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Mediating role of systemic inflammation in the association between volatile organic compounds exposure and periodontitis: NHANES 2011–2014

Zhida Dai[1,2], Zhixiang Zhang[1,2], Qiaobin Hu[1,2], Xinyuan Yu[1,2], Yixi Cao[1,2], Yian Xia[1,2], Yingyin Fu[3,4], Yuxuan Tan[3,4], Chunxia Jing[3,4*] and Chunlei Zhang[1,2*]

Abstract

Background Volatile organic compounds (VOCs) are ubiquitous environmental pollutants which have been suggested to have adverse effects on human health. While the influence of environmental pollutant exposures on periodontitis has attracted elevating attention in recent years, the epidemiological evidence on the association between VOCs exposure and periodontitis was scarce. This study aimed to investigate the potential mediating role of systemic inflammation factors in the complex association between VOCs exposure and periodontitis.

Methods Utilizing data from the National Health and Nutrition Examination Survey (NHANES) 2011–2014, we examined the impacts of VOCs exposure on periodontitis. Concentrations of urinary metabolites of VOCs (mVOCs) were measured using electrospray tandem mass spectrometry to evaluate internal VOCs exposure. Multivariable logistic regression, restricted cubic spline regression (RCS), Bayesian kernel machine regression (BKMR) and Quantile g-computation (QGC) models were performed to investigate the impacts of VOCs exposure on periodontitis. Mediation models were applied to assess the mediated effects of systemic inflammation on the association between mixed VOCs exposure and periodontitis. Besides, we analyzed the association between mixed VOCs exposure and periodontitis in stratified age, gender, and smoking status subgroups.

Results 1,551 participants were ultimately included for further analyses, of whom 45.20% suffering from periodontitis. Multivariable logistic regression and RCS identified positive associations between single urinary mVOCs and periodontitis ($P < 0.05$). Notably, BKMR and QGC models suggested that mixed VOCs exposure was significantly associated with periodontitis, with 2-Aminothiazoline-4-carboxylic acid (ATCA) contributing the most (conditional posterior inclusion probability = 0.997). Moreover, systemic inflammation markers (leukocyte and lymphocyte counts) were found to partly mediate the association between VOCs exposure and periodontitis ($P < 0.05$). No interaction

*Correspondence:
Chunxia Jing
jcxphd@gmail.com
Chunlei Zhang
zclsir@126.com

Full list of author information is available at the end of the article

effect was identified between mixed VOCs exposure and periodontitis in age, gender and smoking status subgroups ($P > 0.05$).

Conclusion This study demonstrated a positive association between VOCs exposure and periodontitis, which was potentially mediated by systemic inflammation factors. Further longitudinal researches are demanded to clarify the underlying mechanisms.

Keywords Periodontitis, Volatile organic compounds (VOCs), Inflammation, National Health and Nutrition Examination Survey (NHANES), Bayesian kernel machine regression (BKMR), Quantile g-computation (QGC), Environment

Introduction

Periodontitis is a common chronic inflammatory disease in tooth-supporting tissues caused by oral microorganisms initially [1]. Besides, according to recent epidemiological studies, approximately 46% of total U.S. adults suffered from periodontitis, while the prevalence of periodontitis has been increasing for decades [2, 3]. Previous studies have indicated that periodontitis was associated with numerous systemic diseases, such as cardiovascular diseases [4, 5], diabetes [6] and chronic kidney diseases [7], bringing heavy burden to public health. Notably, an increasing number of studies have shown that environmental pollutants, including heavy metals [8] and polycyclic aromatic hydrocarbons [9], could be important contributors in the progression of periodontitis.

Volatile organic compounds (VOCs) are ubiquitous environmental pollutants mainly originating from fuel burning, industrial emissions, building materials [10], consumer products containing fragrance [11] and tabaco smoke [12], etc. Previous epidemiological studies have linked VOC exposure with several chronic diseases, such as diabetes [13], kidney dysfunction [14], cardiovascular disorders [15, 16], whereas the epidemiological evidences of the potential impacts of VOCs exposure on periodontitis and oral health were limited. A cross-sectional study including 3,413 participants showed a positive trend between polycyclic aromatic hydrocarbons, a group of semi-VOCs with periodontitis [17]. Another study by Fernanda et al. also considered higher salivary VOCs levels as potential biomarkers of oral cancer [18]. In previous studies, Dong et al. (2024) have revealed the positive correlation between five blood VOCs and periodontitis [19]. Additionally, Kwon et al. (2018) found that VOCs could be inhaled through oral cavity and airways and therefore lead to respiratory health problems [20]. Nonetheless, the relationship between urinary metabolites of VOCs (mVOCs) and periodontitis remains unknown so far.

Recently, a prospective cohort study experiment suggested that exposure to acrylamide, a common type of VOC, could play a critical role in exacerbating inflammation and activating oxidative stress in tissues, leading to disorders and abnormal metabolism [21]. Inflammation was long considered as an essential etiological factor in periodontitis progression [22]. Accumulating data from previous researches indicated that inflammation and oxidative stress induced by VOCs could enhance the prevalence of chronic disorders and organ dysfunction [23]. Based on present evidence, we speculated that VOCs exposure could impact periodontitis via promotion of inflammation. Urinary mVOCs were reliable sources for assessing environmental VOCs exposure in the population [13, 23]. Therefore, we used urinary mVOCs as indicators for VOCs exposure in this study. Utilizing data from NHANES 2011–2014, this study aimed to provide novel epidemiological evidence for the potential mediating role of systemic inflammation factors in the complex association between urinary mVOCs and periodontitis among U.S. adults.

Materials and methods

Study population

NHANES is a large cross-sectional study conducted by U.S. Centers for Disease Control and Prevention (CDC), dedicating to evaluate the health and nutrition status of U.S. population [24]. We enrolled 20,653 participants from cycle 2011–2014 of the NHANES, which contains demographical information, laboratory data, and questionnaires. In NHANES study, only participants aged 30 years and older were eligible for the periodontal examination if they had one or more natural teeth and no health condition requiring antibiotic prophylaxis before periodontal probing [25]. Individuals without complete data on periodontal examination, VOCs measurements and covariates data were excluded. A total of 1,515 participants (adults aged ≥ 30) were ultimately included in the study for further research. Participants selection flow chart could be found in Fig. S1.

This study was approved by The National Center for Health Statistics (NCHS) institutional committee and all participants have signed informed written consent. We adhere to STROBE guidelines for reporting observational studies [26]. The NHANES questionnaire instruments used in this study have been published by NCHS, and could be obtained from the website link for free: (NHANES 2013–2014 Questionnaire Instruments

(cdc.gov)) [27]. More details on NHANES materials and methods are elaborated on the website (www.cdc.gov/nchs/nhanes/).

Measurements of VOCs

Urine specimens from participants were processed, stored frozen at -20°C and then shipped to National Center for Environmental Health for testing. Twenty-six mVOCs were measured using ultra performance liquid chromatography coupled with electrospray tandem mass spectrometry (UPLC-ESI/MSMS). mVOCs with detection rate over 90% were selected in our study for further analyses (Table S1). Fifteen types of mVOCs including 2MHA (2-Methylhippuric acid), 3-4MHA (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), BMA (N-Acetyl-S-(benzyl)-L-cysteine), CEMA (N-Acetyl-S- (2-carboxyethyl)-L-cysteine), CYMA (N-Acetyl-S-(2-cyanoethyl)-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-buten-1-yl)-L-cysteine), PGA (Phenylglyoxylic acid), HPMMA (N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine) were finally selected for further analyses. Parent compounds of mVOCs included in this study could be checked in Table S2. More details can be found in the NHANES Laboratory Procedures Manual [28].

Definition of periodontitis

Periodontal health condition was evaluated through a full-mouth periodontal examination by licensed dental examiners. Six sites on all teeth, excluding third molars [2] were examined to assess clinical attachment loss (AL) and probing depth (PD). Definition of periodontitis was based on the CDC/AAP (CDC, Centers for Disease Control and Prevention; AAP, American Academy of Periodontology) classification definition. Mild periodontitis was defined as at least two interproximal sites with AL≥3 mm and at least two interproximal sites with PD≥4 mm (not on the same tooth) or one site with PD≥5 mm; moderate periodontitis was defined as at least two interproximal sites with AL≥4 mm (not on the same tooth) or at least two interproximal sites with PD≥5 mm (not on the same tooth); severe periodontitis was defined as at least two interproximal sites with AL≥6 mm (not on the same tooth) and at least one interproximal site with PD≥5 mm [29]. Total periodontitis was defined as the combination of mild, moderate, and severe periodontitis. The absence of evidence for mild, moderate or severe periodontitis indicated no periodontitis. As sensitivity analyses, other periodontal metrics were also considered as outcomes: the proportion of sites with periodontal probing depth (PPD)≥4 mm, the proportion of sites with clinical attachment loss (CAL)≥3 mm, mean CAL [30].

Covariates

The covariates in this study included basic demographic information, BMI (body mass index) data, laboratory test, living habits, health conditions and diseases. Demographic information included age, gender, marital status, ethnicity, education level, income level, which was obtained from questionnaires. Marital status was categorized as married/cohabited, widowed/divorced/separated, and never married. Race/ethnicity was grouped into Non-Hispanic White/Black, Mexican American, other Hispanic, and other races. Education level was divided into lower than high school, graduate/GED (General educational development) or equivalent, and college or above. Compared to PIR (poverty income ratio)=1, participants were grouped into the low-income and normal-income levels [31]. BMI was obtained from body examination data and was divided into four groups (<18.5, 18.5–24.9, 25-29.9, ≥30 kg/m^2) [17]. Urinary creatinine concentration, blood cotinine concentration and serum 25(OH)D concentration was tested in laboratory. Of note the serum 25(OH)D concentration was categorized into four groups (<30, 30–50, 50–75, >75 nmol/L) [32]. Information of health condition and diseases was collected and defined by questionnaires. Cardiovascular diseases were defined as meeting one of the following situations:1) Ever told had congestive heart failure; 2) Ever told you had coronary heart disease; 3) Ever told you had angina/angina pectoris; 4) Ever told you had heart attack; 5) Ever told you had a stroke [4]. Diabetes was determined by the questions "Doctor told you have diabetes". Chronic kidney diseases were defined by the questions "Doctor told you have chronic kidney diseases" [33]. Drinking status was divided into "yes" or "no" by the questions "Have you had at least 12 drinks of any type of alcoholic beverage in any one year?". Non-smokers (without tobacco exposure), second-hand smokers, and smokers were distinguished by the comprised questions "Smoked at least 100 cigarettes in life" and blood cotinine concentration (<0.015, 0.015–3.08, > 3.08 ng/mL) [34]. Dental floss usage data was collected through questionnaires and was classified into 4 groups (0, 1–2, 3–4, and 5–7 days per week) [35].

Evaluation of systemic inflammation

Systemic inflammation was assessed using circulatory leukocyte counts, lymphocyte counts, neutrophil counts, and monocyte counts, referring to previous epidemiological researches [36]. Leukocyte counts, lymphocyte counts, neutrophil counts, and monocyte counts were

obtained utilizing complete blood count tests with the Coulter HMX Hematology Analyzer [24].

Statistical methods

Continuous variables were presented as mean and standard deviation (Mean ± SD) for normally distributed data, median and interquartile range (IQR) for skewed data, and comparative analysis was performed by t-test or Kruskal-Wallis test. The categorical variables were expressed as case sample numbers (n) and percentages (%), and compared by chi-square test. Since the distribution of mVOCs was skewed, we performed logarithm transformation for mVOCs to normalize the distribution. Spearman correlation analysis was applied to examine the correlation between urinary metabolites of VOCs included in this study.

Multivariable logistic regression was performed to investigate the association between mVOCs and periodontitis after adjusting for all available covariates including demographic information, comorbidities, and urinary creatinine listed above. The mVOCs were fitted as both continuous and quartiles variables in multivariable logistic regression models, respectively. Other periodontal metrics as outcomes were also fitted in the multivariable logistic regression models as sensitivity analyses. Then we also applied restricted cubic spline (RCS) regression with 3 knots to explore the non-linear associations, using the median values of urinary mVOCs as reference.

Bayesian kernel machine regression (BKMR) and Quantile g-computation (QGC) models were performed to evaluate the effects of mixed VOCs exposure on periodontitis. Hierarchical BKMR analyses utilized the Gaussian predictive process via the algorithm of Markov chain Monte Carlo (MCMC) sampler for 10,000 iterations [37]. Fifteen mVOCs were divided into three groups according to spearman correlation analyses to fit Hierarchical BKMR [38]. Group and conditional posterior inclusion probabilities (PIPs) were applied to estimate the significance of environmental pollution exposures. We also explored the univariate exposure-response function of mVOCs [38]. Considering the BKMR is semi-parametric model and cannot obtain exact estimates, we used the QGC model as a complement. QGC models are emerging statistical methods to assess the linear and nonlinear relationship between mixed exposures and health outcomes, and the weight of each pollutant suggests the corresponding importance in total effects [39]. Both BKMR and QGC were fully adjusted by all available covariates listed above.

Besides, given that age, gender, and smoking status could have potential interaction effects, we also performed stratified analyses based on QGC to explore the association between VOCs exposure and periodontitis in stratified subgroups including aforementioned factors. Finally, we performed mediation models (bootstrap = 1000) to investigate the potential mediating effects of inflammatory markers on the associations between mixed VOCs exposure and periodontitis after adjusting for all available covariates listed above.

The statistical analyses in this study were conducted using R software (version 4.3.1). R packages "rms" (version 6.7-0), "bkmr" (version 0.2.2) "qgcomp" (version 2.15.2), "qgcompint" (version 0.7.0) and "mediation" (version 4.5.0) were used in the present study. A P-value < 0.05 was considered statistically significant.

Results

Descriptive analysis

1,551 Participants were ultimately included in our study, with 45.2% diagnosed with periodontitis and 54.8% without. Table 1 displayed the baseline information for participants, with an average age of 53.1 ± 14.7 years, and an almost equal proportion between males and females (52.4% vs. 47.6%). Participants in the periodontitis group tended to be older, men, non-Hispanic black, had relatively lower education level, higher BMI, with a larger proportion of smoking or passive smoking, higher prevalence of diabetes and chronic kidney diseases, compared with the non-periodontitis group. (P < 0.05). No significant differences were found in other demographic factors (P > 0.05).

Table S1 suggested that the detection rate of all 15 types of urinary mVOCs were > 90%. Fig. S2 presented correlation coefficient matrices, and all mVOCs were positively correlated, with correlation coefficients ranging from 0.02 to 0.97 (All P-values < 0.001).

Association between VOCs exposure and periodontitis by multivariable logistic and RCS regression

Figure 1 showed the positive associations between continuous variables of 2MHA, 3-4MHA, AAMA, AMCC, ATCA, CEMA, CYMA, DHBMA, 3HPMA, MA, MHBMA3, PGA, HPMMA and periodontitis using the fully-adjusted multivariable Logistics model (OR [95%CI]: 1.15 [1.04, 1.15], 1.13 [1.02, 1.24], 1.31 [1.14, 1.51], 1.18 [1.04, 1.35], 1.28 [1.14, 1.45], 1.22 [1.06, 1.40], 1.13 [1.06, 1.21], 1.34 [1.09, 1.67], 1.19 [1.05, 1.34], 1.44 [1.23, 1.69], 1.30 [1.16, 1.47], 1.24 [1.06, 1.46], 1.30 [1.15, 1.47], respectively) (P < 0.05). After dividing all mVOCs into quartiles, consistent trends were found with continuous mVOCs results (Table 2). The sensitivity analyses using the proportion of PPD ≥ 4 mm, the proportion of sites CAL ≥ 3 mm, mean CAL as periodontitis outcomes demonstrated similar statistical trends with the CDC-AAP classification. (Table S3).

The adjusted RCS models demonstrated the dose-response relationships between single urinary mVOCs

Table 1 General characteristics of participants in this study, NHANES 2011–2014 ($N = 1,551$)

		Periodontitis	
	Overall	**Yes**	**No**
Variables	1551	701	850
Age (years)			
Mean (SD)	53.1 (14.7)	55.6 (13.7)	51.1 (15.1)
Gender, n (%)			
Male	812 (52.4)	421 (60.1)	391 (46.0)
Female	739 (47.6)	280 (39.9)	459 (54.0)
Race/Ethnicity, n (%)			
Mexican American	153 (9.9)	85 (12.1)	68 (8.0)
Other Hispanic	159 (10.3)	77 (11.0)	82 (9.6)
White	649 (41.8)	413 (48.6)	236 (33.7)
Black	366 (23.6)	204 (29.1)	162 (19.1)
Other Race	224 (14.4)	99 (14.1)	125 (14.7)
Marriage, n (%)			
Unmarried	205 (13.2)	96 (13.7)	109 (12.8)
Married or cohabited	968 (62.4)	423 (60.3)	545 (64.1)
Divorced	378 (24.4)	182 (26.0)	196 (23.1)
Education level, n (%)			
Less than High school	338 (21.8)	195 (27.8)	143 (16.8)
High school graduate /GED or equivalent	313 (20.2)	162 (23.1)	151 (17.8)
College or above	900 (58.0)	344 (49.1)	556 (65.4)
Ratio of family income to poverty, n (%)			
< 1	295 (19.0)	168 (24.0)	127 (14.9)
≥ 1	1256 (81.0)	533 (76.0)	723 (85.1)
BMI (kg/m^2)			
< 18.5	17 (1.1)	8 (1.1)	9 (1.1)
18.5–24.9	420 (27.1)	172 (24.5)	248 (29.2)
25–29.9	531 (34.2)	252 (35.9)	279 (32.8)
≥ 30	583 (37.6)	269 (38.4)	314 (36.9)
Cardiovascular diseases, n (%)			
No	1410 (90.9)	635 (90.6)	775 (91.2)
Yes	141 (9.1)	66 (9.4)	75 (8.8)
Diabetes status, n (%)			
No	1280 (82.5)	560 (79.9)	720 (84.7)
Yes	225 (14.5)	116 (16.5)	109 (12.8)
Borderline	46 (3.0)	25 (3.6)	21 (2.5)
Chronic kidney diseases, n (%)			
No	1500 (96.7)	669 (95.4)	831 (97.8)
Yes	51 (3.3)	32 (4.6)	19 (2.2)
Smoking status, n (%)			
Nonexposed	738 (30.8)	251 (22.3)	487 (38.3)
Exposed to SHS	1060 (44.3)	466 (41.5)	594 (46.7)
Smokers	219 (9.1)	149 (13.2)	70 (5.5)
Drinking status, n (%)			
No	392 (25.3)	177 (25.2)	215 (25.3)
Yes	1159 (74.7)	524 (74.8)	635 (74.7)
How many days using dental flosses per week? (days/week)			
0	303 (35.6)	262 (37.4)	565 (36.4)
1–2	235 (15.2)	89 (12.7)	146 (17.2)
3–4	210 (13.5)	100 (14.3)	110 (12.9)
5–7	541 (34.9)	250 (35.7)	291 (34.2)
Serum vitamin D (nmol/L)			
< 30	115 (7.4)	73 (10.4)	42 (4.9)

Table 1 (continued)

		Periodontitis	
	Overall	**Yes**	**No**
30 ≤ x < 50	332 (21.4)	166 (23.7)	166 (19.5)
50 ≤ x < 75	557 (35.9)	250 (35.7)	307 (36.1)
> 75	547 (35.3)	212 (30.2)	335 (39.4)
Urinary creatinine (mg/dL)			
Mean (SD)	113.3 (71.5)	117.5 (68.0)	109.9 (74.0)

Note SD, standard deviation; BMI, body mass index; GED, general educational development; SHS, second-hand smoke

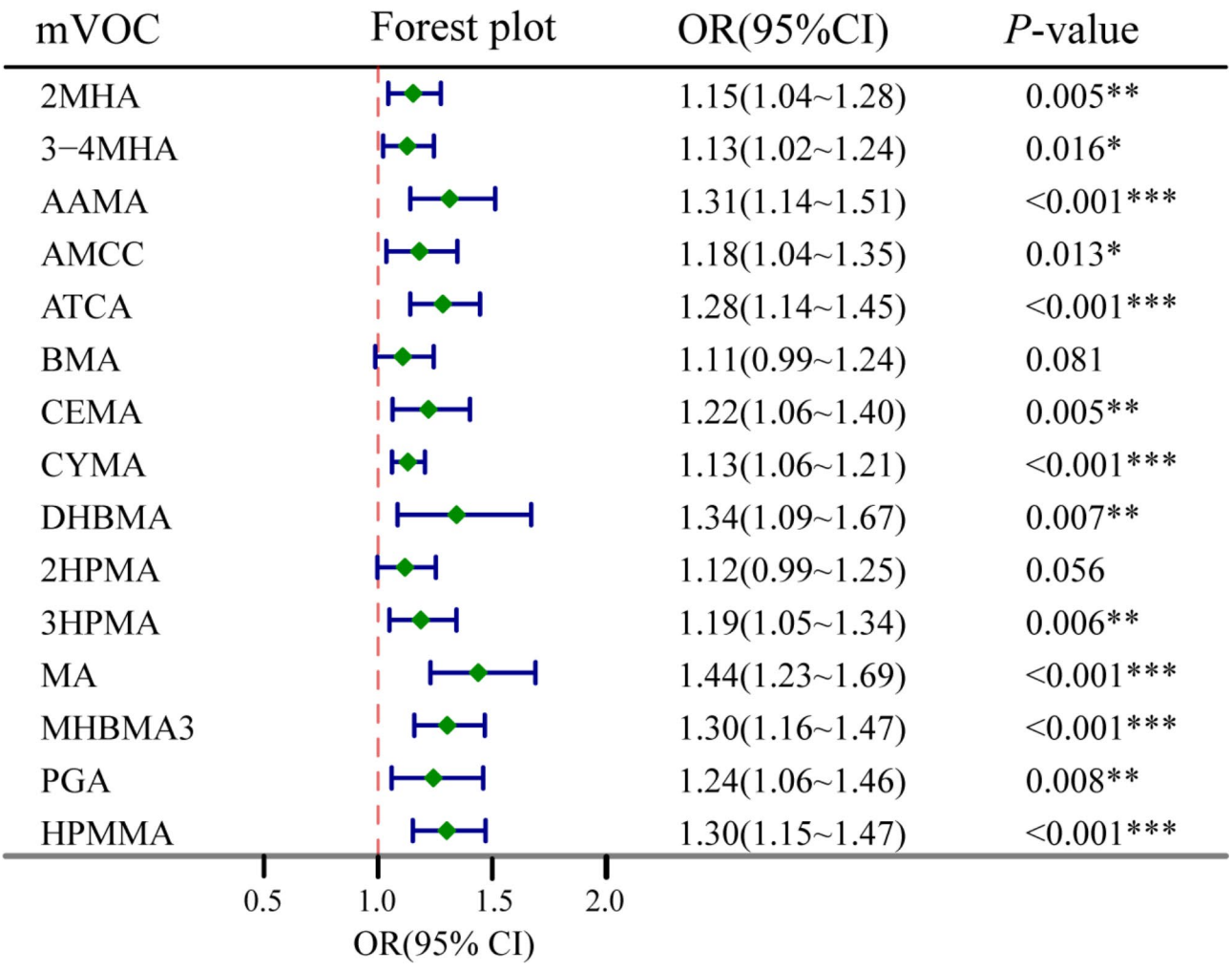

Fig. 1 Association between continuous variate of single mVOC and periodontitis risk using multivariable logistic model (*N* = 1,551). *Note* OR, odds ratio; CI, Confidence interval; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. 2MHA (2-Methylhippuric acid), 3-4MHA (3- and 4-Methylhippuric acid), AAMA (N-Acetyl-S-(2-carbamoylethyl)-L-cysteine), AMCC (N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine), ATCA (2-Aminothiazoline-4-carboxylic acid), BMA (N-Acetyl-S-(benzyl)-L-cysteine), CEMA (N-Acetyl-S- (2-carboxyethyl)-L-cysteine), CYMA (N-Acetyl-S-(2-cyanoethyl)-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-buten-1-yl)-L-cysteine), PGA (Phenylglyoxylic acid), HPMMA (N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine)

exposures and periodontitis (Fig. S3). Wald test showed no significant non-linear correlation between mVOCs and periodontitis in both adjusted and unadjusted RCS models (*P* for non-linear > 0.05). (Table S4)

Association between mixed VOCs exposure and periodontitis by BKMR model

Notably, BKMR analyses identified the positive association between increasing mixed urinary mVOCs levels and elevated periodontitis risk compared to the 25th and the 50th percentiles (Fig. 2A). Besides, conditional

Table 2 Association between quartiles of single mVOC and periodontitis risk using multivariable logistic model (*N* = 1,551)

mVOC	Q1	Q2 OR (95% CI)	Q3 OR (95% CI)	Q4 OR (95% CI)
2MHA	Ref.	1.29(0.95 ~ 1.76)	1.34(0.98 ~ 1.84)	1.58(1.14 ~ 2.21) **
3-4MHA	Ref.	1.46(1.07 ~ 1.21) *	1.21(0.88 ~ 1.67)	1.57(1.11 ~ 2.23) *
AAMA	Ref.	1.10(0.80 ~ 1.52)	1.35(0.97 ~ 1.88)	1.92(1.33 ~ 2.79) ***
AMCC	Ref.	0.85(0.62 ~ 1.17)	1.10(0.79 ~ 1.52)	1.26(0.88 ~ 1.80)
ATCA	Ref.	1.71(1.25 ~ 2.33) ***	1.67(1.21 ~ 2.31) *	2.15(1.53 ~ 3.03) ***
BMA	Ref.	1.49(1.09 ~ 2.05) *	1.56(1.12 ~ 2.17) **	1.55(1.08 ~ 2.22) *
CEMA	Ref.	1.14(0.83 ~ 1.57)	1.35(0.97 ~ 1.89)	1.57(1.08 ~ 2.28) *
CYMA	Ref.	1.24(0.91 ~ 1.70)	0.98(0.70 ~ 1.38)	1.64(1.14 ~ 2.36) **
DHBMA	Ref.	1.34(0.98 ~ 1.85)	1.69(1.18 ~ 2.42) **	2.02(1.30 ~ 3.14) **
2HPMA	Ref.	1.16(0.85 ~ 1.59)	1.26(0.91 ~ 1.75)	1.56(1.11 ~ 2.21) *
3HPMA	Ref.	1.24(0.90 ~ 1.70)	1.06(0.76 ~ 1.49)	1.53(1.08 ~ 2.18) *
MA	Ref.	1.38(1.00 ~ 1.89)	1.47(1.05 ~ 2.07) *	2.00(1.36 ~ 2.94) ***
MHBMA3	Ref.	1.20(0.87 ~ 1.65)	1.50(1.07 ~ 2.11) *	1.91(1.34 ~ 2.73) ***
PGA	Ref.	1.12(0.82 ~ 1.54)	1.46(1.04 ~ 2.06) *	1.23(0.82 ~ 1.82)
HPMMA	Ref.	1.33(0.96 ~ 1.83)	1.38(0.98 ~ 1.96)	2.06(1.44 ~ 2.94) ***

Note Ref, reference. OR, odds ratio; CI, confidence interval; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile. *$P<0.05$; **$P<0.01$; ***$P<0.001$. 2MHA (2-Methylhippuric acid), 3-4MHA (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), BMA (N-Acetyl-S-(benzyl)-L-cysteine), CEMA (N-Acetyl-S- (2-carboxyethyl)-L-cysteine), CYMA (N-Acetyl-S-(2-cyanoethyl)-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-buten-1-yl)-L-cysteine), PGA (Phenylglyoxylic acid), HPMMA (N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine)

PIP represents the importance of each single mVOC in the overall effect. Results in Table S5 indicated that ATCA was the most significant risk factors for periodontitis in mixed mVOCs (conditional PIP = 0.997, group PIP = 0.930) (Table S5). Furthermore, the univariate effects between each single mVOC and periodontitis were estimated when other mVOCs were fixed at the median levels. We observed an increased trend in periodontitis risk with elevating AAMA, ATCA, MHBMA3, HPMMA and MA in Fig. 2B. Additionally, bivariate exposure-response relationship for single urinary mVOC were conducted to examine the effect of individual mVOC on periodontitis when fixing other mVOCs at either 25th, 50th, and 75th percentiles. Fig. S4 showed that the positive effect estimates for ATCA decreased with increasing quantiles of other mVOCs. Finally, the pairwise interactions analysis among urinary mVOCs were examined, while no significant interaction among mVOCs was found (Fig. S5).

Association between VOCs exposure and periodontitis via Quantile g-computation models

QGC models indicated that mixed VOCs exposure was significantly associated with periodontitis (OR [95%CI]: 1.628 [1.325, 2.001], $P<0.001$), which was consistent with BKMR analyses (Fig. 3A). Additionally, Fig. 3B showed the weight of each single mVOC in total effects of mixed VOC exposure on periodontitis, with MHBMA3, ATCA, HPMMA and MA contributing the most positive effects.

Subgroup analyses using QGC models

We conducted stratified analyses using QGC to reveal the potential moderate effect of age, gender, and smoking status. No significant difference was observed between mVOCs and periodontitis in different age, gender and smoking subgroups ($P>0.05$) (Fig. S6), which supported the main analyses in BKMR and QGC models.

Systemic inflammation factors involved in the association between VOCs exposure and periodontitis

Given no interaction effect was found in BKMR analyses (Fig. S5), sum of quartiles of log-transformed mVOCs concentration were used to assess the mixed VOCs exposure for mediation analyses [40]. Figure 4 showed the significant results of mediation analyses. Leukocyte and lymphocyte counts were found to mediate the association between mixed VOCs exposure and periodontitis ($P<0.05$), with proportion of mediation of 5.36%, 3.63%, respectively. While no significant mediation effect was observed for neutrophil and monocyte counts ($P>0.05$).

Discussion

As mentioned above, this study found a significant positive association between single and mixed urinary mVOCs and periodontitis, as well as the mediating role of systemic inflammation. In multivariable logistic models, we found that urinary mVOCs including 2MHA, 3-4MHA, AAMA, AMCC, ATCA, CEMA, CYMA, DHBMA, 3HPMA, MA, MHBMA3, PGA, HPMMA, whose parent compounds were xylene, acrylamide, N, N-Dimethylformamide, cyanide, acrolein, acrylonitrile, 1,3-Butadiene styrene, crotonaldehyde, respectively,

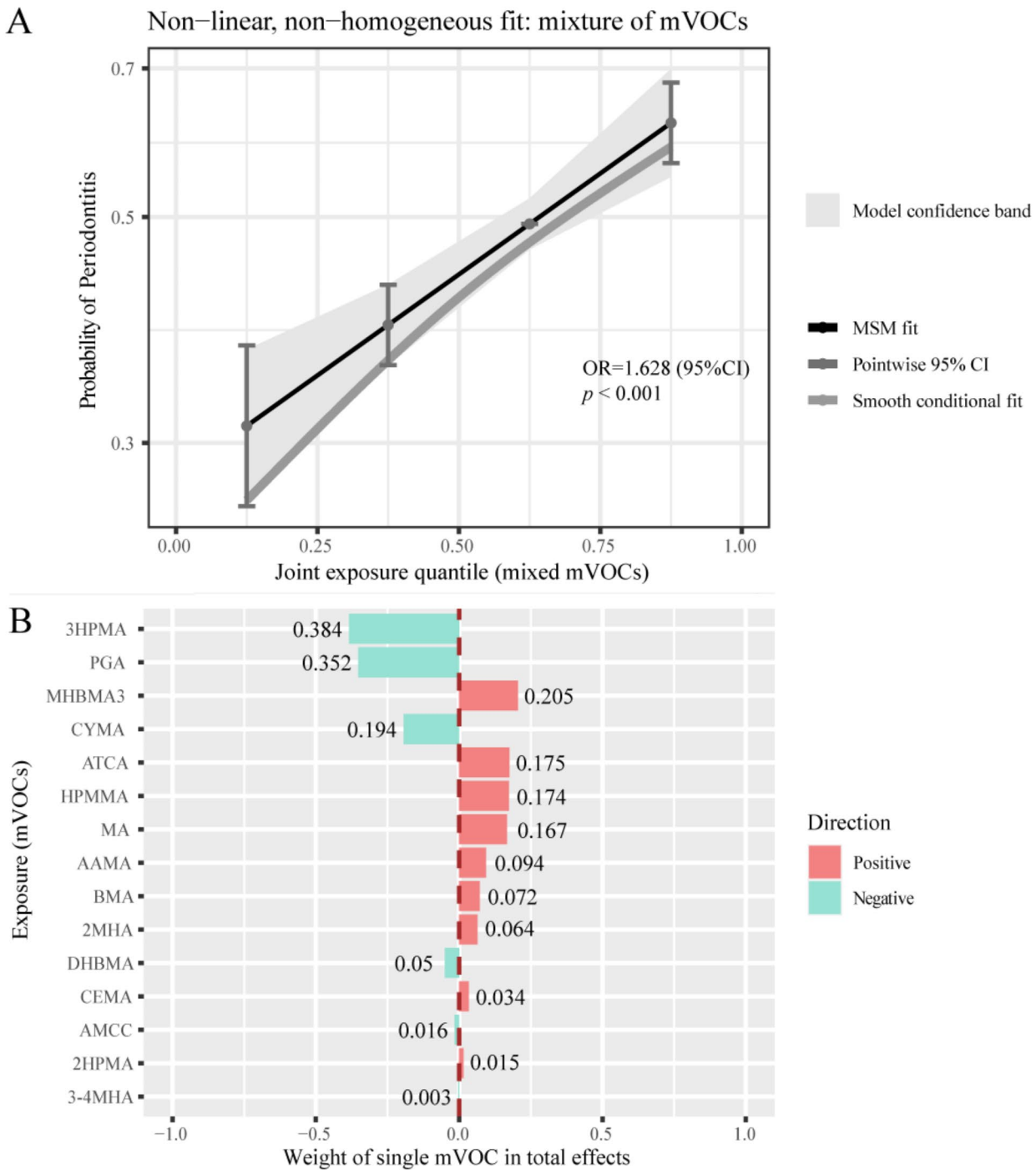

Fig. 3 Association between mixed mVOCs and periodontitis risk estimated by QGC models ($N = 1,551$). **A**: Overall effects of mixed mVOCs on periodontitis estimated by QGC. *Note* MSM fit, fitting marginal structural model. OR, odds ratio; CI, Confidence interval. **B**: Estimated weight of each single mVOC in total effects via QGC models. *Note* 2MHA (2-Methylhippuric acid), 3-4MHA (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), BMA (N-Acetyl-S-(benzyl)-L-cysteine), CEMA (N-Acetyl-S- (2-carboxyethyl)-L-cysteine), CYMA (N-Acetyl-S-(2-cyanoethyl)-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-buten-1-yl)-L-cysteine), PGA (Phenylglyoxylic acid), HPMMA (N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine)

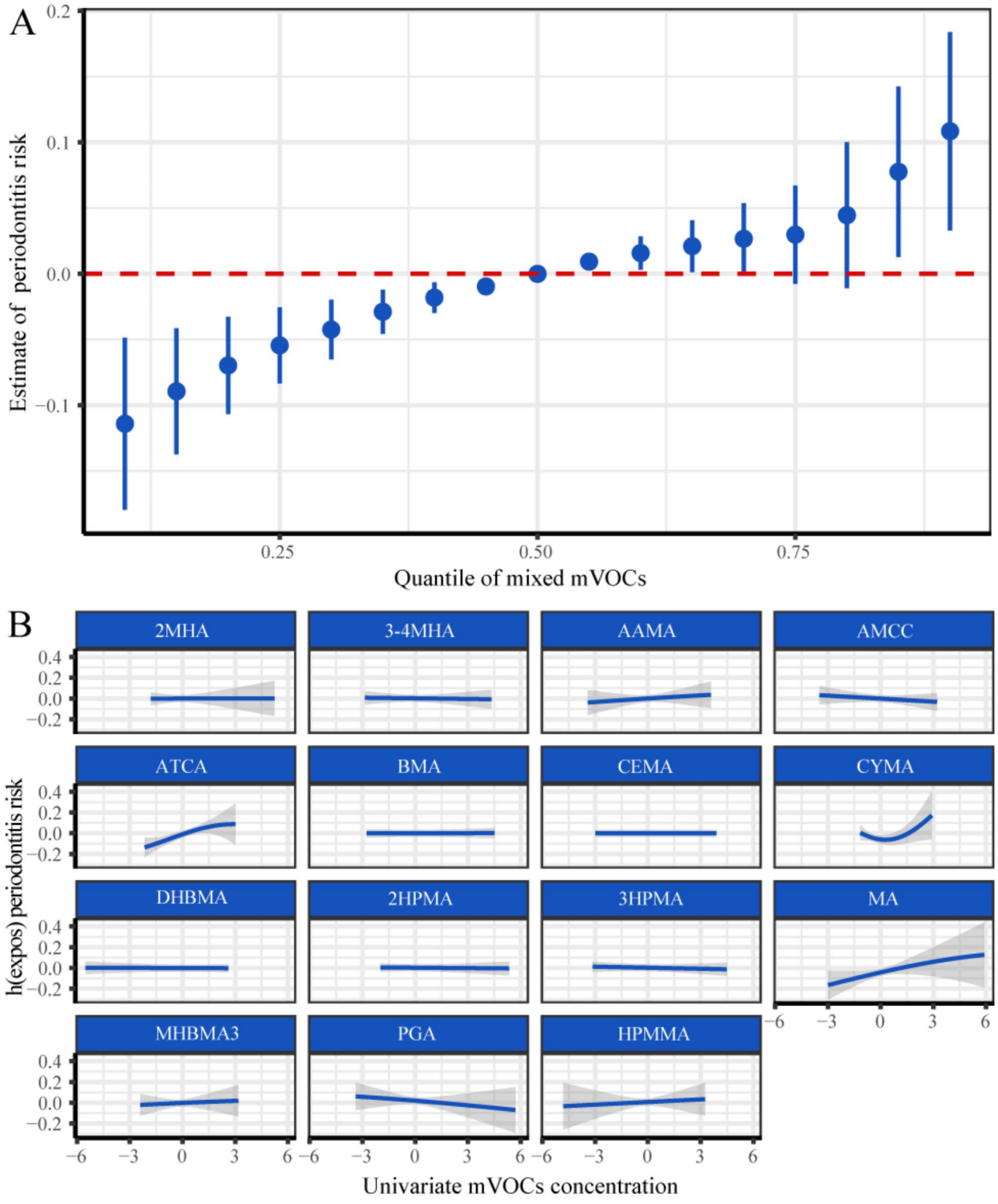

Fig. 2 Association between mixed mVOCs and periodontitis risk estimated by BKMR. ($N = 1,551$). **A** showed the overall effect of mixed urinary mVOCs on periodontitis with 95% confidence interval. **B** showed the correlation of each univariate exposure with periodontitis. *Note* 2MHA (2-Methylhippuric acid), 3-4MHA (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), BMA (N-Acetyl-S-(benzyl)-L-cysteine), CEMA (N-Acetyl-S- (2-carboxyethyl)-L-cysteine), CYMA (N-Acetyl-S-(2-cyanoethyl)-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-buten-1-yl)-L-cysteine), PGA (Phenylglyoxylic acid), HPMMA (N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine)

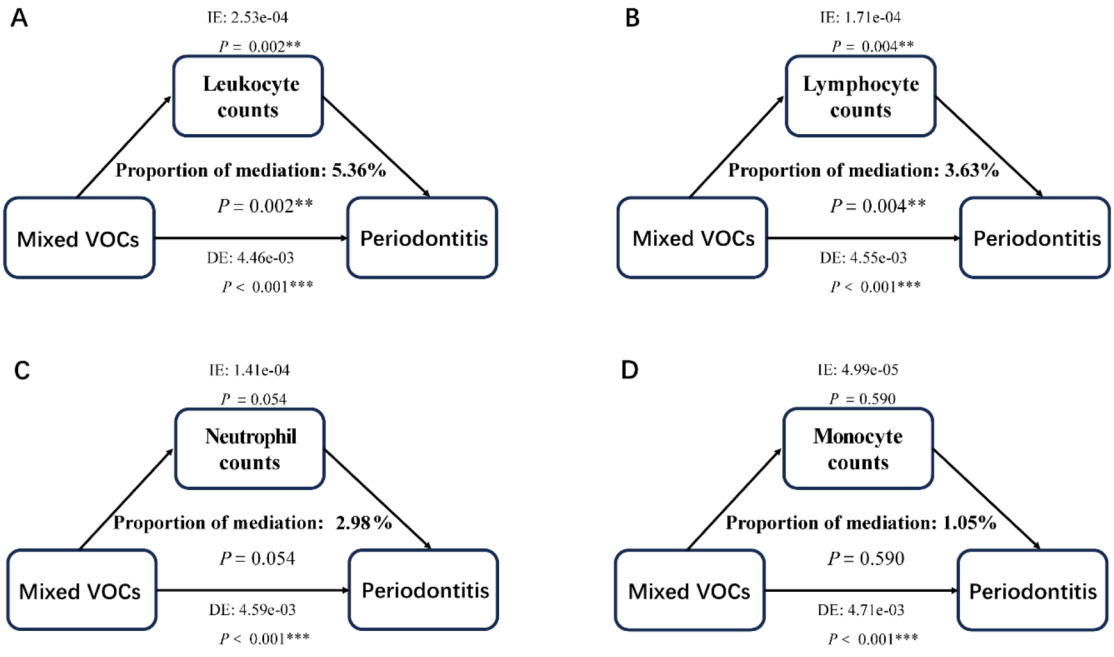

Fig. 4 Estimated proportion of the association between mixed VOCs exposure and periodontitis risk mediated by systemic inflammation factors. *Note***A**: Leukocytes, **B**: Lymphocytes, **C**: Neutrophils, **D**: Monocytes; IE: the estimate of the indirect effect, DE: the estimate of the direct effect, Proportion of mediation = IE/(DE + IE). $^{**}P < 0.01$; $^{***}P < 0.001$

were significantly associated with periodontitis. Furthermore, both BKMR and QGC models showed that mixed VOCs were positively associated with higher risks of periodontitis. No significant interaction was revealed in age, gender, and smoking status subgroups when applying stratified QGC analyses. Notably, mediation analyses suggested that systemic inflammation markers (leukocyte and lymphocyte counts) potentially mediated the association between mixed VOCs exposure and periodontitis.

This study identified a positive association between mixed VOCs exposure and periodontitis, where systemic inflammation potentially played a mediated role (Fig. 4.). Numerous studies have suggested that the progression of periodontitis involves extensive activation of pro-inflammatory cytokines and complex intracellular inflammatory responses [22, 41], in which mixed VOCs exposure could play a critical role [20]. A prospective cohort study suggested that acrylamide(the parent compound of AAMA) could potentially activate inflammation process in adults by inducing plasma C-reactive protein [21]. Additionally, experimental studies also showed the pro-inflammatory role of VOC exposures. For example, evidence from an in *vitro* experiment suggested that acrolein, parent compound of CEMA, could significantly stimulated the production of High-sensitivity C-reactive protein [42]. Li et al. (2020) found that exposure to crotonaldehyde, which could be transformed to HPMMA, could significantly trigger inflammatory processes in rats by induction of pro-inflammatory cytokines including Interleukin-1β, Interleukin-6, and tumor necrosis factor-α (TNF-α) [43]. Another in vivo experiment on rats have shown that acrylonitrile, the parent compound of CYMA, could increase pro-inflammatory mediators including interferon-γ and TNF-α, and consequently inducing cell apoptosis in lungs. Hence, we speculated that elevated expression of pro-inflammatory cytokines induced by VOCs exposure could potentially lead to periodontal tissues damage by exacerbating inflammation in periodontal tissues and causing alveolar bone destruction, ultimately resulting in periodontitis [44]. While subgingival dental plaque was regarded as the main initiation factor for periodontitis [45], systemic inflammation induced by environmental VOC exposure potentially exacerbates the progression of periodontitis, which demands further mechanisms research.

Oxidative stress is another plausible cause for the links between VOCs exposure and periodontitis. It is well recognized that oxidative stress has long been considered a critical factor in connecting environmental pollutant exposure with chronic diseases [46]. A population-based study has suggested that mixed VOCs exposure could play a crucial role in the oxidative stress process

by inducing excessive reactive oxygen species (ROS) or deplete antioxidants, and consequently exacerbate redox imbalance [47]. According to an in vitro experiments, cyanide, which could be further transformed to ATCA, could induce apoptosis in differentiated cells by elevating intracellular ROS levels [48], while excessive ROS could cause nucleic acid damage, protein carbonylation, lipid peroxidation in periodontal tissues [49]. Findings from a cardiomyocytes experiment suggested that crotonaldehyde exposure could lead to extensive oxidative stress, which caused mitochondrial dysfunction and DNA damage in tissues [50]. Furthermore, Ohnishi Li et al. (2009) found that excessive production of ROS could significantly aggravate alveolar bone resorption in mice [51]. Based on previous studies, we hypothesized that accumulation of ROS induced by VOCs exposure, together with excessive consumption of antioxidants could enhance the oxidative stress in periodontal tissues, trigger apoptotic pathway of periodontal ligament stem cells [52] and meanwhile activate differentiation of osteoclasts [53], thus inducing deterioration in periodontal tissues, ultimately elevating periodontitis risks. However, further in *vi*vo/*vitro* studies are needed to verify our hypotheses.

There were several strengths in the present study. This study comprehensively investigated the association between single and mixed urinary mVOCs and periodontitis. Systemic inflammation factors including leukocytes and lymphocytes could potentially mediated the association between mixed VOCs exposure and periodontitis. Moreover, to ensure the robustness and sensitivity of our analyses, we employed the BKMR and QGC models to investigate the joint effects of mixed VOCs exposure on periodontitis. Additionally, subgroups analyses were consistent with the overall population, suggesting the robustness of our analyses. These findings might provide new initiatives for the early prevention and treatment of periodontitis to alleviate the periodontal health burden in the future. Despite the strengths presented above, there were still some limitations in this study. First, the cross-sectional study design was unable to make the causal inference. Second, even though we evaluated the possible confounding variates in the analyses, there may still be some unknown residual confounding factors beyond control. Besides, we were unable to ascertain exposure durations of VOC due to the one-time assessment of mVOCs. Additionally, RCS, BKMR and QGC models do not yet support weighted calculation. In order to maintain consistency with our main analyses, we did not adjust the sample weight in the logistic models, which would make the results less representative. Finally, genetic information and drug usage data were insufficient in the NHANES. Further longitudinal and *in vivo/vitro* studies were demanded to explore the mechanism of impacts of VOCs exposure on the risk of periodontitis.

Conclusion

In summary, the present study revealed the significant association between single and mixed VOCs exposure with periodontitis by comprehensive utilization of five statistical methods. The mediated effect induced by systemic inflammation factors between mixed VOCs exposure and periodontitis was also observed. This study provided an insight into surveillance and public health for periodontal diseases from an environmental health perspective, aiming to raise public awareness of impacts of VOCs exposure on periodontal health and help develop health programs and policy to relieve global health burden in the future.

Abbreviations

2MHA	2-Methylhippuric acid
3-4MHA	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
BMA	N-Acetyl-S-(benzyl)-L-cysteine
CEMA	N-Acetyl-S-(2-carboxyethyl)-L-cysteine
CYMA	N-Acetyl-S-(2-cyanoethyl)-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-buten-1-yl)-L-cysteine
PGA	Phenylglyoxylic acid
HPMMA	N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine
VOCs	Volatile organic compounds
mVOCs	metabolites of volatile organic compounds
NHANES	National Health and Nutrition Examination Survey
RCS	Restricted cubic spline regression
BKMR	Bayesian kernel machine regression
QGC	Quantile g-computation
UPLC-ESI/MSMS	Ultra performance liquid chromatography coupled with electrospray tandem mass spectrometry
BMI	Body Mass Index
OR	Odds ratio
CI	Confidence interval
PIP	Prior inclusion probability
ROS	Reactive oxygen species

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-024-05110-y.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

This study was analyzed using the data provided by the National Health and Nutrition Examination Survey 2011–2014. Data from this survey will be used in epidemiological studies and health sciences research, which helps develop sound public health policy, direct and design health programs and services, and expand the health knowledge for the Nation.

Author contributions

D.Z. originally designed the study, conducted data analysis, and wrote the draft; Z.Z. conducted data analysis and visualized the data; H.Q. acquired and interpretated the data; Y.X. interpretated the data and revised the manuscript; C.Y. visualized the data and revised the manuscript; X.Y. acquired the data and revised the manuscript; F.Y. involved in data curation; T.Y. critically revised the

manuscript; J.C. revised the manuscript, supervised and administrated the study; Z.C. critically revised the manuscript, supervised, administrated and approved the study. All authors reviewed the manuscript.

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Data availability
The publicly available data used in this study can be downloaded for free on NHANES website: https://wwwn.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate
This study used publicly available NHANES data from the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS). The NHANES data usage agreement and the NHANES study protocol (Protocol #2011–14) have been reviewed and approved by the NCHS Research Ethics Review Board (Supplementary Material 2). All participants provided written informed consent before participating.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]School of Stomatology, Jinan University, No.601 Huangpu Ave West, Guangzhou, Guangdong 510632, P. R. China
[2]Department of Stomatology, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong 510632, P. R. China
[3]Department of Preventive Medicine and Public Health, School of Medicine, Jinan University, No.601 Huangpu Ave West, Guangzhou, Guangdong 510632, P. R. China
[4]Guangdong Key Laboratory of Environmental Exposure and Health, Jinan University, Guangzhou, Guangdong 510632, P. R. China

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References

1. Slots J. Periodontitis: facts, fallacies and the future. Periodontol 2000 2017, 75(1):7–23.
2. Eke PIDB, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, Taylor GW, Page RC, Beck JD, Genco RJ. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. J Periodontol. 2015;86(5):611–22.
3. Eke PI, Borgnakke WS, Genco RJ. Recent epidemiologic trends in periodontitis in the USA. Periodontol 2000. 2019;82(1):257–67.
4. Sanz M, Marco del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, Chapple I, Dietrich T, Gotsman I, Graziani F, et al. Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol. 2020;47(3):268–88.
5. Isola G, Polizzi A, Mascitti M, Santonocito S, Ronsivalle V, Cicciù M, Pesce P. Impact of periodontitis on circulating cell-free DNA levels as a measure of cardiovascular disease. Clin Oral Invest. 2023;27(11):6855–63.
6. Polak D, Shapira L. An update on the evidence for pathogenic mechanisms that may link periodontitis and diabetes. J Clin Periodontol. 2017;45(2):150–66.
7. Lertpimonchai A, Rattanasiri S, Tamsailom S, Champaiboon C, Ingsathit A, Kitiyakara C, Limpianunchai A, Attia J, Sritara P, Thakkinstian A. Periodontitis as the risk factor of chronic kidney disease: Mediation analysis. J Clin Periodontol. 2019;46(6):631–9.
8. Won YS, Kim JH, Kim YS, Bae KH. Association of internal exposure of cadmium and lead with periodontal disease: a study of the Fourth Korean National Health and Nutrition Examination Survey. J Clin Periodontol. 2012;40(2):118–24.
9. Sun J, Guo F, Wang L, Han F, Yang J, Gao S. Association of environmental polycyclic aromatic hydrocarbons exposure with periodontitis in NHANES 2009–2014: A mixtures approach. J Periodontol. 2023;95(6):603–13.
10. Xiong J, Zhang P, Huang S, Zhang Y. Comprehensive influence of environmental factors on the emission rate of formaldehyde and VOCs in building materials: Correlation development and exposure assessment. Environ Res. 2016;151:734–41.
11. Temkin AM, Geller SL, Swanson SA, Leiba NS, Naidenko OV, Andrews DQ. Volatile organic compounds emitted by conventional and green cleaning products in the U.S. market. Chemosphere. 2023;341:139570.
12. Huang L, Zhao B, Wang S, Chang X, Klimont Z, Huang G, Zheng H, Hao J. Global Anthropogenic Emissions of Full-Volatility Organic Compounds. Environ Sci Technol. 2023;57(43):16435–45.
13. Wang X, He W, Wu X, Song X, Yang X, Zhang G, Niu P, Chen T. Exposure to volatile organic compounds is a risk factor for diabetes: A cross-sectional study. Chemosphere. 2023;338:139424.
14. Wu M, Liu M, Zhang Y, Wu J, Gao M, Huang F, Chen H, Zhu Z. Serum HDL partially mediates the association between exposure to volatile organic compounds and kidney stones: A nationally representative cross-sectional study from NHANES. Sci Total Environ. 2024;907:167915.
15. Wang X, Chen Z, Cheng D, Cao Y, Xie X, Zhou J, Wu Y, Li X, Yu J, Yang B. Association between urinary metabolites of volatile organic compounds and cardiovascular disease in the general population from NHANES 2011–2018. Ecotoxicol Environ Saf. 2023;264:115412.
16. Zhou X, Zhou X, Wang C, Zhou H. Environmental and human health impacts of volatile organic compounds: A perspective review. Chemosphere. 2023;313:137489.
17. Wu Y, Yang H, Jin W, Wu Y, Yu Y, Chen Q, He B, Yan F, Li Y, Chen F. Association between polycyclic aromatic hydrocarbons and periodontitis: Results from a large population-based study. J Clin Periodontol. 2023;51(4):441–51.
18. Monedeiro F, Monedeiro-Milanowski M, Zmysłowski H, De Martinis BS, Buszewski B. Evaluation of salivary VOC profile composition directed towards oral cancer and oral lesion assessment. Clin Oral Invest. 2021;25(7):4415–30.
19. Dong H, Wang X, Xiao N, Yang X, Zhang X, Niu P, Chen T. Association between volatile organic compounds exposure and periodontitis: A representative cross-sectional study. J Clin Periodontol. 2024;51(10):1359–68.
20. Kwon J-W, Park H-W, Kim WJ, Kim M-G, Lee S-J. Exposure to volatile organic compounds and airway inflammation. Environ Health. 2018;17(1):65.
21. Wang B, Wang X, Yu L, Liu W, Song J, Fan L, Zhou M, Yang M, Ma J, Cheng M, et al. Acrylamide exposure increases cardiovascular risk of general adult population probably by inducing oxidative stress, inflammation, and TGF-β1: A prospective cohort study. Environ Int. 2022;164:107261.
22. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. Periodontol 2000. 2013;64(1):57–80.
23. Yan M, Zhu H, Luo H, Zhang T, Sun H, Kannan K. Daily Exposure to Environmental Volatile Organic Compounds Triggers Oxidative Damage: Evidence from a Large-Scale Survey in China. Environ Sci Technol. 2023;57(49):20501–9.
24. Muñoz Aguilera E, Leira Y, Miró Catalina Q, Orlandi M, Czesnikiewicz-Guzik M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F. Is systemic inflammation a missing link between periodontitis and hypertension? Results from two large population-based surveys. J Intern Med. 2020;289(4):532–46.
25. National Health and Nutrition Examination Survey 2013–2014 Data Documentation, Codebook, and Frequencies. [https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/OHXPER_H.htm]
26. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–7.
27. National Health and Nutrition Examination Survey. NHANES 2013–2014 Questionnaire Instruments [https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/questionnaires.aspx?Cycle=2013-2014] Accessed May.31, 2024.
28. National Health and Nutrition Examination Survey. Laboratory Procedure Manual [https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/labmethods/UVOC_H_MET.pdf]
29. Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-based surveillance of periodontitis. J Periodontol. 2012;83(12):1449–54.
30. Alves-Costa S, Nascimento GG, Peres MA, Li H, Costa SA, Ribeiro CCC, Leite FRM. Sugar-sweetened beverage consumption and periodontitis among adults: A population-based cross-sectional study. J Clin Periodontol. 2024;51(6):712–21.

31. Borrell LN, Crawford ND. Socioeconomic position indicators and periodontitis: examining the evidence. Periodontol 2000. 2011;58(1):69–83.
32. Machado V, Lobo S, Proença L, Mendes JJ, Botelho J. Vitamin D and Periodontitis: A Systematic Review and Meta-Analysis. Nutrients. 2020;12(8):2177.
33. Parsegian K, Randall D, Curtis M, Ioannidou E. Association between periodontitis and chronic kidney disease. Periodontol 2000. 2022;89(1):114–24.
34. Nociti FH, Casati MZ, Duarte PM. Current perspective of the impact of smoking on the progression and treatment of periodontitis. Periodontol 2000. 2014;67(1):187–210.
35. Sälzer S, Graetz C, Dörfer CE, Slot DE, Van der Weijden FA, Scannapieco FA. Contemporary practices for mechanical oral hygiene to prevent periodontal disease. Periodontol 2000. 2020;84(1):35–44.
36. Huang Q, Li S, Wan J, Nan W, He B. Association between ethylene oxide exposure and prevalence of COPD: Evidence from NHANES 2013–2016. Sci Total Environ. 2023;885:163871.
37. Baele G, Lemey P, Rambaut A, Suchard MA, Valencia A. Adaptive MCMC in Bayesian phylogenetics: an application to analyzing partitioned data in BEAST. Bioinformatics. 2017;33(12):1798–805.
38. Bobb JF, Claus Henn B, Valeri L, Coull BA. Statistical software for analyzing the health effects of multiple concurrent exposures via Bayesian kernel machine regression. Environ Health. 2018;17(1):67.
39. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. Environ Health Perspect. 2020;128(4):47004.
40. Zeng X, Chen T, Cui Y, Zhao J, Chen Q, Yu Z, Zhang Y, Han L, Chen Y, Zhang J. In utero exposure to perfluoroalkyl substances and early childhood BMI trajectories: A mediation analysis with neonatal metabolic profiles. Sci Total Environ. 2023;867:161504.
41. Pan W, Wang Q, Chen Q. The cytokine network involved in the host immune response to periodontitis. Int J Oral Sci. 2019;11(3):30.
42. Saiki R, Hayashi D, Ikuo Y, Nishimura K, Ishii I, Kobayashi K, Chiba K, Toida T, Kashiwagi K, Igarashi K. Acrolein stimulates the synthesis of IL-6 and C-reactive protein (CRP) in thrombosis model mice and cultured cells. J Neurochem. 2013;127(5):652–9.
43. Fetoni AR, Paciello F, Rolesi R, Pisani A, Moleti A, Sisto R, Troiani D, Paludetti G, Grassi C. Styrene targets sensory and neural cochlear function through the crossroad between oxidative stress and inflammation. Free Radic Biol Med. 2021;163:31–42.
44. Usui M, Onizuka S, Sato T, Kokabu S, Ariyoshi W, Nakashima K. Mechanism of alveolar bone destruction in periodontitis — Periodontal bacteria and inflammation. Japanese Dent Sci Rev. 2021;57:201–8.
45. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL. Microbial complexes in subgingival plaque. J Clin Periodontol. 2005;25(2):134–44.
46. Møller P, Folkmann JK, Forchhammer L, Bräuner EV, Danielsen PH, Risom L, Loft S. Air pollution, oxidative damage to DNA, and carcinogenesis. Cancer Lett. 2008;266(1):84–97.
47. Chen S, Wan Y, Qian X, Wang A, Mahai G, Li Y, Xu S, Xia W. Urinary metabolites of multiple volatile organic compounds, oxidative stress biomarkers, and gestational diabetes mellitus: Association analyses. Sci Total Environ. 2023;875:162370.
48. Mills EM, Gunasekar PG, Pavlakovic G, Isom GE. Cyanide-Induced Apoptosis and Oxidative Stress in Differentiated PC12 Cells. J Neurochem. 2002;67(3):1039–46.
49. Su H, Gornitsky M, Velly AM, Yu H, Benarroch M, Schipper HM. Salivary DNA, lipid, and protein oxidation in nonsmokers with periodontal disease. Free Radic Biol Med. 2009;46(7):914–21.
50. Pei Z, Zhuang Z, Sang H, Wu Z, Meng R, He EY, Scott GI, Maris JR, Li R, Ren J. α,β-Unsaturated aldehyde crotonaldehyde triggers cardiomyocyte contractile dysfunction: Role of TRPV1 and mitochondrial function. Pharmacol Res. 2014;82:40–50.
51. Ohnishi T, Bandow K, Kakimoto K, Machigashira M, Matsuyama T, Matsuguchi T. Oxidative stress causes alveolar bone loss in metabolic syndrome model mice with type 2 diabetes. J Periodontal Res. 2009;44(1):43–51.
52. He Y, Gan X, Zhang L, Liu B, Zhu Z, Li T, Zhu J, Chen J, Yu H. CoCl2induces apoptosis via a ROS-dependent pathway and Drp1-mediated mitochondria fission in periodontal ligament stem cells. Am J Physiology-Cell Physiol. 2018;315(3):C389–97.
53. Hyeon S, Lee H, Yang Y, Jeong W. Nrf2 deficiency induces oxidative stress and promotes RANKL-induced osteoclast differentiation. Free Radic Biol Med. 2013;65:789–99.

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