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Biological aging mediates the association between volatile organic compounds and cardiovascular disease

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Abstract

Background Evidence for the relationship between individual and combined volatile organic compounds (VOCs) and cardiovascular disease (CVD) is limited. Besides, the mediating role of biological aging (BA) has not been studied. Therefore, this study aimed to examine the association between VOCs and CVD risk and to explore the mediating effects of BA.

Methods Logistic regression models were used to investigate the relationships of metabolites of volatile organic compounds (mVOCs) and BA with CVD. In addition, weighted quantile sum (WQS) regression, adaptive elastic networks, and Environmental Risk Score (AENET-ERS) were utilized to assess overall associations of mixed VOCs co-exposure with CVD. Mediation analyses were used to identify potential mediating effects of BA.

Results In the single-pollutant model, CYMA was shown to be associated with an increased risk of CVD. Additionally, we identified significantly positive associations between the WQS index and CVD (odds ratio (OR) = 1.292, 95% confidence interval (CI): 1.006, 1.660), and DHBMA had the greatest contribution for CVD (0.246). Furthermore, the AENET-ERS results showed that 8 mVOCs were significantly associated with CVD, and ERS was related to an elevated risk of CVD (OR = 1.538, 95%CI: 1.255, 1.884). Three BA indicators mediated the association of the mVOCs mixture with CVD, with mediating effect proportions of 11.32%, 34.34%, and 7.92%, respectively.

Conclusion The risk of CVD was found to increase with both individual and combined exposure to VOCs. BA mediates the positive effects of VOCs on CVD, suggesting that this pathway may be one of the mechanisms of CVD.

Highlights

- Individual and mixed exposure to VOCs were associated with elevated CVD risk.
- DHBMA dominates mixtures of mVOCs for increased CVD risk.
- BA mediates the effect of VOCs mixture exposure on CVD.

Keywords Volatile organic compounds, Mixed exposure, Cardiovascular disease, Environmental risk score, Biological aging

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Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability-related disease worldwide and poses a threat to health [1, 2]. Data from the Global Burden of Disease Study 2019 shows that 523 million people worldwide have CVD, and the number of CVD deaths has steadily increased, reaching 18.6 million as of 2019 [3]. It places an increased burden of disease on individuals and a heavy financial burden on families and society. Therefore, there is an urgent need to identify more risk factors for CVD so that targeted preventive measures can be taken to reduce the risk of the disease. An increasing amount of research suggests that there exists a close association between environmental pollutants and the incidence and death rates of CVD [4–6]. Volatile organic compounds (VOCs) are known to be precursors of $PM_{2.5}$ and ozone, and they have a significant impact on regional environmental pollution [7]. As universal and complex environmental organic pollutants, VOCs include alkanes, olefins, aldehydes, benzenes congeners, and other organic substances, mainly originating from industrial emissions, vehicle exhaust, and fuel combustion [8]. A perspective review, summarizing the health effects of past and current exposure to VOC, has shown that human exposure to VOCs is susceptible to many degenerative diseases such as allergies, obesity, and diabetes [9].

Previous studies have shown that exposure to single VOCs may be closely related to endothelial injury and several kinds of CVD [10]. Toxicology studies in mice demonstrated that acrolein exposure induces vasodilation, dyslipidemia, and platelet activation and thus promotes thrombosis in the organism [11–13]. In vitro and in vivo experiments have shown that acrolein in cigarette smoke may induce endothelial superoxide anion production through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which has been shown to be closely related to endothelial dysfunction [14]. According to a cross-sectional study, exposure to acrolein and 1,3-butadiene was associated with increased systolic blood pressure and decreased reactive congestion index (a measure of endothelial function) [15]. However, as the study population was drawn from a high CVD risk group receiving primary and secondary CVD prevention, selection bias had to be taken into account, which may lead to limited extrapolation of the results. Moreover, most of the previous studies focused on the effect of single VOC on CVD, and in reality, people are not only exposed to one VOC but often to multiple VOCs. One such study, which recruited 603 participants, showed that cumulative VOC risk score showed a strong negative association with CD45dim/CD146+/CD34+cells, suggesting that total VOC exposure has a cumulative effect on pro-angiogenic cells [16], thereby impairing endothelial repair and angiogenesis. Studies exploring the effects of VOC as a mixture on CVD are still scarce to our knowledge. Therefore, the single and mixed effects of VOCs exposure and CVD need to be further explored in large-scale epidemiological investigations.

Unlike actual age, biological age (BA) incorporates risk factors for future disease and early death. Evidence suggests that a variety of environmental pollutants are associated with biological senescence, such as $PM_{2.5}$ [17], perfluoroalkyls [18], and others. It is noteworthy that the results of a previous study showed a significant correlation between individual VOCs and BA [19]. Nonetheless, research evidence on the association of mixed VOC exposure with CVD and whether BA played a mediating effect is limited.

In summary, the purpose of our study was to explore the effects of individual and mixed exposure to VOCs on CVD, and investigate the mediating effect of BA in CVD risk modification due to VOCs exposure through combined utilization of traditional logistic regression, and advanced multi-pollutant assessment methods including weighted quantile sum (WQS) regression, adaptive elastic networks (AENET) and Environmental Risk Score (ERS).

Materials and methods

Study population

The participants of this study were derived from the National Health and Nutrition Examination Survey (NHANES), which is a population-based survey combining interviews and physical examinations to determine the health and nutrition of adults and children in America. The 2011–2018 NHANES database involved 39,156 participants, and urinary metabolites of volatile organic compounds (mVOCs) data were available for 9,176. Of these, we excluded the participants whose data on CVD and covariates were missing, and who were pregnant (n=4,584). Finally, 4,592 participants (age range 20–80 years) were enrolled in the main analysis. In addition, we removed missing values for the variables required in the mediator variable calculation in subsequent mediation analyses. The detailed population screening process is presented in Figure S1. The National Health Statistics Research Ethics Review Board approved the protocol of NHANES, and all participants signed informed consent forms.

Measurement of urinary mVOCs

We used urinary mVOCs concentrations to assess VOC exposure levels. Urine samples were collected from a sub-sample of participants, and stored in frozen (-20℃) conditions until transported to the National Centre for Environmental Health for testing. MVOCs in urine were determined by ultra-performance liquid chromatography and electrospray tandem mass spectrometry

quantification procedure [20], for mVOCs with analysis results below the lower limit of detection (LLOD) were expressed as LLOD/√2. Sixteen mVOCs with > 50% detection rates were included as continuous variables, including 2-methylhippuric acid (2MHA), 3-methylhippuric acid and 4-methylhippuric acid (34MHA), acrylamide mercapturic acid/N-acetyl-S-(2-carbamoylethyl)-L-cysteine (AAMA), N-acetyl-S-(N-methylcarbamoyl)-L-cysteine (AMCC), 2-aminothiazoline-4-carboxylic acid (ATCA), benzyl mercapturic acid/N-acetyl-S-(benzyl)-L-cysteine (BMA), n-propyl mercapturic acid/N-acetyl-S-(n-propyl)-L-cysteine (BPMA), 2-carboxyethyl mercapturic acid/N-acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA), 2-cyanoethyl mercapturic acid/N-acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA), 3,4-dihydroxybutyl mercapturic acid/N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMA), 2-hydroxypropyl mercapturic acid/N-acetyl-S-(2-hydroxypropyl)-L-cysteine (2HPMA), 3-hydroxypropyl mercapturic acid/N-acetyl-S-(3-hydroxypropyl)-L-cysteine (3HPMA), mandelic acid (MA), monohydroxybutenyl mercapturic acid/N-acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine (MHBMA3), phenylglyoxylic acid (PGA), and 3-hydroxypropyl-1-methyl mercapturic acid/N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine (HPMMA).

Assessment of CVD

The definition of CVD was determined using self-reported standardized medical status questionnaires in individual interviews. When interviewees were asked "Has a doctor or other health professional ever told you that you have congestive heart failure/coronary heart disease/angina/heart attack/stroke?" if one of the answers is yes, then he or she was enrolled in the CVD group.

Measurement of mediators

BA biomarkers incorporated Klemera-Doubal Method (KDM), KDMAccel, Phenotypic Age (PA), and PAAccel. KDM was calculated using the Klemera and Doubal method based on 8 biomarkers [21], and PA was calculated based on a previous formula that used actual age and 9 biomarkers [22]. Based on previous studies, we used the BioAge R package (Table S2) to calculate KDM and PA (Table S2) [23]. KDMAccel and PAAccel were calculated as KDM and PA minus actual age, respectively [22].

Covariates

Important covariates were chosen a priori and included age, gender, race, education, poverty income ratio (PIR), body mass index (BMI), drinking, smoking status, activity, and urine creatinine (UCr). All covariate data were obtained from the NHANES database. Specifically, PIR was defined as a family income ratio to the poverty threshold. BMI is calculated as weight (kg) divided by height squared (m^2). Race was divided into Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race. Education level was defined as less than high school, high school or equivalent, and college or above. Drinker was deemed to have at least 12 alcoholic drinks every year. There were three types of smoking status: never smokers (less than 100 cigarettes in a lifetime and currently a nonsmoker), current smokers (more than 100 cigarettes in a lifetime and currently are smokers), and past smokers (more than 100 cigarettes throughout their lifetimes and currently are non-smokers). The determination of the activity was based on whether the individual engaged in any work involving vigorous-intensity physical activity. UCr was determined as a marker of urine dilution and measured by the Jaffe rate reaction of the Beckman Synchronous Analyzer.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and categorical variables as frequency (percentages). Student-*t* tests and chi-square tests were used to compare the differences in baseline characteristics according to whether or not CVD. Correlations between mVOC were assessed using spearman correlation analysis. Because the distributions of mVOCs were deflective, we analyzed the relationship between individual mVOCs and CVD by logistic regression using natural log-transformed data. Generalized linear models were used to analyze the association of individually transformed VOCs with KDM, KDMAccel, PA, and PAAccel. Model 1 was not adjusted for any confounders; and Model 2 adjusted for age, gender, race, education, PIR, BMI, drinking, smoking status, activity, and UCr. To prevent overcorrection, age was excluded from adjustment in the KDM, KDMAccel, PA, and PAAccel analyses. To account for multiple tests, the Benjamini-Hochberg procedure was applied to control the false-discovery rate (FDR) and reported the corrected *P* values as *q* values. Furthermore, restricted cubic splines (RCS), with 3 knots at the 25th, 50th, and 75th percentiles, were exhibited to explore the non-linear relationship of mVOCs with CVD. As previous literature has reported that the association between VOCs exposure and CVD may be influenced by gender and smoking status [24], subgroup analyses according to gender and smoking status were conducted to obtain specific associations between subgroups. Considering the complex multistage probability sampling design, appropriate weights were chosen in the analysis.

WQS regression was performed to estimate the effect of mixtures of mVOCs on the risk of CVD [25]. The data were used as a test set and validation set in the ratio of 4:6 to improve the statistical efficacy. There are 1000

bootstrap steps in the multiple regression model. The elastic network is a regularization method based on Ridge regression and Least absolute shrinkage and selection operator regression, with appropriate cross-validation to make the model more robust, combining both advantages in terms of variable selection [26]. AENET are adaptive versions of elastic networks with higher statistical performance and better variable selection to reduce the coefficients of less important predictors to zero [27]. Based on 5-fold cross-validation to select the most appropriate tuning parameters, we used AENET to filter the CVD-related mVOCs from 16 predictors and obtain the corresponding β values. ERS was calculated using beta coefficients adopted from AENET for not only main effects but also squared terms of metal concentrations as well as all the combinations of pairwise linear interactions [28]. Afterward, the logistic regression model was performed to investigate the relationships of ERS with CVD, and quartiles stratified analysis of ERS was added after adjusting for all possible covariates.

Mediator analyses were used to examine the role of mediators in the mechanisms of CVD risk modification due to mixed exposures to VOCs. All analyses were performed using the SPSS (Version 21.0; SPSS Inc., Chicago IL, USA), and R studio (R Version 4.2.1). Results of P or $q<0.05$ were considered statistically significant.

Results

Characteristics of study participants

The general characteristics of the 4,592 subjects are shown in Table 1, with the weighted prevalence of CVD in the analytic sample was 37.3%. Except for UCr and KDMAccel, all the characteristics were statistically significant differences between the non-CVD and CVD groups (all $P<0.05$). The participants of the CVD group were significantly older, had greater BMI, had lower PIR, had higher KDM, PA, and PAAccel, and the proportion

Table 1 Characteristics of the study participants (weighted)

Characteristics	Overall	Non-CVD	CVD	*P* value
Age, years, mean ± SD	47.6 ± 16.8	46.1 ± 16.3	64.1 ± 13.4	**< 0.001**
Gender, %				**0.002**
Male	49.8	49.1	58.1	
Female	50.2	50.9	41.9	
Race, %				**0.003**
Mexican American	7.6	7.9	3.4	
Other Hispanic	6.0	6.1	4.9	
Non-Hispanic White	67.4	66.8	74.5	
Non-Hispanic Black	11.1	11.0	12.0	
Others race	7.9	8.1	5.2	
Education, %				**< 0.001**
Less than high school	12.6	12.0	20.2	
High school or equivalent	22.9	22.3	29.1	
College or above	64.5	65.7	50.7	
PIR, %				**< 0.001**
≤ 1.3	21.5	21.2	26.0	
1.3–3.5	35.7	34.8	46.1	
> 3.5	42.7	44.0	27.9	
BMI, kg/m^2, mean ± SD	29.4 ± 7.0	29.4 ± 7.0	30.3 ± 7.0	**0.031**
Drinker, %	72.9	73.5	66.3	**0.013**
Smoking status, %				**< 0.001**
Never	55.3	56.7	39.4	
Current	18.4	18.0	22.9	
Past	26.3	25.3	37.7	
Activity, %	23.2	23.8	16.5	**0.017**
UCr, mg/dL, mean ± SD	114.2 ± 76.9	114.6 ± 77.7	109.0 ± 67.1	0.250
KDM, years, mean ± SD	37.5 ± 25.7	35.9 ± 25.1	54.1 ± 25.5	**< 0.001**
KDMAccel, mean ± SD	-10.8 ± 20.4	-10.8 ± 20.0	-10.3 ± 24.2	0.808
PA, years, mean ± SD	47.1 ± 18.4	45.2 ± 17.6	66.8 ± 15.1	**< 0.001**
PAAccel, mean ± SD	-1.2 ± 5.6	-1.5 ± 5.3	2.4 ± 7.7	**< 0.001**

Bolded data meant with a $P<0.05$

Abbreviations: CVD, cardiovascular disease; SD, standard deviation; PIR, poverty-income ratio; BMI, body mass index; UCr, urine creatinine; KDM, Klemera–Doubal Method; PA, Phenotypic Age

of males and lack of exercise was higher (all $P<0.05$). Besides, among all participants, 49.8% were men, 67.4% were Non-Hispanic White, 64.5% qualifications were college or above, 72.9% were drinkers, 55.3% were never smoker, and 23.2% were engaged in the vigorous-intensity physical activity.

In addition, the Spearman correlation coefficients between the urinary levels of 16 mVOCs are shown in Figure S2. All the analytes show positive correlations between 0.112 and 0.877 (all $P<0.01$). Table S1 indicates the abbreviations, detection rates, LLODs, and distributions of 16 urinary mVOC concentrations in the total population. The median concentration of DHBMA (326.0 μg/L) was the highest, followed by 3HPMA (254.0 μg/L), HPMMA (248.0 μg/L), and PGA (212.5 μg/L).

Single mVOCs and CVD risk

After adjusting for covariates and multiple corrections, the weighted logistic regression model analyzed the relationships between mVOCs and CVD, and the results are shown in Fig. 1. ATCA was negatively associated with CVD (odds ratio (OR)=0.795, 95% confidence interval (CI): 0.650, 0.973) in the adjusted model ($P=0.027$). CEMA, CYMA, and 3HPMA were positively associated with CVD risk. Their ORs (95%CIs) were 1.275 (1.031,1.577), 1.186 (1.073,1.309), and 1.240 (1.037,1.483), respectively. A significant association between CYMA and CVD was found despite FDR correction ($q=0.02$).

Weighted RCS curves were further generated to explore the nonlinearity of mVOCs with CVD (Figure S3). We observed a linear association of CEMA, CYMA, 2HPMA, 3HPMA, and PGA with CVD (P for nonlinearity>0.05), while a significant non-linear relationship was observed between 34MHA, AMCC, ATCA, DHBMA, MHBMA3, HPMMA and CVD (P for nonlinearity were 0.0019, 0.0001, 0.0358, 0.0288, 0.0010, 0.0100).

We furthermore explored the possible relationships of ln (mVOCs) concentration with CVD according to subgroups (Figure S4). When subgroup analyzes were performed according to gender stratification, CYMA was still found to be significantly associated with CVD (men: 1.214(1.060,1.390), $P=0.006$. women: 1.147(1.001,1.314), $P=0.048$), in addition to sex-specific differential results for ATCA, CEMA, 2HPMA, and 3HPMA, but unfortunately these association disappeared after FDR correction. Among current smokers, 34MHA, AMCC, CEMA, CYMA, 3HPMA, MA, MHBMA3, and HPMMA was

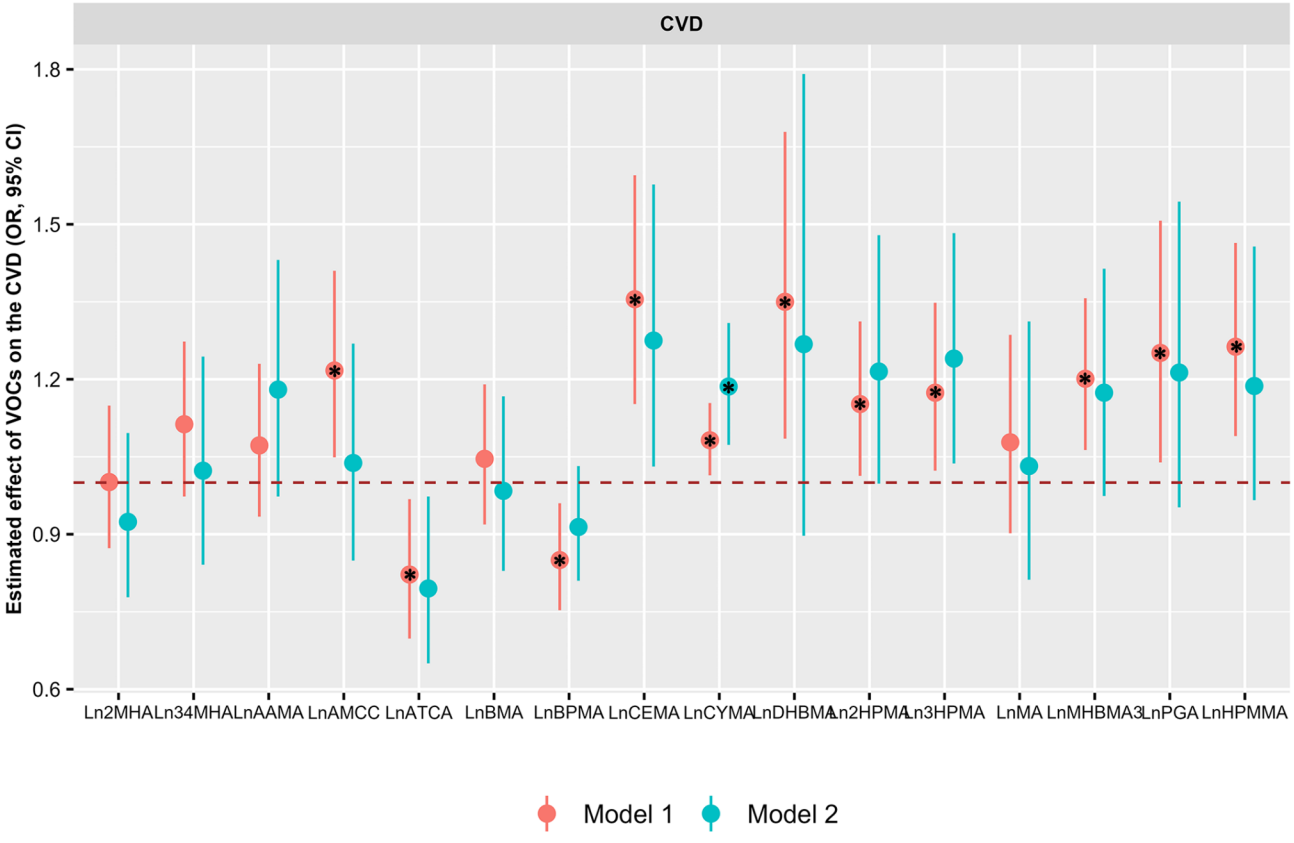

Fig. 1 Adjusted odds ratios for associations between individual mVOCs and the risk of CVD. Model 1: unadjusted. Model 2: adjusted for age, gender, race, education, PIR, BMI, drinking status, smoking status, activity, and urine creatinine. Abbreviations: VOCs, volatile organic compounds; CVD, cardiovascular disease; Ln-, natural log-transformed; OR, odd ratio; CI, confidence interval; q value, false discovery rate (FDR) - corrected *P* value. *q < 0.05

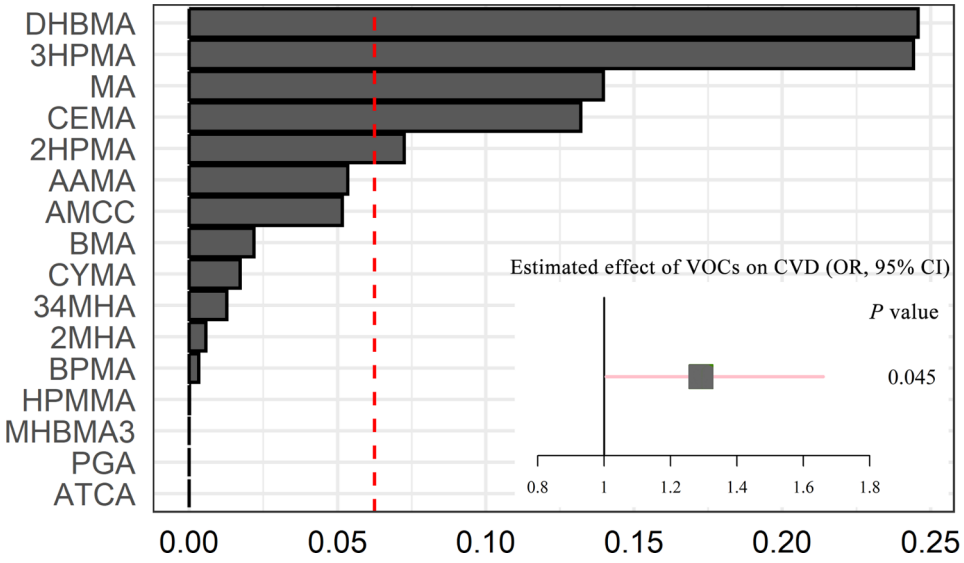

Fig. 2 The WQS regression estimated weights of each of the selected mVOCs that were more relevant to CVD risk. The model was adjusted for age, gender, race, education, PIR, BMI, drinking, smoking status, activity, and urine creatinine. Abbreviations: mVOCs, metabolites of volatile organic compounds; WQS, Weighted Quantile Sum; CVD, cardiovascular disease; Ln-, natural log-transformed

Table 2 Associations between mixed mVOCs levels (ERS), BA, OBS, and CVD

	Continuous	Q1	Q2	Q3	Q4	*P*-trend
ERS	**1.538 (1.255, 1.884)**	Ref	1.074 (0.718, 1.607)	**1.681 (1.032, 2.739)**	**2.565 (1.507, 4.365)**	**< 0.001**
KDM	**1.028 (1.018, 1.038)**	Ref	**2.251 (1.052, 4.817)**	**4.226 (2.346, 7.612)**	**9.177 (4.796, 17.558)**	**< 0.001**
KDMAccel	1.002 (0.991, 1.014)	Ref	0.630 (0.331, 1.198)	0.610 (0.296, 1.260)	0.921 (0.433, 1.960)	0.836
PA	**1.077 (1.058, 1.096)**	Ref	3.002 (0.925, 9.744)	**11.040 (3.443, 9.744)**	**30.891 (1.044, 91.404)**	**< 0.001**
PAAccel	**1.090 (1.058, 1.124)**	Ref	1.485 (0.744, 2.966)	**2.613 (1.441, 4.739)**	**4.736 (2.523, 8.889)**	**< 0.001**

Bolded data meant with a $P<0.05$

Abbreviations: ERS, Environmental Risk Scores; BA, biological aging; Q, quartile; Ref, reference; KDM, Klemera–Doubal Method; PA, Phenotypic Age; CVD, cardiovascular disease

The model was adjusted for age, gender, race, education, PIR, BMI, drinking, smoking status, activity, and urine creatine. Age was excluded from adjustment in the KDM and PA analyses

associated with an increased risk of CVD even after strict FDR correction (all q<0.05). In addition, statistical interaction of smoking status groups was observed in the association of AMCC (*P* interaction=0.022) and HPMMA (*P* interaction=0.041) with CVD.

Multiple VOC co-exposure and CVD risk

As depicted in Fig. 2, WQS regression models were employed to examine the association of mVOCs mixtures with CVD. The CVD risk was also significantly elevated with increasing quartiles of the WQS index (OR: 1.29, 95% CI: 1.01, 1.66), and the weight of the WQS index was dominated by DHBMA (0.246) and 3HPMA (0.244), followed by MA (0.140), CEMA (0.132) and 2HPMA (0.073). Further subgroup analyses using WQS to represent mixed exposures to VOCs showed almost no significant differences (Table S3).

AENET was performed to screen for mVOCs that were more relevant to CVD risk. Results show that 8 (2MHA, ATCA, BPMA, CEMA, DHBMA, 2HPMA, 3HPMA, PGA) of 16 urinary concentrations of mVOCs were associated with CVD. The β coefficients of CEMA, DHBMA, 2HPMA, 3HPMA, and PGA were positive, while the other three mVOCs (2MHA, ATCA, and BPMA) were negative. Afterward, the remaining variables of interest after screening were used to construct ERS to assess the impact of mixtures of mVOCs on CVD and to incorporate multivariate-adjusted logistic regression models (Table 2). The results showed that a per-1 unit increase in ERS was related to the elevated risk of CVD (OR=1.538, 95%CI: 1.255, 1.884). Higher ERS quartiles increased CVD risk compared to the Q1 group reference, with ORs and 95% CIs of 1.681 (1.032, 2.739), 2.565 (1.507, 4.365) for Q3 and Q4 respectively. Again, the results of the trend test remain consistent with the above (*P*-trend<0.001).

Mediating role of BA

As shown in Table 2, three markers of BA were found to be significantly and positively associated with the risk of CVD (*P*<0.05) with OR (95%CI) of 1.028 (1.018, 1.038),

Table 3 Regression coefficients (95% CI) in BA associated with mixed mVOCs levels (ERS)

	Continuous	Q1	Q2	Q3	Q4	*P*-trend
KDM	**3.028 (1.331, 4.724)**	Ref	0.910 (-2.793, 4.613)	0.868 (-3.153, 4.889)	**6.234 (1.639, 10.829)**	**0.016**
KDMAccel	-0.133 (-1.436, 1.171)	Ref	1.113 (-1.862, 4.089)	-0.529 (-3.611, 2.553)	-0.730 (-3.989, 2.529)	0.414
PA	**3.885 (2.453, 5.316)**	Ref	0.142 (-2.774, 3.059)	1.891 (-1.054, 4.837)	**8.263 (4.964, 11.563)**	**<0.001**
PAAccel	**0.664 (0.148, 1.179)**	Ref	0.354 (-0.671, 1.379)	0.409 (-0.492, 1.310)	**1.241 (0.069, 2.412)**	**0.037**

Bolded data meant with a $P<0.05$

Abbreviations: CI, confidence interval; BA, biological aging; ERS, Environmental Risk Scores; Q, quartile; Ref, reference; KDM, Klemera–Doubal Method; PA, Phenotypic Age

The model was adjusted for age, gender, race, education, PIR, BMI, drinking, smoking status, activity, and urine creatine. Age was excluded from adjustment in the KDM and PA analyses

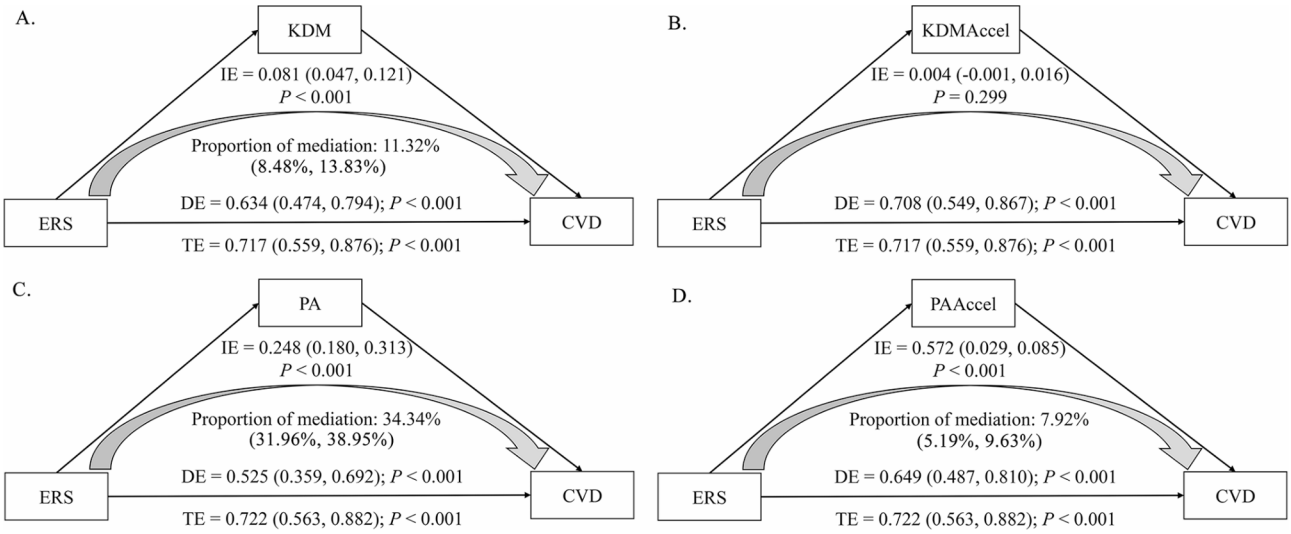

Fig. 3 Mediation analyses on the association between VOCs exposure and CVD risk. The model was adjusted for age, gender, race, education, PIR, BMI, drinking, smoking status, activity, and urine creatine. Age was excluded from adjustment in the KDM and PA analyses. Abbreviations: ERS, Environmental Risk Scores; KDM, Klemera–Doubal Method; PA, Phenotypic Age; TE, total effect; DE, direct effect; IE, indirect effect; CVD, cardiovascular disease

1.077 (1.058, 1.096), and 1.090 (1.058, 1.124), respectively. And the generalized linear model results showed that the mixture of mVOCs (represented by ERS) was also significantly related to KDM, PA, and PAAccel in Table 3 ($P<0.05$). And the trend test likewise obtained similar results (all the P-trend<0.05). Figure 3 presents the mediating effect of BA on the association of the effect of mVOCs mixture with CVD. In the mediation analysis, the proportion of ERS on increased CVD risk mediated by KDM (indirect effect: 0.081) was 11.32%, PA (indirect effect: 0.248) was 34.34%, and PAAccel (indirect effect: 0.572) was 7.92%.

Sensitivity analyses

When the WQS index was used to represent the level of mixed exposure to VOCs for the mediation analysis, as shown in Table S4, the results of the mediation showed that the four indicators of the BA exerted a partial mediation effect, with mediation ratios of 15.87%, 1.89%, 43.33%, and 18.39%, respectively.

Discussion

Our study used a variety of statistical strategies to evaluate the effects of individual and mixed VOC exposure on CVD and to discover factors in mixtures that contributed significantly to outcomes. The main findings are described as below: (1) When assessing the effect of individual VOCs on CVD, it was found that several mVOCs significantly increased the CVD risk. (2) Mixed exposure modeling showed that VOCs mixtures can significantly increase CVD risk, with DHBMA accounting for the main contribution. (3) BA played mediating roles in the relationship between co-exposure to VOCs and CVD correlation.

It was shown that CYMA was positively associated with CVD, with the corresponding parent compound was acrylonitrile. Notably, CEMA and 3HPMA positively affected CVD by the $P<0.05$ criterion as well. Evaluation of the mixed exposure effects of VOCs yielded similar conclusions that VOCs can increase the risk of CVD in humans and are more significant at high levels. The mixed effect was dominated by DHBMA, 3HPMA, MA, CEMA, and 2HPMA.

Previous cross-sectional studies have shown that exposure to VOCs (ethylbenzene/styrene, benzene, xylene, and 1,3-butadiene) exacerbates the risk of CVD by depleting circulating angiogenic cells in a study with participants aged 25–70 years [16, 29]. Exposure to ethylene oxide has been associated with angina pectoris, heart attack, and other CVDs in a large, representative American population, and may also induce CVD through inflammatory responses and abnormalities in fatty acid metabolism [30]. Experimental evidence demonstrates that exposure to acrolein affects endothelial function [31, 32]. These are consistent with our findings on the relationship between VOCs and CVD. Moreover, in our study, an association of acrolein, 1,3-butadiene, and propylene oxide with CVD was found [33]. To our knowledge, although there is no direct evidence that acrylonitrile is associated with CVD risk, it has been shown in animal studies to induce oxidative stress by decreasing glutathione levels and superoxide dismutase activity [34]. Acrylonitrile was significantly associated with elevated 8-OHdG levels, providing evidence that acrylonitrile may increase the risk of CVD [35]. Consequently, although there was no direct evidence that several VOCs are associated with CVD, they are associated with oxidative stress and are capable of inducing vascular dysfunction, making it highly likely that they increase the risk of CVD [15, 36].

We found that senescence has a mediating role in increasing CVD risk from VOCs exposure. Evidence for this can be found in the previous literatures. One study reported that environmental exposures may lead to alterations in gene regulation through altered DNA methylation and histone modifications and promote genetic changes associated with aging [37]. Exposure to a mixture of airborne chemicals, such as VOCs and polycyclic aromatic hydrocarbons (PAHs), can significantly increase the acceleration of epigenetic aging biomarkers [38]. Dichlorobenzene (a volatile organic compound) is one of the main factors in the positive correlation between co-exposure to multiple chemical pollutants and acceleration of DNA mPhenoage [19]. Moreover, several studies have shown that exposure to VOCs can significantly increase oxidative stress biomarkers, both at the animal and population levels [31, 39, 40]. Animal studies have shown that chronic inhalation of VOCs at low concentrations can cause significant effects on oxidative stress indices in mice [41]. According to previous studies, oxidative stress and inflammation are important mechanisms that contribute to aging and CVD [42].

The WQS regression method positively associated the mVOC mixing index and CVD. Among the VOCs associated with CVD, DHBMA, 3HPMA, MA, CEMA, and 2HPMA were the most significant contributors to the elevated risk of CVD. The result was generally consistent with AENET. A recent population-based study found that DHBMA and 3HPMA were associated with endothelial dysfunction in non-smokers by measuring the reactive congestion index [15]. And endothelial cell dysfunction is thought to be the initiating factor in several CVDs. Furthermore, the ERS calculated in this study similarly demonstrated that exposure to VOCs can elevate the risk of CVD, providing a new basis for determining the combined hazard effect of VOCs.

Subgroup analyses revealed that smoking status influenced the effect of VOCs on CVD. This association was even more pronounced among current smokers, which is easily explained by the fact that one of the main sources of VOCs is smoke from burning tobacco. The low detection of certain VOCs in non-smokers also contributes to this. Common sources of exposure to 1,3-butadiene are associated with products of incomplete fuel combustion and cigarette smoke, and a review suggests that both epidemiological and experimental evidence support a role for 1,3-butadiene in the development of atherosclerosis and an increased risk of coronary heart disease mortality [43]. The Louisville Healthy Heart Study also discovered that urinary 3HPMA's ability to reduce the abundance of specific circulating angiogenic cell sub-populations was associated with an elevated risk of CVD [36].

Several strengths of this study deserve mention. To our knowledge, the present study is the first to explore the associations of the mVOC mixture index, which represents the co-exposure level of VOCs, with CVD. Considering that populations are often exposed to multiple VOCs simultaneously; it is more valuable to explore the public health implications of the combined exposure effects of multiple VOCs. Second, the construction of ERS using AENET takes into account the complex relationships between individual mVOCs of mixtures and further explores the relationship between mVOC mixtures and CVD, providing a potential causal relationship. ERS can also be used as a predictive model to assess risk prediction for specific health endpoints in future studies. Additionally, we identified mediators in the pathway of increased CVD risk due to exposure to VOCs, namely BA. Finally, our study sample size was relatively large, including 4,592 adults Americans. It makes the conclusions can be generalized to other American adults.

Nevertheless, there are some limitations in the present study. Firstly, the current research may be unable to prove a causal relationship due to the cross-sectional design. Secondly, misclassification of exposures can occur due to the several hours half-life of urine mVOCs and single point samples. Furthermore, the analysis was adjusted for a range of variables, but the results may be affected by residual confounding factors. In addition, the accuracy of using several urinary mVOCs to indicate relative VOC exposure needs further clarification as many

VOCs' in vivo metabolic mechanisms are not sufficiently detailed. Overall, more prospective studies and relevant experimental studies should be conducted to substantiate the findings of this study.

Conclusions

The present study discovered that both individual and multiple VOC co-exposures can elevate the CVD risk in American adults. Urinary metabolites of 1,3-butadiene contributed the most to the positive effect of the mixture on CVD. In addition, the association between VOCs exposure and CVD is partly mediated by BA. However, more longitudinal studies and animal experiments are required to verify our findings and clarify the underlying mechanism.

Abbreviations

VOCs	Volatile organic compounds
CVD	Cardiovascular disease
mVOCs	Metabolites of volatile organic compounds
WQS	Weighted quantile sum
AENET-ERS	Adaptive elastic networks and Environmental Risk Score
NHANES	National Health and Nutrition Examination Survey
KDM	Klemera–Doubal Method
PA	Phenotypic Age
PIR	Poverty income ratio
BMI	Body mass index
UCr	Urine creatinine
2MHA	2-methylhippuric acid
34MHA	3-methylhippuric acid 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	Benzyl mercapturic acid/N-acetyl-S-(benzyl)-L-cysteine
BPMA	n-propyl mercapturic acid/N-acetyl-S-(n-propyl)-L-cysteine
CEMA	2-carboxyethyl mercapturic acid/N-acetyl-S-(2-carboxyethyl)-L-cysteine
CYMA	2-cyanoethyl mercapturic acid/N-acetyl-S-(2-cyanoethyl)-L-cysteine
DHBMA	3,4-dihydroxybutyl mercapturic acid/N-acetyl-S-(3:4-dihydroxybutyl)-L-cysteine
2HPMA	2-hydroxypropyl mercapturic acid/N-acetyl-S-(2-hydroxypropyl)-L-cysteine
3HPMA	3-hydroxypropyl mercapturic acid/N-acetyl-S-(3-hydroxypropyl)-L-cysteine
MA	mandelic acid; MHBMA3:monohydroxybutenyl mercapturic acid/N-acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine
PGA	Phenylglyoxylic acid
HPMMA	3-hydroxypropyl-1-methyl mercapturic acid/N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine

Supplementary Information

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Supplementary Material 1

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Author contributions

QC and YS contributed significantly to the conceptualization, design, and execution of the study. They collaborated closely in drafting and revising the manuscript, ensuring its accuracy and cohesiveness. CH, ZJ, QG, XM, GZ, SC, JW, and YW actively participated in data clarification and analysis, adding valuable insights to the interpretation of the results. CW, ZM, JH and WH provided extensive guidance and supervision throughout the research project, ensuring its scientific integrity and rigor. They also made substantial contributions to result interpretation and participated in meticulous manuscript revisions, ensuring its high quality and accuracy. All authors read and approved the final manuscript.

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Data availability

Publicly available datasets were analyzed in this study. All the raw data used in this study are derived from the public NHANES data portal (https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx).

Declarations

Ethics approval and consent to participate

The NHANES database is publicly available and has been approved by the Institutional Review Board of the National Center for Health Statistics. All participants provided written informed consent during their participation in the national survey conducted in the United States.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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