consequently, 14 mVOCs were included in the final analysis: 2MHA (2-Methylhippuric acid), 3,4-MHA (3- and 4-Methylhippuric acid), AAMA (N-Acetyl-S-(2-carbamoylethyl)-L-cysteine), AMCC (N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine), ATCA (2-Aminothiazoline-4-carboxylic acid), SBMA (N-Acetyl-S-(benzyl)-L-cysteine), HMPMA (N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine), CEMA (N-Acetyl-S-(2-carboxyethyl)-L-cysteine), DHBMA (N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine), 2HPMA (N-Acetyl-S-(2-hydroxypropyl)-L-cysteine), 3HPMA (N-Acetyl-S-(3-hydroxypropyl)-L-cysteine), MA (Mandelic acid), MHBMA3 (N-Acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine), and PGA (Phenylglyoxylic acid). Table S1 provides a summary of these 14 mVOCs and their corresponding parent VOCs.

Assessment of UFR

UFR was assessed following the standardized protocol detailed in the NHANES MEC Laboratory Procedures Manual. Participants were instructed to record the time of their last void before arriving at the Mobile Examination Center (MEC). Upon arrival, they were asked to provide a full urine sample. The time of this void was meticulously recorded. To ensure sufficient sample volume for various assays, participants could provide up to three voids during their MEC visit, with the volume and time of each void accurately documented. The total urine volume (sum of all voids) and the total time duration (from the last void before the MEC to the completion of the last void at the MEC) were used to calculate the UFR. The UFR (in mL/min) was calculated using the formula: UFR = Total Urine Volume (mL)/Total Time Duration (min). For detailed operation, please refer to the operation manual on the official website (https://wwwn.cdc.gov/nchs/data/nhanes/public/2019/manuals/2020-MEC-Laboratory-Procedures-Manual-508.pdf).

Potential covariates

To limit the effect of confounding variables on our research findings, we ran covariate-adjusted analyses. The demographic variables accounted for included gender, age, race/ethnicity, education level, poverty-to-income ratio (PIR), body mass index (BMI), waist circumference, smoking and drinking habits, as well as medical histories of diabetes mellitus (DM) and hypertension. These characteristics were rigorously retrieved from the NHANES database to achieve a robust statistical correction.

Statistical analysis

Given the high skewness in the elemental mVOCs and UFR data, we conducted a log10 (ln) treatment to normalize the distribution and limit the influence of outliers. We present continuous variables are as medians with interquartile ranges (IQR), whereas categorical variables as frequencies with matching percentages. We applied Spearman's correlation test for the evaluation of the links among mVOCs.

We investigated the connection between urine mVOCs mixtures and UFR by use of multivariate linear regression alongside three advanced mixture analysis methodologies: Bayesian kernel machine regression (BKMR), weighted quantile sum (WQS), and quantile g-computation (Qgcomp). These methodologies allow us to examine nonlinear exposure correlations and interactions, enabling a thorough assessment of how various urinary mVOCs collectively affect UFR. The BKMR model, ideal for strongly linked exposures, offers an adaptable method to estimate the multivariable exposure-response function [17, 18]. It used 25,000 iterations of the Markov chain Monte Carlo sampler for its execution. The WQS index was constructed based on the quartiles of urine mVOCs [19, 20]. The Qgcomp model, a novel method integrating WQS regression with fundamental g computation, was also utilized [21].

We performed a gender-stratified analysis across all models to investigate whether the connection between urinary mVOCs and UFR differed between male and female participants. All statistical analyses were implemented by use of R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria), with a

Table 1. Basic characteristics of the participants included in this study

Characteristics	Overall, N = 3370 (100%)	Gender		*P* Value
		Female, N = 1667 (49%)	Male, N = 1703 (51%)	
Age group				0.4
< 45	1504 (45%)	738 (44%)	766 (45%)	
45-60	798 (24%)	410 (25%)	388 (23%)	
≥ 60	1068 (32%)	519 (31%)	549 (32%)	
Race				0.13
Mexican American	413 (12%)	207 (12%)	206 (12%)	
Non-Hispanic Black	783 (23%)	363 (22%)	420 (25%)	
Non-Hispanic White	1307 (39%)	655 (39%)	652 (38%)	
Other Hispanic	377 (11%)	202 (12%)	175 (10%)	
Other/multiracial	490 (15%)	240 (14%)	250 (15%)	
BMI group				< 0.001
< 25	991 (29%)	501 (30%)	490 (29%)	
25-30	1094 (32%)	462 (28%)	632 (37%)	
≥ 30	1285 (38%)	704 (42%)	581 (34%)	
Drink group				< 0.001
No	873 (26%)	593 (36%)	280 (16%)	
Yes	2497 (74%)	1074 (64%)	1423 (84%)	
Smoke group				< 0.001
Never	1897 (56%)	1091 (65%)	806 (47%)	
Past	803 (24%)	293 (18%)	510 (30%)	
Current	670 (20%)	283 (17%)	387 (23%)	
Education				0.009
9-11th Grade	404 (12%)	187 (11%)	217 (13%)	
College Graduate or above	918 (27%)	462 (28%)	456 (27%)	
High School Grad/GED	713 (21%)	325 (19%)	388 (23%)	
Less Than 9th Grade	296 (8.8%)	137 (8.2%)	159 (9.3%)	
Some College or AA degree	1038 (31%)	556 (33%)	482 (28%)	
PIR group				0.4
≥ 1.3	2310 (69%)	1133 (68%)	1177 (69%)	
< 1.3	1060 (31%)	534 (32%)	526 (31%)	
Marital Status				< 0.001
Divorced	357 (11%)	217 (13%)	140 (8.2%)	
Living with partner	307 (9.1%)	152 (9.1%)	155 (9.1%)	
Married	1686 (50%)	746 (45%)	940 (55%)	
Never married	701 (21%)	334 (20%)	367 (22%)	
Separated	94 (2.8%)	53 (3.2%)	41 (2.4%)	
Widowed	225 (6.7%)	165 (9.9%)	60 (3.5%)	
Age (years)	48 (33, 63)	48 (33, 62)	48 (33, 63)	> 0.9
BMI (kg/m^2)	27.9 (24.3, 32.6)	28.4 (24.0, 33.7)	27.7 (24.5, 31.6)	0.016
PIR	2.11 (1.10, 4.20)	2.12 (1.08, 4.10)	2.10 (1.11, 4.26)	0.5
Waist circumference (cm)	98.2 (87.7, 109.3)	96.6 (85.4, 108.2)	100.0 (89.8, 110.0)	< 0.001
UFR (mL/min)	0.82 (0.53, 1.33)	0.80 (0.50, 1.34)	0.84 (0.56, 1.32)	0.025
TC (mmol/L)	4.86 (4.19, 5.59)	4.97 (4.29, 5.64)	4.78 (4.09, 5.51)	< 0.001
HDL-C (mmol/L)	1.32 (1.09, 1.60)	1.45 (1.19, 1.73)	1.19 (1.01, 1.42)	< 0.001
ALT (IU/L)	21 (16, 28)	18 (15, 23)	24 (19, 32)	< 0.001

AST (IU/L)	23 (19, 28)	21 (18, 25)	25 (21, 29)	< 0.001
ALB (g/L)	43 (41, 45)	42 (40, 44)	44 (42, 46)	< 0.001
GGT (IU/L)	19 (14, 29)	16 (12, 24)	23 (16, 34)	< 0.001
TP (g/L)	71 (69, 75)	71 (68, 74)	72 (69, 75)	< 0.001
ALP (IU/L)	64 (52, 78)	64 (51, 79)	64 (52, 78)	0.7
HbA1c (%)	5.5 (5.2, 5.9)	5.5 (5.2, 5.9)	5.5 (5.3, 5.9)	0.028
UA (μmol/L)	321 (268, 381)	280 (238, 333)	357 (309, 405)	< 0.001
SCr (μmol/L)	76 (63, 89)	65 (57, 75)	86 (76, 98)	< 0.001
BUN (mmol/L)	4.64 (3.57, 5.71)	4.28 (3.21, 5.36)	4.64 (3.93, 5.71)	< 0.001
Urinary albumin (mg/L)	7.6 (4.0, 16.7)	7.0 (3.7, 15.7)	8.0 (4.3, 18.1)	< 0.001
Urinary creatinine (mg/dL)	104 (60, 162)	84 (48, 137)	126 (76, 181)	< 0.001
Urinary ACR (mg/g)	7.10 (4.62, 13.28)	7.96 (5.40, 14.45)	6.11 (4.05, 12.01)	< 0.001
DM				0.033
No	2791 (83%)	1404 (84%)	1387 (81%)	
Yes	579 (17%)	263 (16%)	316 (19%)	
Hypertension				0.6
No	2184 (65%)	1088 (65%)	1096 (64%)	
Yes	1186 (35%)	579 (35%)	607 (36%)	

Note: ACR, Albumin creatinine ratio; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DM, diabetes mellitus; DBP, diastolic blood pressure; GGT, gamma-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; PIR, poverty-to-income ratio; SCr, serum creatinine; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid; UFR, urine flow rate.

two-tailed $P < 0.05$ being statistically significant.

Results

Population characteristics

Table 1 delineates the principal demographic and baseline attributes of the research cohort. The research examined participants whose median age reached 48 years, with 51% (n = 1,703) being male, who likewise shared a median age of 48 years. The predominant demographic of participants was Non-Hispanic White (39%), with 31% having completed some college or obtained an AA degree. Baseline comparisons showed that male participants exhibited elevated levels of alcohol consumption, smoking, waist circumference, glycated hemoglobin (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total protein (TP), uric acid (UA), serum creatinine (SCr), blood urea nitrogen (BUN), urinary albumin, urinary creatinine, and UFR.

Distribution and correlation of urinary mVOCs

Table S2 presents descriptive information about the concentrations of the 14 urine mVOCs. HPMMA and DHBMA were detected in almost all subjects, with DHBMA exhibiting the greatest amounts and MHBMA3 the lowest among the mVOCs. Men had markedly elevated levels of almost all mVOCs compared to women, with the exception of ATCA.

We implemented a Spearman correlation analysis for investigating the links among the 14 mVOCs, as seen in **Figure 1**. In addition to robust relationships among metabolites derived from the same chemical, the Spearman correlation coefficients ranged from 0.27 to 0.87. Significantly, 3HPMA demonstrated positive associations with CEMA and HMPMA (r = 0.81 and r = 0.84, respectively), while MHBMA3 was positively correlated with 3HPMA and HMPMA (r = 0.82 and r = 0.87, respectively). Additionally, 2MHA exhibited a positive correlation with 34MHA (r = 0.87), and MA showed a positive correlation with PGA (r = 0.82).

Association between mVOCs and UFR by linear regression

The weighted linear regression analyses, shown in Tables S3, S4, demonstrate that after controlling for all variables, a substantial negative association exists between all urine mVOCs and UFR throughout the whole population

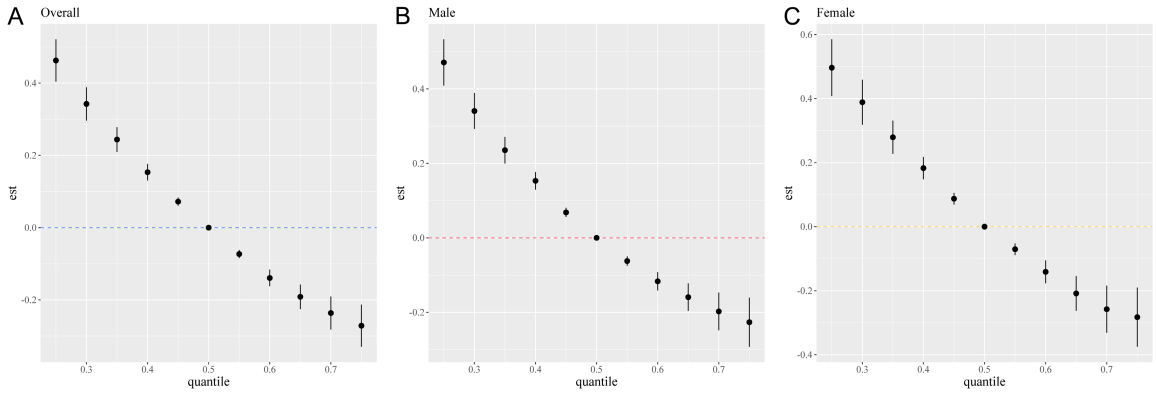

Figure 1. Spearman correlation analysis of urinary concentrations of 14 metabolites of volatile organic compounds.

and among male and female subgroups (all $P < 0.001$). Subsequent stratified analysis by mVOCs quartiles revealed that individuals in the higher quartiles (Q2-Q4) had a substantially lower UFR than those in the lowest quartile (Q1) for all mVOCs (all $P < 0.001$).

The single and overall effects of mVOCs on UFR by the BKMR model

Figure 2 depicts the overall correlation between the amalgamation of mVOCs and UFR over the whole study cohort, as well as within male and female subgroups. When all confounding variables received adjustment, a steady downward trend was noted between the combination of urinary mVOCs and UFR, especially between the 25th and 75th percentiles, signifying a substantial negative connection.

Figure S2 illustrates the exposure-response connections between certain mVOCs and UFR while keeping other mVOCs as their median concentrations (50th percentile). Compounds like AAMA, AMCC, ATCA, SBMA, DHBMA, and 34MHA had negative associations with UFR across all subjects, whereas 3HPMA and MHBMA3 revealed favorable relationships. CEMA and 2HPMA had a negative link with UFR in both the general population and among men, whereas HMPMA showed negative associations in both the general population and among females. PGA had a negative connection with UFR exclusively in males.

Figure S3 analyzes the impacts of various mVOCs on UFR under single-exposure conditions, while maintaining other mVOCs at the 25th, 50th, and 75th percentiles. Marked negative correlations with UFR were seen for PGA (among all participants and female subgroups) and 34MHA (among all participants and male subgroups). DHBMA revealed inverse correlations with UFR in both male and female subgroups, but not in the general population. Conversely, a significant positive connection was discovered between 3HPMA and UFR when other mVOCs reached their 25th percentile, and between MHBMA3 and UFR when other mVOCs reached their 50th percentile, in all research groups. The posterior inclusion probability (PIP) study unveiled that ATCA, CEMA, DHBMA, 3HPMA, 34MHA, and PGA (all with PIP = 1.0) were the most influential in affecting UFR. In men, ATCA, DHBMA, and 34MHA (all with PIP = 1.0) contributed the most significantly to UFR effects. In females, CEMA, DHBMA, and PGA, all exhibiting a high PIP of 1.0, were inversely correlated with UFR. Comprehensive PIP findings are given in Table S5.

WQS regression model and Qgcomp model

We initially concentrated our investigation on the adverse aspect of the connection. Upon adjusting for all possible confounders, the WQS score displayed a significant inverse connection with UFR across all study groups (all $P < 0.05$). PGA exerted the most significant influence on total UFR at 16.12%, followed by ATCA at 15.70% and AAMA at 14.98%. DHBMA was the predominant chemical in both male and female categories, accounting for 25.97% and 22.93%, respectively. Further study, limited to the negative correlation between mixed mVOCs and UFR, produced no meaningful results. Further information is displayed in **Figure 3**.

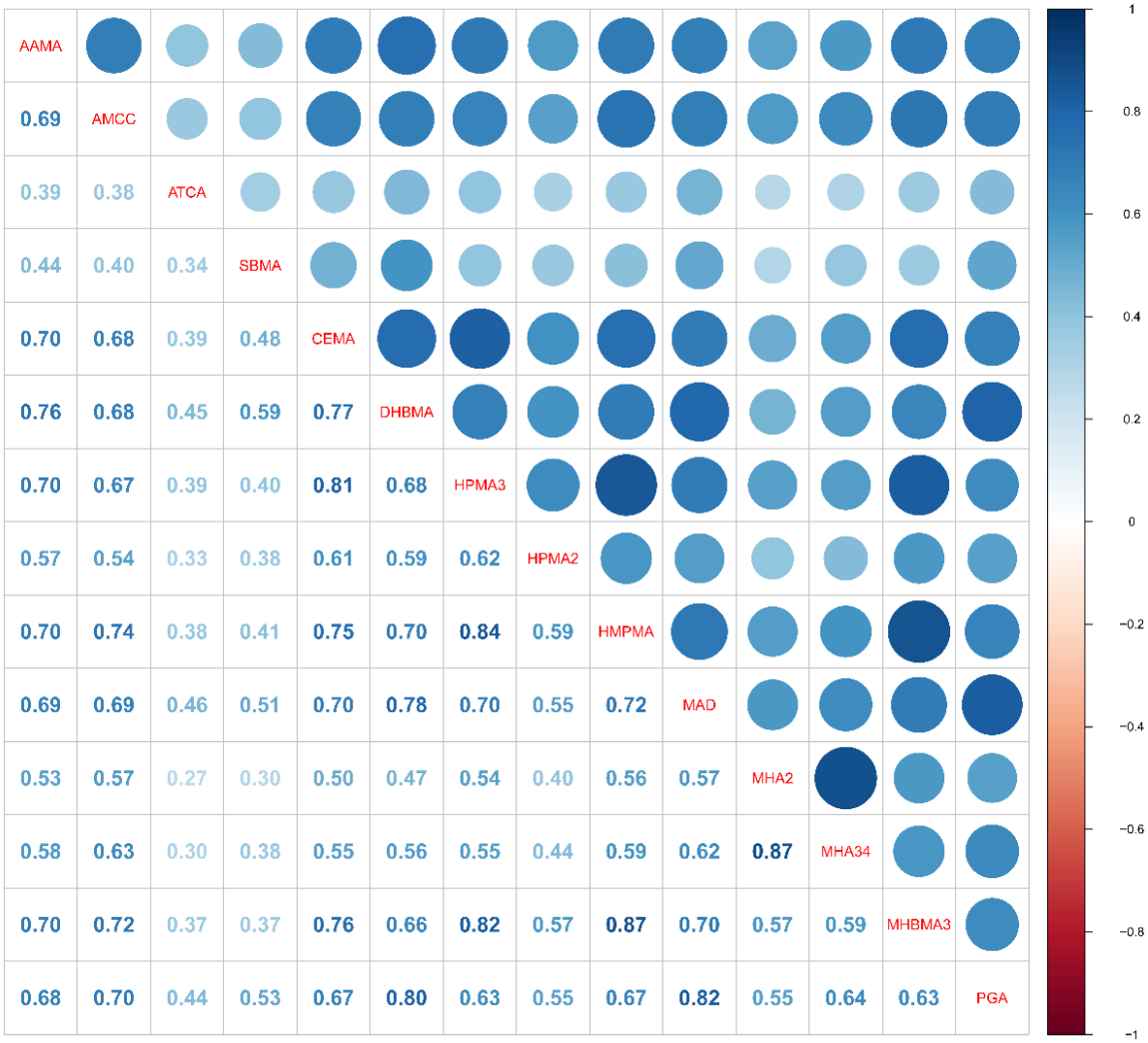

Figure 2. Combined effects of the urinary mVOCs mixture on UFR estimated by the BKMR model. All the concentrations of urinary mVOCs, ranging from the 25th to the 75th percentile in increments of 5, were contrasted with those at the 50th percentile. mVOCs, metabolites of volatile organic compounds; UFR, urine flow rate; BKMR, Bayesian kernel machine regression.

The Qgcomp model exhibited a pattern analogous to that of the WQS model outputs. The Qgcomp index displayed a negative link to UFR across all research groups (all $P < 0.05$). Regarding individual mVOCs, urinary 3HPMA exhibited the most significant beneficial contribution to the total impact at 64.80%, followed by MHBMA3 at 35.20%. Conversely, urinary DHBMA exhibited the highest negative weight at 20.68%, whereas PGA registered at 13.24%. In male and female subgroups, urinary 3HPMA exhibited the highest positive weight at 55.10% and the highest negative weight at 92.03%, whereas DHBMA showed weights of 22.54% and 24.25% for negative and positive associations, respectively. A thorough overview of these results is provided in **Figure 4**.

Discussion

This large population-based study analyzed 3,370 adult participants in the United States from 2011 to 2020 to assess the potential correlation between exposure to mVOCs and UFR. Our research employed several statistical methods to clarify the link between mVOCs exposure and UFR. The multivariate linear regression model indicated that elevated urine levels of mVOCs were substantially and inversely correlated with UFR, a result consistent across genders. To evaluate the cumulative

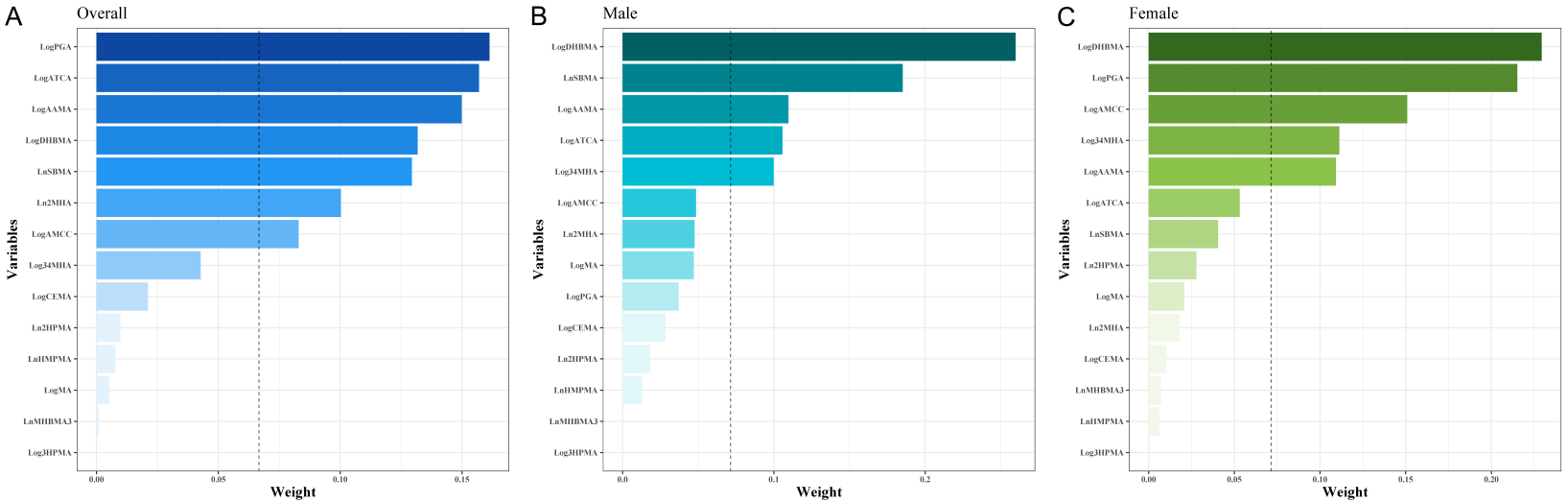

Figure 3. Estimated WQS regression weights in the association of urinary mVOCs mixture with UFR. WQS, weighted quantile sum; mVOCs, metabolites of volatile organic compounds; UFR, urine flow rate.

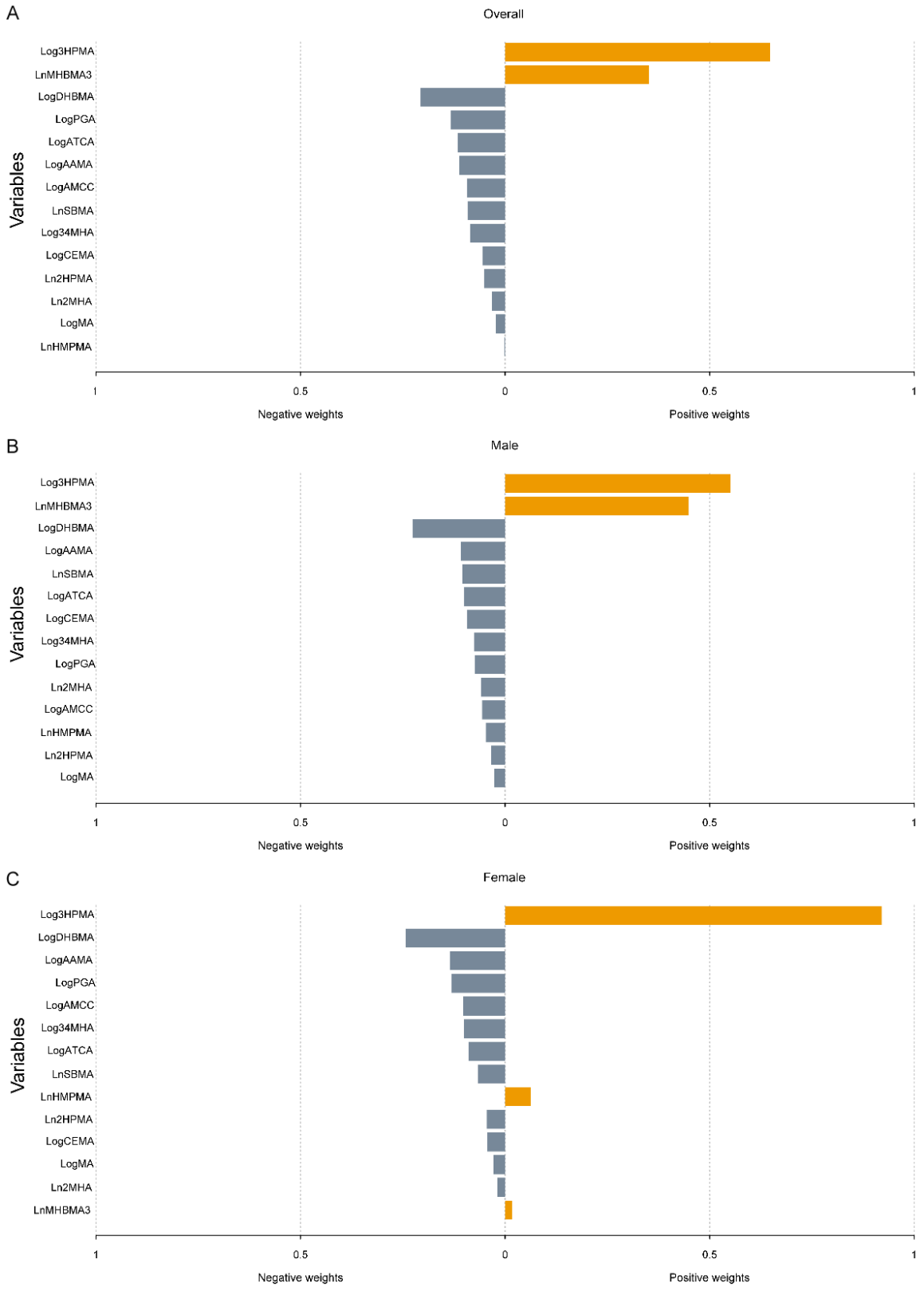

Figure 4. The weights of qgcomp model in the association of urinary mVOCs mixture with UFR. Qgcomp, quantile g-computation; mVOCs, metabolites of volatile organic compounds; UFR, urine flow rate.

effects of mVOCs mixtures and tackle the intricacies of non-linear and non-additive connections, along with possible interactions among mVOCs, we utilized BKMR, WQS, and Qgcomp models. The results repeatedly revealed a substantial negative connection between the combination of mVOCs and UFR. DHBMA and PGA were the principal contributors to the observed results, yet DHBMA showed the most significant negative weight. To our knowledge, this is the first study to report a significant negative association between mixed mVOCs exposure and UFR.

The human liver uses cytochrome P450 to metabolize VOCs into hydroxylated and ring-opening metabolites, which are then eliminated in urine after exposure. mVOCs, being more stable biomarkers than their parent chemicals, have reduced volatility and an extended biological half-life in urine relative to blood, rendering them appropriate for assessing VOC exposure.

The urine reflex is a multifaceted system governed by nerve transmission, detrusor activity, and the bladder outlet. 1,3-butadiene and ethylbenzene serve as the precursor chemicals for DHBMA and PGA, respectively. Comprehensive investigations of multi-omics data regarding epigenetic alterations in individuals exposed to mVOCs [22], such as ethylbenzene, indicate that DNA hypermethylation downregulates eight genes, potentially diminishing synapse density and dendritic complexity. A study including 310 individuals exposed to 1,3-butadiene [23] revealed that it qualifies as a neurotoxin, inducing temporary neurological hazards in the majority of patients, but around 6% (18 patients) exhibited permanent neurotoxicity that requires further longitudinal investigation. Clinical and pathological research has associated chronic exposure to VOCs with numerous neuropsychiatric disorders, such as distractibility, hallucinations, impaired impulse control, dementia, and respiratory complications [24-26], indicating that VOCs pass through the blood-brain barrier (BBB) to cause detrimental effects on development and maintenance of the nervous system. VOCs can cause direct neurotoxicity in neuronal cells, potentially resulting in cellular damage or death, which may interfere with the nervous system's control of the bladder and therefore affect UFR [27]. In vitro investigations have demonstrated that acute exposure to whole VOCs in gasoline can diminish cell viability, compromise cell membrane integrity, and trigger DNA damage in A549 cells [28].

The detrusor and pelvic floor form the key muscle groups that control the process of urination. Chiu et al. [16] investigated the correlation between UFR and muscular strength utilizing the NHANES database, providing insights into the possible causes of decreased UFR concerning bladder contractility. Inflammation is a contributing component in several urinary disorders, resulting in inadequate detrusor muscle function [29]. A study in Wuhan, central China, investigated how urinary mVOCs related to oxidative stress biomarkers in the general population [30], concluding that 1,3-butadiene is a high-priority hazardous VOC for management, while DHBMA and PGA exhibited significant positive associations with oxidative stress biomarkers (8-OHdG and 8-OHG). Primavera et al. [31] observed that 42 workers exposed to 1,3-butadiene at a petrochemical facility had a notable reduction in glutathione transferase enzymatic activity and a substantial elevation in glutathionylated hemoglobin inside red blood cells. Currently, evidence regarding the association between mVOCs and smooth muscle function remains limited.; nonetheless, it may be hypothesized that mVOCs may indirectly influence detrusor function during urine storage and voiding, resulting in voiding symptoms or an underactive bladder.

Our findings gain further support from a previous investigation utilizing the NHANES database. Chiu et al. [16] demonstrated a significant positive association between handgrip strength and UFR, suggesting that systemic muscle strength may serve as a surrogate for detrusor muscle contractility, or that shared physiological factors like overall health status and neuromuscular integrity underpin both skeletal muscle strength and efficient bladder emptying. While Chiu et al. focused on a functional outcome (muscle strength), our study identifies a potential environmental cause for the impairment of this very system. It is plausible that exposure to mVOCs, through the mechanisms of neurotoxicity [23, 26] and oxidative stress [30] as discussed above, contributes to a generalized decline in neuromuscular function. This could manifest as both reduced skeletal muscle strength (as might be reflected in

handgrip) and impaired detrusor muscle contractility or neurological control of the micturition reflex, ultimately leading to a decreased UFR. Therefore, our results extend the observation made by Chiu et al. by proposing that exposure to specific environmental toxicants, such as VOCs and their metabolites, could be an underlying factor contributing to the link between poorer physiological function and reduced UFR.

The predominant causes of bladder outlet blockage are bladder tumors and benign prostatic hyperplasia (BPH) in males. Research indicates that prolonged exposure to VOCs might markedly elevate the occurrence of bladder cancers [32]. Obstructed urination may arise when cancerous tissue detaches or when the tumor obstructs the internal bladder opening, or when cancer infiltrates the ureteral orifice. Evidence suggests that the cytotoxic effects of VOCs may result in cellular damage and alterations in tissue structure inside the prostate [33]. VOCs may elevate oxidative stress, resulting in cellular and DNA damage, which might facilitate the aberrant growth of prostate cells [34].

In the examination of the nonlinear exposure-response connection between individual mVOCs and UFR inside the BKMR model, we discovered that 3HPMA and MHBMA3 displayed a positive connection with UFR. Comparable results were noted in the Qgcomp model, with positive weights of 0.648 and 0.352 for 3HPMA and MHBMA3, respectively. In the multivariate regression analysis, all of these mVOCs, including 3HPMA and MHBMA3, exhibited a negative correlation with UFR. Upon examining our dataset and analytic code for inaccuracies, we identified no discrepancies. The potential rationale is that multiple linear regression analysis presumes linear associations among variables, but BKMR is a nonparametric technique that identifies nonlinear correlations and interactions among variables. If the actual interactions among mVOCs are nonlinear, linear regression may fail to effectively represent these relationships, but BKMR may yield alternative insights. The negative correlation between the overall impact of mVOCs and UFR may stem from the detrimental effects of certain mVOCs counterbalancing the beneficial effects of others, leading to an overall adverse association of the pollutants.

This study, to our knowledge, marks the initial thorough investigation into the relationship between urine mVOCs and the prevalence of UFR in a nationally representative population. This study emphasizes the need of examining the co-exposure impacts of several mVOCs on public health, acknowledging the simultaneous exposure of the population to various mVOCs. Recognizing the possible interactions among various mVOCs, we utilized a range of mixture analysis techniques, including weighted multivariate linear regression, BKMR, WQS regression, and Qgcomp models, to comprehensively evaluate the link between mVOCs mixtures and UFR.

This study possesses many drawbacks. First, this was cross-sectional research, reflecting only the individuals' condition at the time of assessment, indicating that the research cannot establish cause-effect relationships so additional prospective studies must validate the final results. Second, the utilization of urine mVOCs may not exclusively indicate environmental exposures, and environmental exposure assessment remained incomplete because there were insufficient data on ambient VOCs. Future research may improve by including extensive data to deepen the comprehension of exposure-transformation-effect relationships between mVOCs and UFR.

Conclusions

In conclusion, our cross-sectional study demonstrated that exposure to both individual mVOCs and mVOC mixtures is associated with reduced UFR. DHBMA and PGA were the primary factors contributing to the reduced UFR. Future longitudinal studies are crucial to validate these correlations and to devise methods for early intervention to avert reductions in UFR.

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Disclosure of conflict of interest

None.

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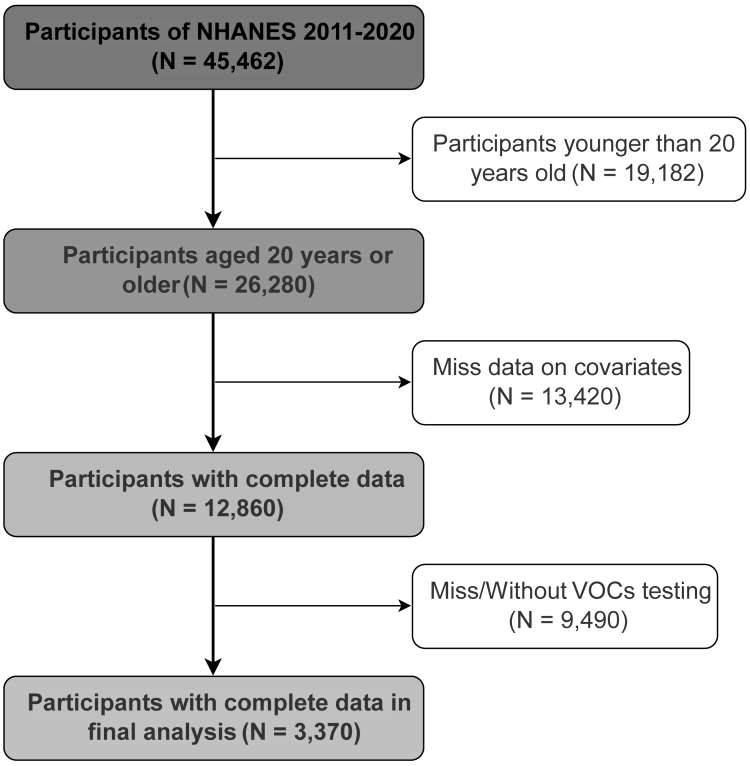

Figure S1. The flowchart of the participants selected from the NHANES.

Table S1. mVOCs selected for investigation in this study

mVOCs	Parent compounds	Abbreviations	Detection rate	LLOD (ng/ml)
N-Acetyl-S-(2-carbamoylethyl)-L-cysteine	Acrylamide	AAMA	99.64%	2.20
N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine	N, N-Dimethylformamide	AMCC	99.79%	6.26
2-Aminothiazoline-4-carboxylic acid	Cyanide	ATCA	95.42%	15.0
N-Acetyl-S-(benzyl)-L-cysteine	Toluene	SBMA	99.33%	0.50
N-Acetyl-S-(2-carboxyethyl)-L-cysteine	Acrolein	CEMA	99.21%	6.96
N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine	1,3-Butadiene	DHBMA	99.95%	5.25
N-Acetyl-S-(3-hydroxypropyl)-L-cysteine	Acrolein	3HPMA	99.86%	3.0
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine	Propylene oxide	2HPMA	94.70%	5.30
N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine	Crotonaldehyde	HMPMA	99.98%	1.70
Mandelic acid	Styrene	MA	98.57%	12.0
2-Methylhippuric acid	Xylene	2MHA	93.37%	5.0
3- and 4-Methylhippuric acid	Xylene	34MHA	99.64%	8.0
N-Acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine	1,3-Butadiene	MHBMA3	97.04%	0.60
Phenylglyoxylic acid	Ethylbenzene	PGA	99.05%	12.0

Table S2. Distribution of mVOCs in urine

Characteristics	Overall, N = 3370 (100%)	Gender		*P* Value
		Female, N = 1667 (49%)	Male, N = 1703 (51%)	
AAMA (ng/mL)	50.1 (26.1, 99.9)	42.0 (21.8, 84.4)	58.6 (31.1, 115.0)	< 0.001
AMCC (ng/mL)	149.0 (74.9, 303.0)	138.0 (66.6, 289.0)	161.5 (83.7, 314.0)	< 0.001
ATCA (ng/mL)	112.0 (53.3, 220.5)	147.0 (72.1, 282.0)	84.6 (42.5, 170.3)	< 0.001
SBMA (ng/mL)	6.74 (3.58, 13.20)	6.53 (3.32, 13.20)	6.93 (3.88, 13.10)	0.041
CEMA (ng/mL)	103.0 (53.0, 191.0)	84.2 (43.3, 166.0)	119.0 (66.0, 209.0)	< 0.001
DHBMA (ng/mL)	309.0 (178.0, 493.5)	272.0 (152.8, 454.3)	357.5 (211.0, 522.0)	< 0.001
3HPMA (ng/mL)	252.0 (129.0, 509.0)	195.0 (96.1, 431.5)	303.0 (170.8, 587.5)	< 0.001
2HPMA (ng/mL)	31.10 (16.20, 59.50)	26.50 (13.90, 55.83)	34.90 (19.50, 62.40)	< 0.001
HMPMA (ng/mL)	254.0 (136.5, 498.0)	218.0 (109.0, 435.0)	284.5 (163.0, 557.0)	< 0.001
MA (ng/mL)	137.0 (78.2, 235.0)	120.0 (68.2, 211.0)	155.0 (90.7, 256.0)	< 0.001
2MHA (ng/mL)	31.2 (13.8, 77.2)	26.0 (11.7, 66.4)	37.1 (16.3, 85.2)	< 0.001
34MHA (ng/mL)	210.0 (89.8, 547.0)	179.0 (72.6, 496.0)	248.0 (108.0, 588.3)	< 0.001
MHBMA3 (ng/mL)	5.37 (2.71, 11.45)	4.36 (2.22, 9.44)	6.26 (3.52, 13.33)	< 0.001
PGA (ng/mL)	206.0 (113.5, 353.0)	178.5 (100.0, 314.3)	234.0 (137.0, 383.3)	< 0.001

Note: mVOCs, metabolites of volatile organic compounds; AAMA, N-acetyl-S-(2-carbamoylethyl)-L-cysteine; AMCC, N-acetyl-S-(N-methylcarbamoyl)-L-cysteine; ATCA, 2-aminothiazoline-4-carboxylic acid; SBMA, N-acetyl-S-(benzyl)-L-cysteine; CEMA, N-acetyl-S-(2-carboxyethyl)-L-cysteine; DHBMA, N-acetyl-S-(3:4-dihydroxybutyl)-L-cysteine; 3HPMA, N-acetyl-S-(3-hydroxypropyl)-L-cysteine; 2HPMA, N-acetyl-S-(2-hydroxypropyl)-L-cysteine; HMPMA, N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; MA, mandelic acid; 2MHA, 2-methylhippuric acid; 34MHA, 3-and 4-methylhippuric acid; MHBMA3, N-acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine; PGA, phenylglyoxylic acid.

Table S3. Association between continuous urinary mVOCs and UFR

Characteristics	Overall			Male			Female		
	Exp (Beta)	95% CI	*P* value	Exp (Beta)	95% CI	*P* value	Exp (Beta)	95% CI	*P* value
LogAAMA	0.37	0.33, 0.42	<0.001	0.41	0.37, 0.46	<0.001	0.33	0.29, 0.39	< 0.001
LogAMCC	0.36	0.32, 0.41	<0.001	0.39	0.34, 0.44	<0.001	0.34	0.29, 0.40	< 0.001
LogATCA	0.73	0.70, 0.77	<0.001	0.77	0.74, 0.81	<0.001	0.69	0.65, 0.74	< 0.001
LnSBMA	0.72	0.70, 0.75	< 0.001	0.73	0.70, 0.76	< 0.001	0.72	0.68, 0.75	< 0.001
LogCEMA	0.37	0.33, 0.41	< 0.001	0.40	0.35, 0.44	< 0.001	0.34	0.29, 0.40	< 0.001
LogDHBMA	0.21	0.18, 0.25	< 0.001	0.23	0.20, 0.27	< 0.001	0.20	0.16, 0.25	< 0.001
Log3HPMA	0.47	0.42, 0.51	< 0.001	0.48	0.43, 0.53	< 0.001	0.46	0.40, 0.52	< 0.001
Ln2HPMA	0.51	0.48, 0.55	< 0.001	0.53	0.48, 0.58	< 0.001	0.50	0.45, 0.56	< 0.001
LnHMPMA	0.67	0.64, 0.71	< 0.001	0.69	0.66, 0.73	< 0.001	0.66	0.61, 0.71	< 0.001
LogMA	0.31	0.27, 0.35	< 0.001	0.36	0.31, 0.41	< 0.001	0.27	0.23, 0.32	< 0.001
Ln2MHA	0.77	0.74, 0.79	< 0.001	0.78	0.74, 0.81	< 0.001	0.75	0.71, 0.79	< 0.001
Log34MHA	0.48	0.44, 0.53	< 0.001	0.51	0.46, 0.56	< 0.001	0.46	0.40, 0.53	< 0.001
LnMHBMA3	0.72	0.68, 0.75	< 0.001	0.75	0.72, 0.78	< 0.001	0.69	0.64, 0.74	< 0.001
LogPGA	0.29	0.25, 0.34	< 0.001	0.34	0.30, 0.39	< 0.001	0.25	0.20, 0.31	< 0.001

Note: mVOCs, metabolites of volatile organic compounds; UFR, urine flow rate; AAMA, N-acetyl-S-(2-carbamoylethyl)-L-cysteine; AMCC, N-acetyl-S-(N-methylcarbamoyl)-L-cysteine; ATCA, 2-aminothiazoline-4-carboxylic acid; SBMA, N-acetyl-S-(benzyl)-L-cysteine; CEMA, N-acetyl-S-(2-carboxyethyl)-L-cysteine; DHBMA, N-acetyl-S-(3:4-dihydroxybutyl)-L-cysteine; 3HPMA, N-acetyl-S-(3-hydroxypropyl)-L-cysteine; 2HPMA, N-acetyl-S-(2-hydroxypropyl)-L-cysteine; HMPMA, N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; MA, mandelic acid; 2MHA, 2-methylhippuric acid; 34MHA, 3-and 4-methylhippuric acid; MHBMA3, N-acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine; PGA, phenylglyoxylic acid; CI: confidence interval.

Table S4. Association between quartered urinary mVOCs and UFR

Characteristics	Overall			Male			Female		
	Exp (Beta)	95% CI	*P* value	Exp (Beta)	95% CI	*P* value	Exp (Beta)	95% CI	*P* value
LogAAMA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.54	0.50, 0.59	< 0.001	0.56	0.50, 0.63	< 0.001	0.48	0.42, 0.56	< 0.001
Q3	0.46	0.41, 0.51	< 0.001	0.46	0.41, 0.51	< 0.001	0.38	0.33, 0.44	< 0.001
Q4	0.37	0.33, 0.42	< 0.001	0.38	0.33, 0.43	< 0.001	0.30	0.26, 0.35	< 0.001
LogAMCC Quantile									
Q1	Reference			Reference			Reference		
Q2	0.58	0.53, 0.63	< 0.001	0.66	0.58, 0.74	< 0.001	0.51	0.43, 0.60	< 0.001
Q3	0.47	0.42, 0.52	< 0.001	0.51	0.45, 0.56	< 0.001	0.41	0.34, 0.49	< 0.001
Q4	0.37	0.32, 0.42	<0.001	0.39	0.34, 0.46	< 0.001	0.31	0.26, 0.37	< 0.001
LogATCA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.69	0.61, 0.78	< 0.001	0.67	0.60, 0.76	< 0.001	0.66	0.57, 0.76	< 0.001
Q3	0.56	0.49, 0.63	< 0.001	0.56	0.50, 0.63	< 0.001	0.49	0.42, 0.57	< 0.001
Q4	0.44	0.38, 0.50	< 0.001	0.52	0.45, 0.59	< 0.001	0.39	0.34, 0.46	< 0.001
LnSBMA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.61	0.56, 0.67	< 0.001	0.62	0.54, 0.70	< 0.001	0.59	0.52, 0.68	< 0.001
Q3	0.50	0.46, 0.54	< 0.001	0.50	0.45, 0.54	< 0.001	0.46	0.40, 0.53	< 0.001
Q4	0.43	0.40, 0.46	< 0.001	0.43	0.39, 0.47	< 0.001	0.40	0.35, 0.45	< 0.001
LogCEMA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.57	0.52, 0.62	< 0.001	0.58	0.51, 0.65	< 0.001	0.47	0.40, 0.54	< 0.001
Q3	0.49	0.46, 0.53	< 0.001	0.48	0.43, 0.53	< 0.001	0.42	0.36, 0.49	< 0.001
Q4	0.41	0.37, 0.44	< 0.001	0.40	0.35, 0.45	< 0.001	0.33	0.29, 0.38	< 0.001
LogDHBMA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.51	0.47, 0.54	< 0.001	0.53	0.48, 0.58	< 0.001	0.43	0.37, 0.50	< 0.001
Q3	0.39	0.36, 0.43	< 0.001	0.40	0.36, 0.45	< 0.001	0.33	0.28, 0.38	< 0.001
Q4	0.33	0.30, 0.36	< 0.001	0.33	0.30, 0.37	< 0.001	0.26	0.23, 0.30	< 0.001
Log3HPMA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.63	0.58, 0.69	< 0.001	0.63	0.56, 0.71	< 0.001	0.54	0.48, 0.61	< 0.001
Q3	0.56	0.51, 0.60	< 0.001	0.54	0.49, 0.60	< 0.001	0.46	0.40, 0.52	< 0.001
Q4	0.52	0.47, 0.57	< 0.001	0.49	0.44, 0.55	< 0.001	0.43	0.38, 0.48	< 0.001
Ln2HPMA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.59	0.55, 0.65	< 0.001	0.61	0.55, 0.68	< 0.001	0.55	0.48, 0.63	< 0.001
Q3	0.52	0.47, 0.58	< 0.001	0.53	0.47, 0.60	< 0.001	0.44	0.39, 0.51	< 0.001
Q4	0.47	0.43, 0.51	< 0.001	0.47	0.42, 0.52	< 0.001	0.40	0.35, 0.46	< 0.001
LnHMPMA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.55	0.50, 0.59	< 0.001	0.56	0.50, 0.62	< 0.001	0.47	0.41, 0.55	< 0.001
Q3	0.48	0.44, 0.52	< 0.001	0.47	0.42, 0.52	< 0.001	0.38	0.34, 0.44	< 0.001
Q4	0.45	0.40, 0.50	< 0.001	0.44	0.39, 0.50	< 0.001	0.38	0.33, 0.44	< 0.001
LogMA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.55	0.49, 0.61	< 0.001	0.59	0.52, 0.66	< 0.001	0.48	0.42, 0.57	< 0.001
Q3	0.43	0.38, 0.48	< 0.001	0.44	0.39, 0.50	< 0.001	0.37	0.32, 0.44	< 0.001
Q4	0.36	0.32, 0.40	< 0.001	0.38	0.34, 0.43	< 0.001	0.30	0.26, 0.35	< 0.001

Ln2MHA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.65	0.60, 0.70	< 0.001	0.70	0.62, 0.78	< 0.001	0.61	0.53, 0.70	< 0.001
Q3	0.58	0.53, 0.64	< 0.001	0.58	0.51, 0.65	< 0.001	0.54	0.46, 0.63	< 0.001
Q4	0.45	0.40, 0.51	< 0.001	0.47	0.41, 0.53	< 0.001	0.44	0.37, 0.52	< 0.001
Log34MHA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.59	0.54, 0.64	< 0.001	0.60	0.53, 0.67	< 0.001	0.50	0.43, 0.58	< 0.001
Q3	0.56	0.51, 0.62	< 0.001	0.56	0.50, 0.62	< 0.001	0.48	0.40, 0.57	< 0.001
Q4	0.41	0.36, 0.46	< 0.001	0.41	0.36, 0.47	< 0.001	0.35	0.30, 0.42	< 0.001
LnMHBMA3 Quantile									
Q1	Reference			Reference			Reference		
Q2	0.60	0.54, 0.66	< 0.001	0.62	0.55, 0.70	< 0.001	0.48	0.41, 0.56	< 0.001
Q3	0.52	0.48, 0.57	< 0.001	0.53	0.48, 0.60	< 0.001	0.41	0.36, 0.48	< 0.001
Q4	0.50	0.44, 0.57	< 0.001	0.49	0.43, 0.56	< 0.001	0.38	0.31, 0.45	< 0.001
LogPGA Quantile									
Q1	Reference			Reference			Reference		
Q2	0.54	0.48, 0.60	< 0.001	0.60	0.53, 0.68	< 0.001	0.48	0.41, 0.56	< 0.001
Q3	0.41	0.37, 0.46	< 0.001	0.45	0.40, 0.50	< 0.001	0.35	0.30, 0.41	< 0.001
Q4	0.34	0.31, 0.38	< 0.001	0.36	0.32, 0.40	< 0.001	0.28	0.24, 0.33	< 0.001

Note: mVOCs, metabolites of volatile organic compounds; UFR, urine flow rate; AAMA, N-acetyl-S-(2-carbamoylethyl)-L-cysteine; AMCC, N-acetyl-S-(N-methylcarbamoyl)-L-cysteine; ATCA, 2-aminothiazoline-4-carboxylic acid; SBMA, N-acetyl-S-(benzyl)-L-cysteine; CEMA, N-acetyl-S-(2-carboxyethyl)-L-cysteine; DHBMA, N-acetyl-S-(3:4-dihydroxybutyl)-L-cysteine; 3HPMA, N-acetyl-S-(3-hydroxypropyl)-L-cysteine; 2HPMA, N-acetyl-S-(2-hydroxypropyl)-L-cysteine; HMPMA, N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; MA, mandelic acid; 2MHA, 2-methylhippuric acid; 34MHA, 3-and 4-methylhippuric acid; MHBMA3, N-acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine; PGA, phenylglyoxylic acid; CI: confidence interval.

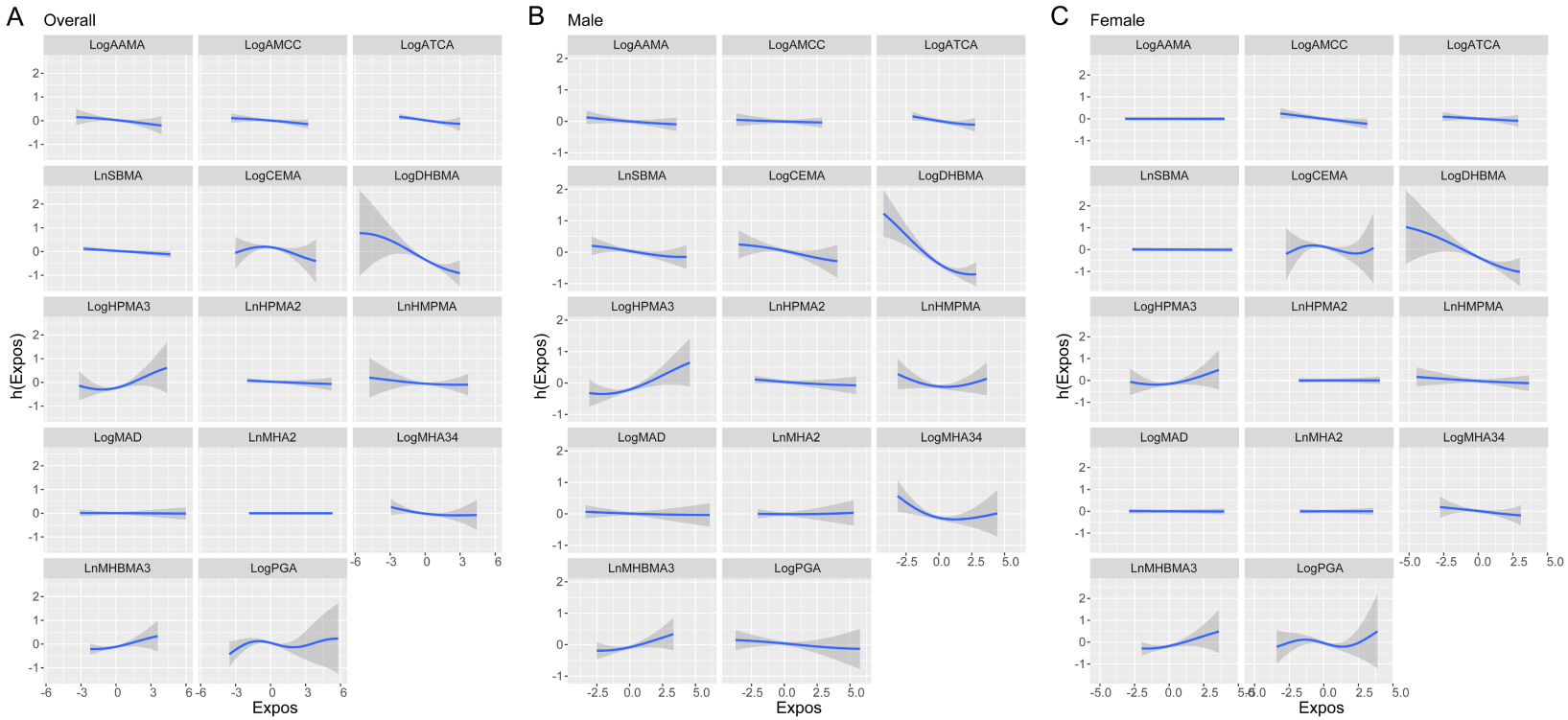

Figure S2. Univariate nonlinear exposure-response relationship between single mVOCs and UFR estimated by the BKMR model.

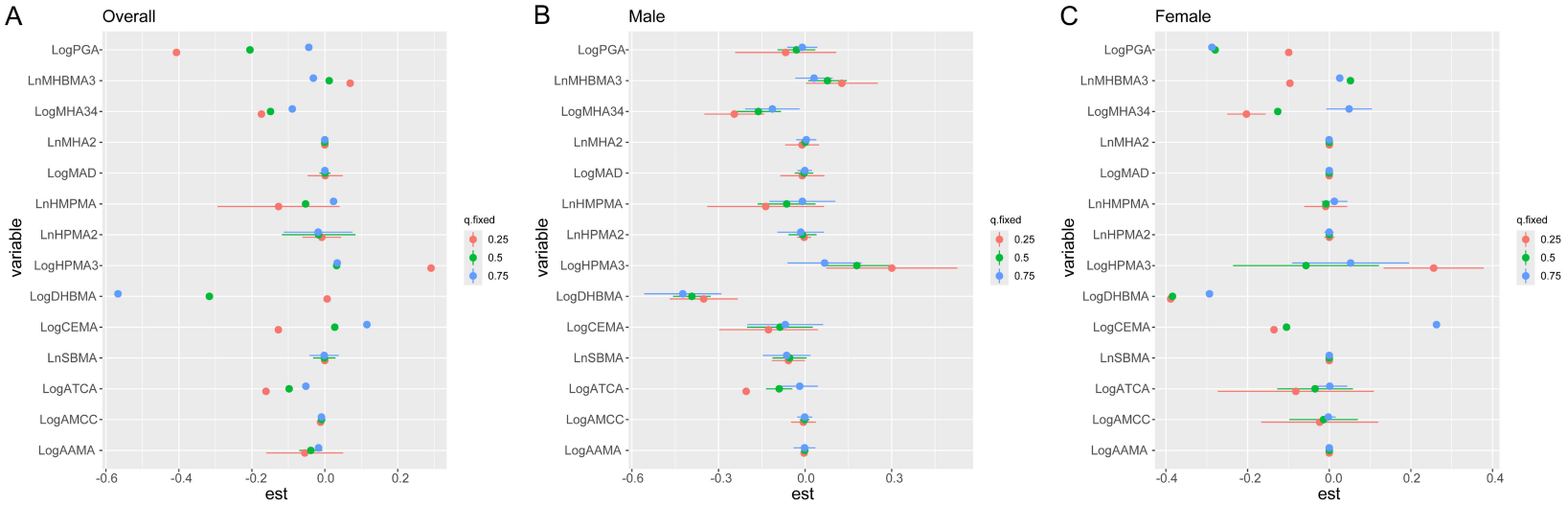

Figure S3. Effect of single mVOCs on UFR at the 25%, 50%, and 75% quartiles (estimates and 95% confidence intervals).

Table S5. Detailed PIP results for the BKMR model

mVOCs	PIP		
	Overall	Male	Female
AAMA	0.3320	0.1613	8.00E-05
AMCC	0.1250	0.0654	0.088
ATCA	1.0	1.0	0.3963
SBMA	0.0064	0.8148	4.00E-04
CEMA	1.0	0.7497	1.0
DHBMA	1.0	1.0	1.0
3HPMA	1.0	0.9261	0.9503
2HPMA	0.1199	0.1378	0.0039
HMPMA	0.5350	0.6271	0.0844
MA	0.0066	0.0650	0.0022
2MHA	0	0.1454	0.004
34MHA	1.0	1.0	0.9761
MHBMA3	0.6290	0.8239	0.9974
PGA	1.0	0.3712	1.0

Note: PIP, posterior inclusion probability; mVOCs, metabolites of volatile organic compounds; AAMA, N-acetyl-S-(2-carbamoylethyl)-L-cysteine; AMCC, N-acetyl-S-(N-methylcarbamoyl)-L-cysteine; ATCA, 2-aminothiazoline-4-carboxylic acid; SBMA, N-acetyl-S-(benzyl)-L-cysteine; CEMA, N-acetyl-S-(2-carboxyethyl)-L-cysteine; DHBMA, N-acetyl-S-(3:4-dihydroxybutyl)-L-cysteine; 3HPMA, N-acetyl-S-(3-hydroxypropyl)-L-cysteine; 2HPMA, N-acetyl-S-(2-hydroxypropyl)-L-cysteine; HMPMA, N-acetyl-S-(3-hydroxy-propyl-1-methyl)-L-cysteine; MA, mandelic acid; 2MHA, 2-methylhippuric acid; 34MHA, 3-and 4-methylhippuric acid; MHBMA3, N-acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine; PGA, phenylglyoxylic acid.