scientific reports

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Association between urinary volatile organic compound metabolites and sarcopenia in the US general population: a cross-sectional NHANES study from 2011 to 2018

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Volatile organic compound (VOC) is a prevalent form of pollutant that has been linked to various human ailments, yet their connection to sarcopenia remains uncertain. This study seeks to examine the potential association between exposure to mixtures of metabolites of volatile organic compounds (mVOCs) and sarcopenia, while also investigating the potential mediating effects of oxidative stress and inflammation. Data from the 2011–2018 National Health and Nutrition Examination Survey (NHANES) were utilized for the analysis of the relationship between mVOCs and sarcopenia through logistic regression. The least absolute shrinkage and selection operator (LASSO) regression model was employed to identify key mVOCs, while the quantile-g computation model (qgcomp) and bayesian kernel machine regression (BKMR) models were utilized to examine the association between mVOC mixtures and sarcopenia. Potential mediating factors were explored through mediating analysis. Of the 2908 participants included in the study, 246 individuals (8.5%) were found to have sarcopenia. Logistic regression analysis revealed that five urinary VOC metabolites were positively correlated with an increased risk of sarcopenia. The key mVOCs identified through the LASSO method were further analyzed using qgcomp, which showed a 47% average increase in the risk of sarcopenia when exposed to a mixture of mVOCs (OR = 1.47, 95% CI 1.14–1.91). Four mVOCs components (DHBMA, 3HPMA, ATCA and 3,4MHA) have the largest weight. The BKMR results further confirm this joint association. Furthermore, Mediation analysis revealed that inflammation and oxidative stress mediate the relationship between exposure to mVOCs and sarcopenia. In conclusion, our study provides evidence suggesting that VOC exposure is linked to a heightened risk of sarcopenia, with inflammation and oxidative stress potentially serving as mediators in this relationship. It is recommended that additional cohort studies be conducted to validate these findings.

Keywords Sarcopenia, Volatile organic compounds, Inflammation, Oxidative stress, NHANES, Mixture exposure

Abbreviations

NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
NIH	National Institutes of Health
VOCs	Volatile organic compounds
mVOCs	Metabolites of VOCs
ASM	Appendicular skeletal muscle

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OR	Odds ratio
CI	Confidence interval
IQR	Interquartile range
RCS	Restricted cubic spline
LASSO	Least absolute shrinkage and selection operator
MSE	Minimum mean squared error
qgcomp	Quantile-g computation
BKMR	Bayesian kernel machine regression
PIP	Posterior inclusion probability
ADE	Average of direct effects
ACME	Average causal mediation effects
TE	Total effects
LLOD	The lower limit of detection
CEMA	*N*-Acetyl-*S*-(2-carboxyethyl)-L-cysteine
3HPMA	*N*-Acetyl-*S*-(3-hydroxypropyl)-L-cysteine
AAMA	*N*-Acetyl-*S*-(2-carbamoylethyl)-L-cysteine
CYMA	*N*-Acetyl-*S*-(2-cyanoethyl)-L-cysteine
HMPMA	*N*-Acetyl-*S*-(3-hydroxypropyl-1-methyl)-L-cysteine
ATCA	2-Aminothiazoline-4-carboxylic acid
PGA	Phenylglyoxylic acid
MA	Mandelic acid
AMCC	*N*-Acetyl-*S*-(N-methylcarbamoyl)-L-cysteine
2HPMA	*N*-Acetyl-*S*-(2-hydroxypropyl)-L-cysteine
SBMA	*N*-Acetyl-*S*-(benzyl)-L-cysteine
2MHA	2-Methylhippuric acid
3,4-MHA	3-and 4-Methylhippuric acid
DHBMA	*N*-Acetyl-*S*-(3,4-dihydroxybutyl)-L-cysteine
MHBMA3	*N*-Acetyl-*S*-(4-hydroxy-2-butenyl)-L-cysteine
ALP	Alkaline phosphatase
WBC	White blood cell
GGT	γ-Glutamyltransferase
BMI	Body mass index
CVD	Cardiovascular disease
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
UACR	Urine albumin-to-creatinine ratio

Sarcopenia is a medical condition marked by the rapid deterioration of skeletal muscle mass and function[1], with a prevalence in the global general population estimated to range from 5 to 10%[2]. The condition increases the risk of falls, hospitalization, cognitive decline, and mortality, among other adverse outcomes, thus imposing a substantial burden on global healthcare systems[3–6]. Factors such as age, nutritional status, sedentary lifestyle, and various chronic illnesses prevalent in the population are commonly identified as underlying causes of sarcopenia[7–9]. An increasing body of recent research indicates the influence of environmental pollution on sarcopenia, encompassing factors such as the use of solid fuels for cooking, ambient PM2.5 levels, exposure to heavy metals (particularly manganese), and the presence of phthalates in the environment[10–13]. Given the widespread nature of environmental pollution in the population, the identification of risk factors linked to pollution exposure in relation to sarcopenia holds significant implications for mitigating the prevalence of this condition and alleviating the global health burden.

Volatile organic compounds (VOCs) are prevalent air pollutants present in aerosol form and are extensively dispersed throughout human production and living environments [14]. These compounds primarily originate from industrial processes, vehicle and household emissions, disinfection products, and various other sources, ultimately enter the human body through inhalation, ingestion, and dermal contact. Consequently, VOC exposure poses a health risk to individuals of diverse backgrounds and age groups[15]. Previous research has demonstrated that VOCs are associated with an elevated risk of various diseases, including chronic obstructive pulmonary disease, cancer, reproductive defects, diabetes and hypertension [16–19]. Specifically, acrolein has been found to potentially hinder muscle regeneration and induce muscle atrophy in mice by inhibiting Akt signaling[20]. The existing literature provides limited evidence regarding the relationship between VOCs and sarcopenia. Given that the human body typically encounters a combination of VOCs in real-world scenarios, and that various VOC monomers may exhibit synergistic or antagonistic effects, further investigation into the potential association between exposure to mixtures of VOCs and sarcopenia is warranted.

Numerous studies have demonstrated the role of inflammation and oxidative stress in the pathogenesis and progression of sarcopenia[21–23]. Additionally, research has indicated that the presence of VOCs can cause inflammation in the body as well as oxidative stress[24]. Animal studies have further shown that exposure to volatile organic compounds leads to an elevation in splenic lymphocytes, eosinophils, and neutrophils[25]. Furthermore, analysis of human urine samples by Pal et al. revealed a significant positive correlation between volatile organic compound metabolite concentration and biomarkers of oxidative stress[26]. The relationship between VOCs and sarcopenia remains unclear, and it is unclear whether inflammation and oxidative stress may mediate this relationship.

Metabolites of volatile organic compounds (mVOCs) present in urine offer several benefits, including extended half-life, non-invasive sampling, and high specificity. Consequently, they serve as ideal biomarkers for accurately reflecting the levels of VOCs within living organisms[27]. This study utilized data from the National Health and Nutrition Examination Survey (NHANES) to employ logistic regression, quantile-g computation (qgcomp) and bayesian kernel machine regression (BKMR) models in order to evaluate the independent and combined relationships between mVOCs and sarcopenia in the urine of adult individuals. The study also aimed to identify the key monomer VOCs responsible for these associations. Furthermore, mediation analyses were conducted as well in order to explore the potential mediating effects of inflammation markers and oxidative stress markers on the relationships described above.

Materials and method

Study design and participants

The NHANES program, administered by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention, employs a sophisticated, multi-stage sampling methodology to evaluate the nutritional and health status of both adults and children in the United States (https://www.cdc.gov/nchs/nhanes/index.htm). Ethical approval for the program has been granted by the NCHS Institutional Ethics Review Committee, and all participants provided written informed consent prior to their involvement. This study utilized data from the NHANES dataset spanning the years 2011–2018, as this particular phase of the survey included comprehensive information on urine mVOC concentration and muscle mass.

Figure 1 illustrates that the NHANES program enlisted a total of 39,156 participants between 2011 and 2018. Exclusions were made for individuals under 20 years of age (n = 11,085), those with missing urine mVOCs data (n = 16,539), and those lacking muscle mass data (n = 2988) or covariate data (n = 165). Consequently, 2908 volunteers met the criteria for inclusion in the study.

Exposure ascertainment

Data on 18 urine mVOCs were consistently detected and reported across four rounds of NHANES conducted in the years 2011–2012, 2013–2014, 2015–2016, and 2017–2018. The quantification of urinary mVOCs concentration was achieved using ultra-high performance liquid chromatography combined with electrospray ionization tandem mass spectrometry (UPLC-ESI/MSMS)[27]. Values of mVOCs below the lower detection limit (LLOD) were substituted with LLOD/$\sqrt{2}$[28]. The complete names and LLOD values of the 18 mVOCs are detailed in Table S1.

The detection rates of 18 urine mVOCs were calculated (Table S2), and in order to enhance the robustness and reliability of the findings, *N*-Acetyl-*S*-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (2CaHEMA), *N*-Acetyl-*S*-(2-hydroxyethyl)-L-cysteine (2HEMA), and *N*-Acetyl-*S*-(n-propyl)-L-cysteine (BPMA) were omitted due to their detection rates falling below 80% in four consecutive cycles. In this study, 15 urinary mVOC concentrations were assessed as exposure variable ultimately, including 2-Methylhippuric acid (2MHA), 3- and 4-Methylhippuric acid (34MHA), *N*-Acetyl-*S*-(2-carbamoylethyl)-L-cysteine (AAMA), *N*-Acetyl-*S*-(*N*-methylcarbamoyl)-L-cysteine (AMCC), 2-Aminothiazoline-4-carboxylic acid (ATCA), *N*-Acetyl-*S*-(benzyl)-L-cysteine (SBMA), *N*-Acetyl-*S*-(2-carboxyethyl)-L-cysteine (CEMA), *N*-Acetyl-*S*-(2-cyanoethyl)-L-cysteine (CYMA), *N*-Acetyl-*S*-(3,4-dihydroxybutyl)-L-cysteine (DHBMA), *N*-Acetyl-*S*-(2-hydroxypropyl)-L-cysteine (2HPMA), *N*-Acetyl-*S*-(3-hydroxypropyl)-L-cysteine (3HPMA), Mandelic acid (MA), *N*-Acetyl-*S*-(4-hydroxy-2-butenyl)-L-cysteine (MHBMA3), Phenylglyoxylic acid (PGA) and *N*-Acetyl-*S*-(3-hydroxypropyl-1-methyl)-L-cysteine (HPMMA). The maternal form and corresponding official abbreviations are displayed in Table S3.

Urinary creatinine serves as a fundamental indicator of renal function and human metabolic capability. Adjusting for creatinine levels helps mitigate potential biases in urinary mVOCs concentrations stemming from external factors, such as individual metabolic capacity. In the NHANES dataset, urinary creatinine and mVOCs concentrations were measured in units of mg/dL and ng/mL, respectively. The adjusted concentration of urinary mVOCs in relation to creatinine levels is expressed in units of ng/ (0.01 mg Cr). Furthermore, the urine creatinine-adjusted mVOCs underwent a natural logarithmic transformation (ln transformation) in order to achieve a normal distribution of data.

Outcome ascertainment

The National Institutes of Health (NIH) guidelines were utilized in this study to establish a definition for muscle disease, with the criteria being a ratio of appendicular skeletal muscle mass (ASM) to body mass index (BMI) of < 0.789 in men and < 0.512 in women[29]. ASM refers to the total lean body mass in the arms and legs, excluding bone. Muscle mass measurements were conducted using a Hologic QDR-4500A fan-beam densitometer through whole-body DXA scanning. To ensure the safety and accuracy of the study, individuals who were pregnant within the past 7 days, weighed over 136 kg, and were taller than 196 cm were excluded from the DXA examination.

Covariates and mediators

Controlled for potential confounding factors encompass social demographic data (age, gender, race, education level, family income), lifestyle behavior characteristics (BMI, sedentary behavior, physical activity, total caloric intake, smoking status, alcohol consumption), presence of comorbidities such as hypertension, diabetes, cardiovascular disease (CVD), cancer, chronic kidney disease (CKD), and blood lipid levels. Hypertension is defined as an individual diagnosed by a healthcare provider as having high blood pressure, or having a persistent systolic blood pressure > = 140 mmHg or diastolic blood pressure > = 90 mmHg, or an individual taking antihypertensive medications. People with diabetes are defined as those who answered "yes" to both of the following questions :(a) fasting blood glucose level > = 126 mg/dL or glycosylated hemoglobin concentration > = 6.5%; (b) "Has your doctor diagnosed you with diabetes?" "or" Are you currently taking insulin? CVD encompasses conditions such

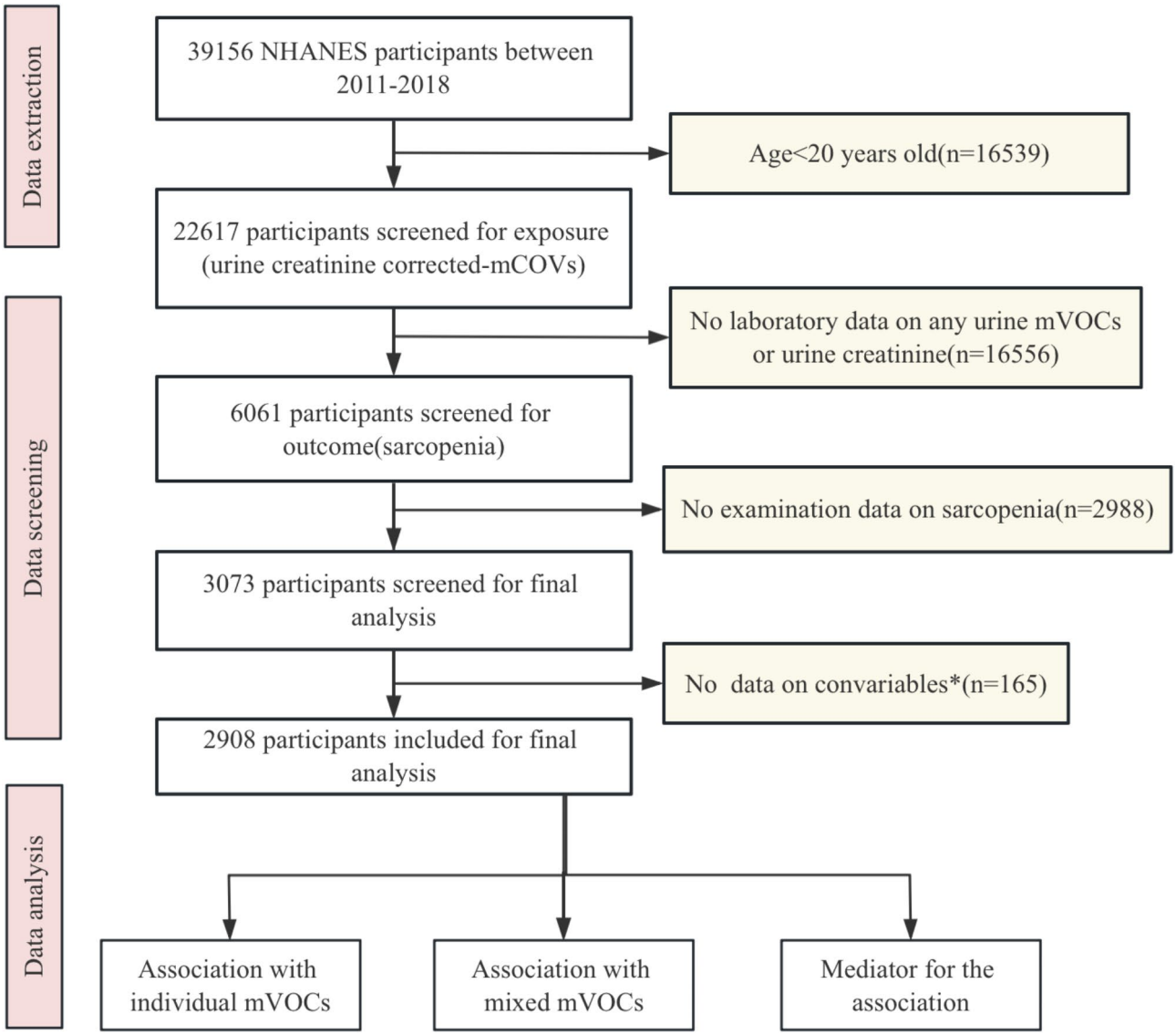


Fig. 1. Flow chart of participants selected for final analysis. *Covariates included sociodemographic data (age, sex, race, education level, family income), lifestyle characteristics (body mass index, sedentary behavior, physical activity, total caloric intake,smoking status, alcohol consumption), presence of comorbidities (hypertension, diabetes, cardiovascular disease, cancer, chronic kidney disease), and lipid profile. NHANES, National Health and Nutrition Examination Survey; mVOCs, metabolites of volatile organic compounds.

as coronary heart disease, angina, heart failure, and stroke. Participants who received a diagnosis of cancer or any type of tumor were classified as having cancer. The CKD-EPI creatinine equation was utilized to determine an estimated glomerular filtration rate (eGFR), with an eGFR < 60 ml/(min·1.73 m^2) or a urine albumin-to-creatinine ratio (UACR) > 30 mg/g indicating a diagnosis of CKD. In accordance with prior research, various markers were used to assess oxidative stress, including serum bilirubin and γ-glutamyltransferase (GGT), and chronic inflammation was determined by white blood cell (WBC) counts and serum alkaline phosphatase (ALP). Studies using NHANES commonly measure oxidative stress and inflammation with these parameters[30,31].

Statistical analysis

The participants were categorized according to the presence of sarcopenia. A Wilcoxon rank sum test and a Chi-square test were used for the descriptive analysis to examine differences between the two groups. Median and interquartile range (IQR) were utilized for continuous variables, while percentages were used for categorical variables. The relationship between sarcopenia and urinary mVOCs was investigated by three distinct weighted multivariate logistic regression models. To visualize the relationship, restricted cubic spline (RCS) curves were used. In order to investigate the co-exposure patterns and co-toxic effects of mVOCs, the Spearman correlation test was used.

Volatile organic compounds frequently coexist in intricate combinations within the environment, resulting in a significant level of collinearity and correlation among mVOCs. In order to address this potential collinearity, we employed a multi-covariate-adjusted least absolute shrinkage and selection operator (LASSO) regression model to pinpoint crucial mVOCs linked to the susceptibility of sarcopenia[32]. The quantile-based g computing model (qgcomp) was employed to examine the collective impact of mixed exposure and key mVOCs on sarcopenia[33]. This model enables pollutants within the mixture to exhibit positive, negative, and neutral effects simultaneously, facilitating the estimation of the cumulative influence of selected key mVOCs on sarcopenia. Additionally, it allows for the evaluation of the relative contribution of each component of the mixture in both positive and negative directions, offering the benefits of minimal deviation and consistent outcomes.

The metabolites identified through LASSO regression were subsequently integrated into the bayesian kernel machine regression (BKMR) model to investigate the collective influence of mixed mVOC exposure on sarcopenia and the relative significance of individual metabolites[34]. Markov Chain Monte Carlo (MCMC) was used to generate 10,000 iterations of the model following adjustment for all covariates. The model examined the effect of a specific quartile of exposure levels compared to the median, analyzing the exposure–response curve for each metabolite while maintaining the remaining mVOC exposure at the median level. Additionally, the study examined the variations in outcome association for each metabolite at the 75th and 25th percentiles while fixing the remaining variables at the 25th, 50th, and 55th percentiles, respectively. The BKMR model samples the contribution of each variable through the MCMC method to generate the importance distribution of each variable. Posterior Inclusion Probability (PIP) is the posterior probability value of the distribution. The higher the PIP, the more important the variable is to the result in the model. PIP takes into account the uncertainty of the model and provides a more comprehensive assessment of the importance of the variable.

In order to examine the potential mediating role of inflammatory markers (leukocyte and alkaline phosphatase) and oxidative stress markers (serum bilirubin and γ-glutamyltransferase) in the relationship between mVOCs and sarcopenia, we used the "mediation" package in R to conduct our mediation analysis. The mVOCs identified as having the greatest impact, as determined by the qgcomp and BKMR models, were considered as autonomous predictors, indicators of inflammation and oxidative stress as mediators, and sarcopenia as outcome variables. Average of direct effects (ADE), average causal mediation effects (ACME), and total effects (TE) were computed using a non-parametric bootstrapping method (100 resamples).

Results

Population characteristics

According to Table 1, participants in the study are described by their demographic and health characteristics. Out of the total sample of 2,908 individuals, 246 were identified as having sarcopenia. Participants with sarcopenia were more likely to be older, of Mexican descent, have a lower education level and household income, exercise less, consume fewer calories, smoke less, consume less alcohol, and be obese compared to those without sarcopenia. And they exhibited a higher likelihood of presenting with high blood pressure, diabetes mellitus, cardiovascular diseases, cancer, chronic kidney disease, low high-density lipoprotein (HDL) levels. Table S4 shows the comparison of baseline characteristics between the included and excluded populations. Except for race and drinking status, there were no significant differences in other characteristics, suggesting that the included population was well representative.

Individual mVOCs and sarcopenia risk

The relationship between individual mVOCs and sarcopenia was examined using a logistic regression model. Following adjustment for all demographic and health-related variables outlined in the methodology, it was determined that DHBMA, 3,4MHA, CEMA, 3HPMA and ATCA exhibited statistically significant positive associations with an elevated likelihood of sarcopenia. For each incremental unit change in the transformed Ln variable, the OR (95% CI) for sarcopenia were found to be 1.86 (1.25, 2.90), 1.30 (1.07, 1.58), 1.36 (1.02, 1.81), 1.17 (1.03, 1.37), and 1.26 (1.01, 1.56) as illustrated in Fig. 2. Conversely, the remaining components of mVOCs did not exhibit statistically significant effects. Table S5 presents the logistic regression model utilizing quartiles of logarithmically transformed VOC metabolites. Specifically, 3,4MHA (Q3, Q4), ATCA (Q4), CEMA (Q3, Q4), CYMA (Q2, Q3), DHBMA (Q4), and 3HPMA (Q3, Q4) exhibit positive correlations with an elevated risk of sarcopenia.

The relationship between mVOCs and sarcopenia was analyzed using multivariable-adjusted restricted cubic spline curves (Figure S1). Linear associations were observed between DHBMA, 3HPMA, ATCA and 3,4MHA with sarcopenia (overall $p < 0.05$; nonlinear $p > 0.05$), while nonlinear associations were found between CEMA and sarcopenia (overall $p < 0.05$; nonlinear $p < 0.05$). No significant correlations were observed between other components of mVOCs and sarcopenia (overall $p > 0.05$).

LASSO regression for screening key mVOCs

Spearman analysis revealed significant positive correlations among all mVOCs, with correlation coefficients ranging from 0.07 to 0.86 (Figure S2). Subsequently, a LASSO model was employed to identify key mVOCs metabolite components that exhibit stronger associations with sarcopenia (Fig. 3). Figure 3a illustrates the relationship between the mean square error change (MSE) and the logarithmic transformation penalty parameter (λ) in the LASSO regression analysis. An optimal λ value of 0.00186 ($\log(\lambda) = -6.28$) was selected based on the minimum MSE criterion. At this point, the model has the best fit. Figure 3b illustrates the lasso regression path that identified a subset of mVOCs deemed more pertinent in the optimal LASSO model. Specifically, nine rows of mVOCs intersected with the dashed lines in the panel, including 3, 4MHA, AAMA, AMCC, ATCA, SBMA, DHBMA, 2HPMA, 3HPMA, and MHBMA3, which were identified as mVOCs with greater relevance to sarcopenia.

Characteristic	Non-sarcopenia (n = 2662)	Sarcopenia (n = 246)	*p*-value
Age, (years)	39 (29, 49)	46 (32, 55)	< 0.001
Gender, n (%)			0.6
Male	1,330 (50%)	125 (51%)	
Female	1,333 (50%)	120 (49%)	
Race, n (%)			< 0.001
Mexican American	337 (12.7%)	83 (33.9%)	
Other Hispanic	287 (10.8%)	43 (17.6%)	
Non-Hispanic white	919 (34,5%)	55 (22.4%)	
Non-Hispanic Black	604 (22.7%)	16 (6.5%)	
Other/multiracial	516 (19.4%)	48 (19.6%)	
Education level, n (%)			< 0.001
Less than 9th grade	139 (5.2%)	39 (15.9%)	
9–11th grade (includes 12th grade with no diploma)	305 (11.5%)	33 (13.5%)	
High school graduate/GED	569 (21.4%)	67 (27.3%)	
Some college or AA	868 (32.6%)	61 (24.9%)	
College graduate or above	782 (29.4%)	45 (18.4%)	
PIR, (%)			0.021
< 1	558 (21%)	59 (24.1%)	
1 ~ 4	1,353 (50.8%)	141 (57.6%)	
≥ 4	752 (28.2%)	45 (18.4%)	
Drinking, (%)			0.004
Never drink	643 (24.1%)	87 (35.5%)	
1–5/ month	1,370 (51.4%)	132 (53.9%)	
5–10/ month	284 (10.7%)	10 (4.1%)	
10 + / month	366 (13.7%)	16 (6.5%)	
Smoking, (%)			0.034
Never smoke	1,626 (61.1%)	150 (61.2%)	
Former smoker	435 (16.3%)	57 (23.3%)	
Current smoker	602 (22.6%)	38 (15.5%)	
Sedentary time, (minutes)	360 (240, 540)	300 (240, 480)	0.2
Physical activity, (%)			0.001
0 MET-min/week	659 (21%)	91 (34%)	
0–599 MET-min/week	292 (11%)	29 (9.5%)	
> 600 MET-min/week	1,711 (68%)	126 (57%)	
Energy intake, (g/day)	2,066 (1,575, 2,647)	1,852 (1,447, 2,528)	0.016
BMI, (kg/m^2)	27 (24, 32)	34 (29, 39)	< 0.001
Hypertension, (%)	739 (27.8%)	93 (38%)	0.016
Diabetes, (%)	324 (12.2%)	59 (24.1%)	< 0.001
CVD, (%)	94 (3.5%)	19 (7.8%)	0.004
Cancer, (%)	99 (3.7%)	16 (6.5%)	0.006
CKD, (%)	238 (8.9%)	35 (14.3%)	0.026
HDL-C, (mg/dl)	51 (42, 62)	46 (40, 56)	0.003
TC, (mg/dl)	187 (162, 215)	188 (169, 215)	0.4

Table 1. Baseline characteristics of included subjects. The median and interquartile range for continuous variables: the *p*-value was calculated by the Wilcoxon rank-sum test. % for categorical variables: the *p* value was calculated by weighted chi-square test. PIR, poverty impact ratio; MET, metabolic equivalent; BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

Mixed VOC exposure and sarcopenia in the qgcomp model

Following the utilization of LASSO regression screening, an analysis of the qgcomp model was conducted to assess the overall impact of a mixture of mVOCs on sarcopenia. The findings revealed that for each quantile change in the mVOCs mixture, there was a corresponding increase in the risk of sarcopenia (OR = 1.47, *P* = 0.003) (Fig. 4). Furthermore, DHBMA, 3HPMA, ATCA and 3,4MHA emerged as the four most significant pollutant components in the positive direction, with respective contribution weights of 31.7%, 26.1%, 18.0%, and 14.0% (Table S6).

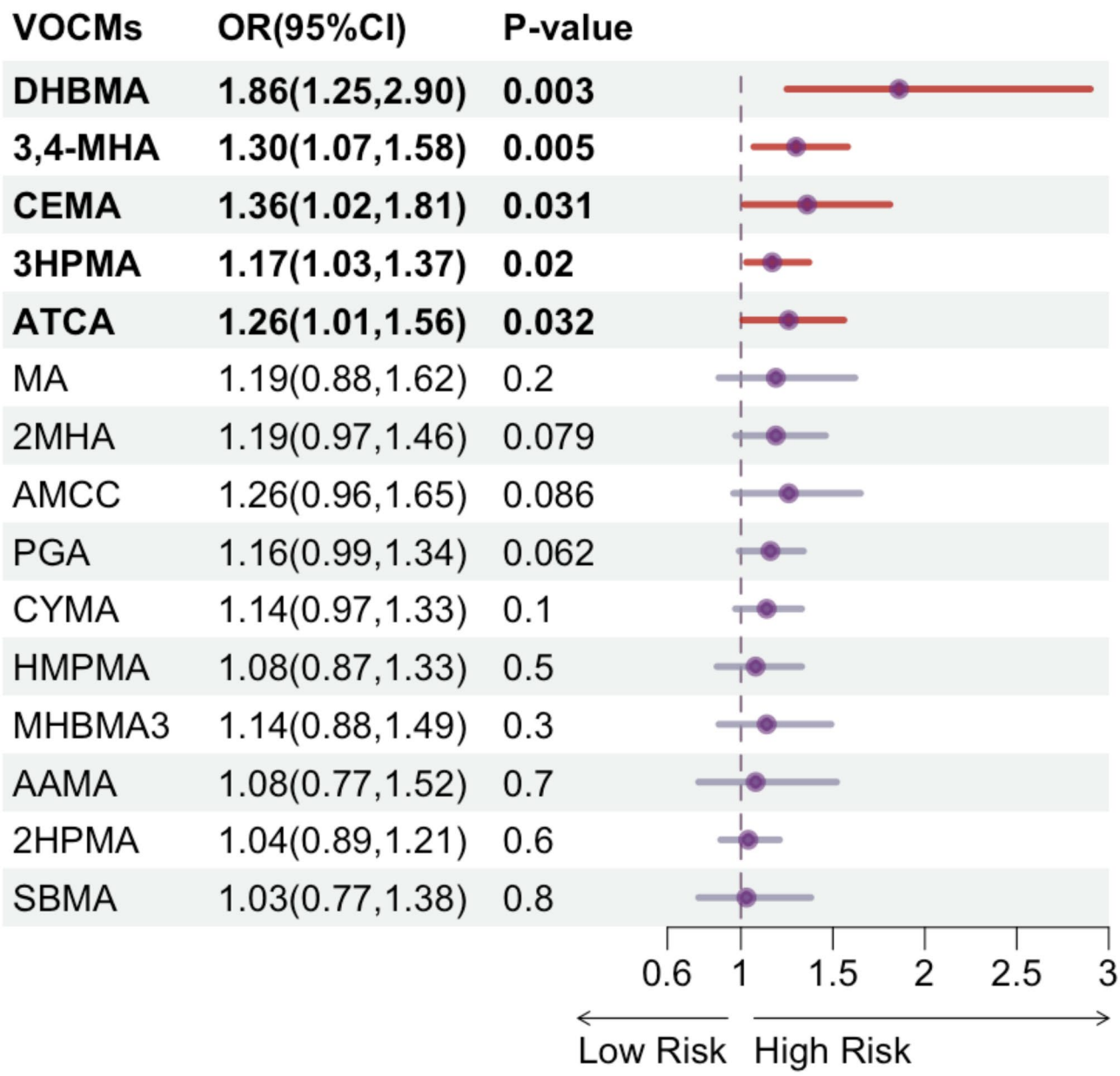


Fig. 2. Association of individual urinary mVOCs with sarcopenia risk. All mVOCs were adjusted for urinary creatinine and then logarithmized. Covariates included sociodemographic data (age, sex, race, education level, family income), lifestyle characteristics (body mass index, sedentary behavior, physical activity, total caloric intake, smoking status, alcohol consumption), presence of comorbidities (hypertension, diabetes, cardiovascular disease, cancer, chronic kidney disease), and lipid profile. VOCM, volatile organic compound metabolites; OR, odds ratio; CI, confidence interval; 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; SAMA, *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-butenyl)-L-cysteine; PGA, Phenylglyoxylic acid; HPMMA, *N*-Acetyl-*S*-(3-hydroxypropyl-1-methyl)-L-cysteine.

Mixed mVOC exposure and sarcopenia in the BKMR model

An assessment of the collective impact of mVOC mixtures on sarcopenia was performed using the BKMR model, as depicted in Fig. 5. Analysis in Fig. 5a indicates a notable escalation in the risk of sarcopenia when all mVOCs are at or above the 55th percentile compared to the 50th percentile. Notably, when controlling for other metabolites at the median level, the levels of DHBMA, 3HPMA, ATCA and 3,4MHA exhibited a statistically significant positive correlation with the risk of sarcopenia, as illustrated in Fig. 5b. PIPs for these associations

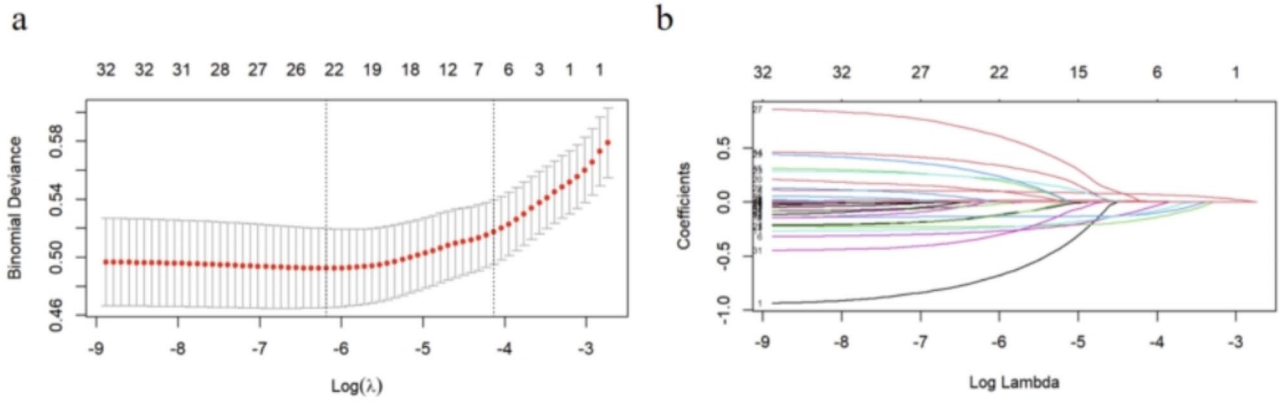


Fig. 3. LASSO regression analysis of 15 mVOCs associated with sarcopenia. Annotation a indicates the association between the change in MSE and the penalty parameter (λ) of the logarithmic transformation. The red dashed line and its error bars are the values of the mean MSE and the corresponding 95% CI. The black dashed line on the left is the optimal value of λ to calculate the minimum MSE, while the black dashed line on the right is the λ value in the simplest model obtained at one standard error of the minimum MSE. Annotation b corresponds to the screening path of mVOCs associated with sarcopenia risk. LASSO, least absolute shrinkage and selection operator; mVOCs, metabolites of volatile organic compounds. The independent variables include 15 mVOC concentrations with creatinine correction and logarithmic transformation. Covariates included sociodemographic data (age, sex, race, education level, family income), lifestyle characteristics (body mass index, sedentary behavior, physical activity, total caloric intake, smoking status, alcohol consumption), presence of comorbidities (hypertension, diabetes, cardiovascular disease, cancer, chronic kidney disease), and lipid profile.

were found to be 0.651, 0.292, 0.225 and 0.148 respectively, as shown in Fig. 5d. The study found a significant inverse relationship between the level of MHBMA3 and the risk of sarcopenia, with a posterior inclusion probability (PIP) of 0.341. Figure 5c illustrates the positive effects of DHBMA, 3HPMA, ATCA and 3,4MHA on sarcopenia while holding the remaining metabolites constant at the 25th, 50th, and 75th percentiles, respectively.

Inflammation and oxidative stress mediate the association between mVOCs and sarcopenia

Table 2 illustrates the intermediary function of inflammatory markers and oxidative stress markers in the correlation between mVOCs and sarcopenia. White blood cell count and bilirubin content are identified as potential mediators. Specifically, white blood cell count significantly mediates the relationship between ATCA, DHBMA, and 3HPMA and sarcopenia, with mediated proportions of 7.6%, 6.3%, and 14% respectively. Additionally, bilirubin significantly mediates the association between ATCA, DHBMA, and 3HPMA and sarcopenia, with mediated proportions of 10.7%, 12.2%, and 15% respectively ($P < 0.05$).

Covariates included sociodemographic data (age, sex, race, education level, family income), lifestyle characteristics (body mass index, sedentary behavior, physical activity, total caloric intake, smoking status, alcohol consumption), presence of comorbidities (hypertension, diabetes, cardiovascular disease, cancer, chronic kidney disease), and lipid profile.

mVOCs, metabolites of volatile organic compounds; 3,4MHA, 3- and 4-Methylhippuric acid; ATCA, 2-Aminothiazoline-4-carboxylic acid; DHBMA, *N*-Acetyl-*S*-(3,4-dihydroxybutyl)-L-cysteine; 3HPMA, *N*-Acetyl-*S*-(3-hydroxypropyl)-L-cysteine.

Stratified analysis

Both qgcomp and BKMR model analyses identified DHBMA, 3HPMA, ATCA and 3,4MHA as the primary monomers contributing to mVOCs components associated with sarcopenia. Subsequently, a subgroup analysis focusing on these monomers was conducted, revealing a consistent positive correlation with sarcopenia across various subgroups, as detailed in Table S7-10. Furthermore, gender and BMI were identified as potential modifiers affecting the impact of ATCA and DHBMA on sarcopenia ($p = 0.023$, $p = 0.048$).

Discussion

Our research is the initial investigation to assess the separate and combined relationships between urinary mVOCs and sarcopenia, along with the potential mediating effects of inflammatory and oxidative stress markers. The primary outcome of our study are as follows: (1) In logistic regression analysis, several mVOCs monomers exhibited a significant positive correlation with the likelihood of sarcopenia. (2) The qgcomp model and the BKMR model indicate a significant positive association between mixed exposure to mVOCs and the risk of sarcopenia. Specifically, DHBMA, 3HPMA, ATCA and 3,4MHA were identified as the four metabolites with the greatest impact, originating from acrolein, 1,3-butadiene, cyanide, and xylene. (3) White blood cell and bilirubin were identified as potential mediators in the relationship between mVOCs and sarcopenia.

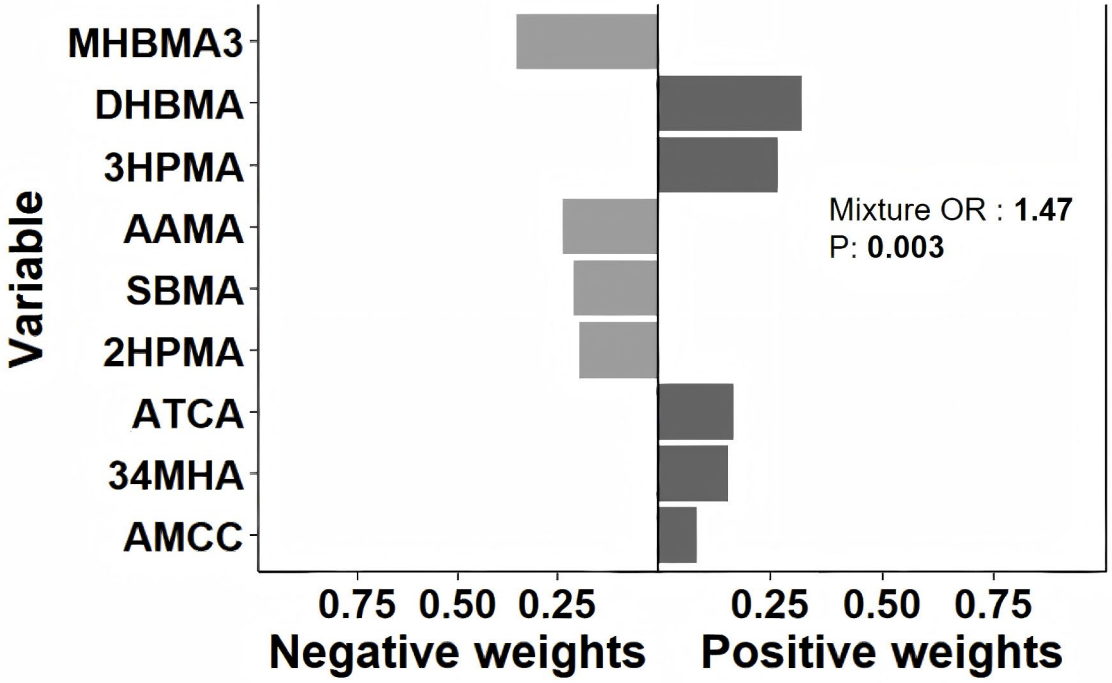
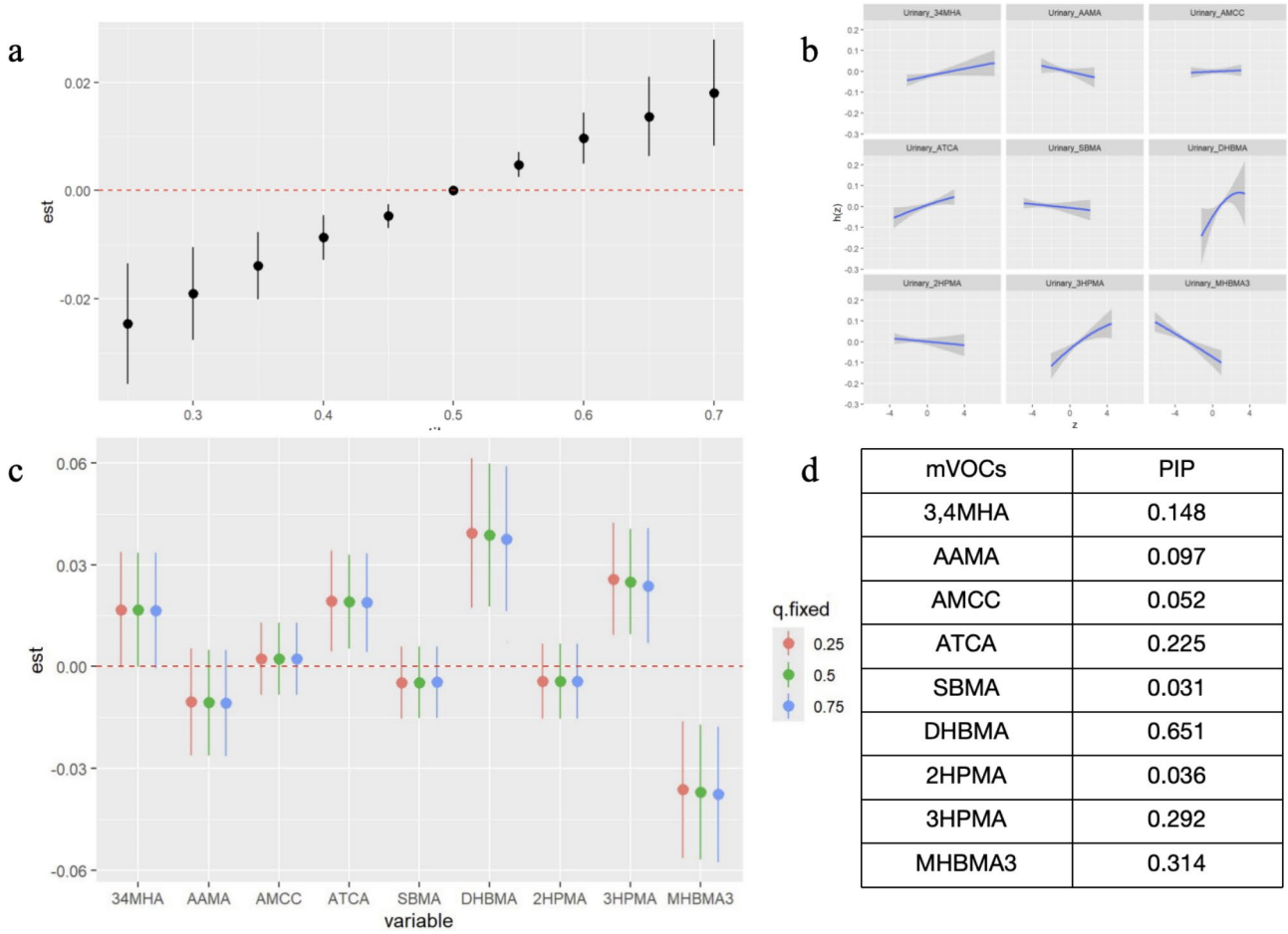


Fig. 4. The qgcomp model established based on the association between the LASSO selected mVOCs mixture and sarcopenia. Adjustments were made based on sociodemographic data (age, sex, race, education level, household income), lifestyle characteristics (body mass index, sedentary behavior, physical activity, total caloric intake, smoking status, alcohol consumption), the presence of comorbidities (hypertension, diabetes, cardiovascular disease, cancer, chronic kidney disease), and lipid profile. LASSO, least absolute shrinkage and selection operator; qgcomp: quantile-g computation; mVOCs, metabolites of volatile organic compounds; 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; SAMA, *N*-Acetyl-*S*-(benzyl)-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; MHBMA3, *N*-Acetyl-*S*-(4-hydroxy-2-butenyl)-L-cysteine.

Our study used three models to address the combined effects of mixed mVOC exposure on sarcopenia. LASSO is a regularization method designed to handle high-dimensional data, especially when predictors exhibit multicollinearity. It selects important variables by reducing the coefficients of less influential predictors to zero. This ensures that only the most relevant variables are retained in the model[35]. In our study, LASSO identified 9 key mVOCs that contribute to sarcopenia risk. Qgcomp is a powerful tool for estimating the combined effects of exposure mixtures. Unlike LASSO, which focuses on individual predictors, qgcomp evaluates the overall impact of adding all exposure factors in a mixture simultaneously. It can resolve collinearity issues between exposures and provide estimates of the total effect of a mixture and the directional contributions of individual components[33]. In our study, qgcomp showed that exposure to mixtures significantly increased the risk of sarcopenia, with specific mVOC (such as DHBMA, 3HPMA, ATCA and 3,4-MHA) making the largest contribution to the overall effect. BKMR is a flexible, non-parametric method for modeling complex non-linear relationships and interactions between variables. Its advantage is that it can simulate nonlinear relationships and interactions in mixtures[34,36]. In our study, BKMR also confirmed the overall mixture effects observed by qgcomp and also highlighted the nonlinearity between specific mVOC. Relationships and interactions are further confirmation and supplement to the qgcomp model.

Recently, there has been a growing global interest in the relationship between environmental pollutants and sarcopenia. A cross-sectional research of 12,723 individuals demonstrated a link between indoor solid fuel usage and prolonged exposure to ambient PM2.5 with an increased risk of sarcopenia in the Chinese adult population[37]. Additionally, Yang et al. discovered a positive correlation between urinary phthalate metabolites and prevalence of sarcopenia in American adults[13]. Jauregui-Zunzunegui et al. discovered that exposure to glyphosate may pose a potential risk for reduced grip strength and heightened physical limitations[38]. Animal studies indicate that acrolein could potentially lead to muscle atrophy and delayed muscle regeneration in mice by impeding the Akt signaling pathway[20] . Nevertheless, there remains a dearth of systematic investigations



mVOCs	PIP
3,4MHA	0.148
AAMA	0.097
AMCC	0.052
ATCA	0.225
SBMA	0.031
DHBMA	0.651
2HPMA	0.036
3HPMA	0.292
MHBMA3	0.314

Fig. 5. BKMR model established based on the association between LASSO-selected mVOCs mixture and sarcopenia. Annotation a shows the association diagram of the overall effect of the mixture with sarcopenia, and estimates the change in sarcopenia risk when all metabolites are fixed at different percentiles at the same time compared with when they are fixed at the median. Annotation b shows the exposure–response cross-section of a single metabolite with sarcopenia when other metabolites are fixed at the median. Annotation c shows the difference in the association of a single metabolite with the outcome of sarcopenia at the 75th and 25th percentiles when the remaining mVOCs metabolites are fixed at the 25th, 50th and 75th percentiles, respectively. Annotation d shows the posterior inclusion probability (PIP) of the BKMR model. Covariates included sociodemographic data (age, sex, race, education level, family income), lifestyle characteristics (body mass index, sedentary behavior, physical activity, total caloric intake, smoking status, alcohol consumption), presence of comorbidities (hypertension, diabetes, cardiovascular disease, cancer, chronic kidney disease), and lipid profile. LASSO: least absolute shrinkage and selection operator; BKMR: bayesian kernel machine regression; mVOCs, metabolites of volatile organic compounds; 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; SAMA, *N*-Acetyl-*S*-(benzyl)-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; MHBMA3, *N*-Acetyl-*S*-(4-hydroxy-2-butenyl)-L-cysteine.

on the association between volatile organic compounds and sarcopenia. Our research conducted a thorough analysis of the correlation between volatile organic compound monomers and mixtures and sarcopenia, ultimately confirmed the positive impact of VOCs on the risk of sarcopenia. This study contributes valuable evidence from an environmental perspective to aid in the prevention of sarcopenia.

Emerging research suggests that inflammation and oxidative stress are closely link to the development of sarcopenia. Studies conducted on animals have demonstrated a notable rise in reactive oxygen species (ROS) levels within the soleus muscle of denervated mice or fasting C2C12 myotubes[39]. Additionally, Sun et al. discovered that IL-6 reduces energy metabolism and activates immune receptors, which contribute to skeletal muscle atrophy[40]. Recent clinical studies have provided evidence indicating elevated levels of bilirubin and γ-glutamyltransferase in individuals with sarcopenia, suggesting a potential link between oxidative stress and the development of sarcopenia [41]. Lee et al. also reported an independent association between higher and white blood cell counts and sarcopenia in Korean populations[23]. Furthermore, exposure to VOCs has been demonstrated to trigger inflammatory and oxidative stress reactions in the body, potentially contributing to various diseases.

Result	mVOCs	Mediator	Indirect effect (*P*-value)	Direct effect (*P*-value)	Total effect (*P*-value)	Mediation proportions
Sarcopenia	3,4MHA	White blood cell	0.000199(0.38)	0.013188(< 0.001)	0.013386(< 0.001)	NA
		Alkaline phosphatase	− 0.000105(0.48)	0.013500(< 0.001)	0.013395(< 0.001)	NA
		Bilirubin	− 0.00079(0.06)	0.014596(< 0.001)	0.013806(< 0.001)	NA
		Gamma glutamyl transferase	− 0.000252(0.18)	0.013866(< 0.001)	0.013614(< 0.001)	NA
	ATCA	**White blood cell**	**0.001075(0.02)**	**0.013077(0.04)**	**0.014151(0.04)**	**7.6%**
		Alkaline phosphatase	− 0.000294(0.24)	0.014431(0.02)	0.014137(0.02)	NA
		Bilirubin	**0.001514(0.04)**	**0.012577(0.02)**	**0.014091(0.02)**	**10.7%**
		Gamma glutamyl transferase	1.64e−05(0.96)	1.46e-02(0.02)	0.0147(0.02)	NA
	DHBMA	**White blood cell**	**0.001981(0.02)**	**0.029344(< 0.001)**	**0.031325(< 0.001)**	**6.3%**
		Alkaline phosphatase	0.001048(0.34)	0.031559(< 0.001)	0.032607(< 0.001)	NA
		Bilirubin	**0.003893(0.04)**	**0.027924(< 0.001)**	**0.031817(< 0.001)**	**12.2%**
		Gamma glutamyl transferase	0.000537(0.24)	0.031365(< 0.001)	0.031902(< 0.001)	NA
	3HPMA	**White blood cell**	**0.001914(0.04)**	**0.011726(0.02)**	**0.01364(0.02)**	**14%**
		Alkaline phosphatase	4.06e−04(0.12)	0.0135(0.02)	0.0139(0.02)	NA
		Bilirubin	**0.00216(0.04)**	**0.01228(0.04)**	**0.01444(0.02)**	**15%**
		Gamma glutamyl transferase	− 0.000114(0.72)	0.01363(0.02)	0.013516(0.02)	NA

Table 2. Mediation analysis between mVOCs and sarcopenia. Bold indicates significant mediating relationships.

Animal studies have demonstrated that exposure to VOCs can lead to a notable elevation levels of ROS, IL-8, IL-4, and white blood cells in lung[24]. Acrolein has been shown to induce toxicity by modulating oxidative stress and apoptosis in human umbilical vein endothelial cells[42]. Pal et al. discovered a significant positive correlation between mVOCs concentration and oxidative stress biomarkers[26]. Given the shared pathological pathway, it is justifiable to investigate the potential correlation between VOC exposure and the development of sarcopenia via inflammation and oxidative stress. Our research revealed that white blood cell count and bilirubin play a significant role in mediating the relationship between ATCA, DHBMA, 3HPMA and sarcopenia. It is hypothesized that exposure to VOCs may heighten the likelihood of developing sarcopenia by inducing inflammation and oxidative stress within the body. It is worth mentioning that although leukocytes and bilirubin are reliable indicators of systemic inflammation and oxidative stress[43,44], these markers may not fully capture the local oxidative stress or inflammatory processes in skeletal muscle. Future studies should explore muscle-specific biomarkers, such as 4-HNE or cytokine expression in muscle tissue, to more directly assess the effects of exposure to mVOCs on sarcopenia. In addition, some pathological mechanisms not mentioned in this study, such as mitochondrial disorders, may also play an important mediating role in the association between mVOC and sarcopenia. Mitochondrial dysfunction is associated with skeletal muscle atrophy, and its mechanisms include impaired ATP production, increased ROS, and interrupted cell signaling pathways. Secondly, mVOC metabolism can cause mitochondrial disorders[45]. For example, volatile organic compounds such as acrolein and benzene can induce mitochondrial damage, leading to apoptosis and insufficient cellular energy. This suggests that mitochondrial damage may be a potential pathway for mVOCs to cause muscle atrophy[46]. Future studies should explore these pathways to provide a more comprehensive understanding of pathophysiology.

The multivariate-adjusted RCS curve showed that 3,4-MHA, DHBMA, ATCA, and 3HPMA showed a significant linear relationship with sarcopenia, and the risk of sarcopenia showed a linear upward trend with the increase of exposure to the corresponding maternal pollutants, which indicated that These pollutants may increase the risk of sarcopenia through cumulative dose-related mechanisms (such as oxidative stress, inflammation, and interference with protein metabolism)[26,47–49]. For CEMA and 2HPMA, the curves show an inverted "U"-shaped relationship, whereby moderate levels of CEMA and 2HPMA exposure present the greatest risk, while low or high exposure levels present lower risks. This may be because at moderate exposure levels, metabolites may reach a critical threshold for inducing oxidative stress or inflammation, thereby maximizing the effects on muscle function. At high exposure levels, the body may alleviate the toxicity of metabolites by activating antioxidant or detoxification mechanisms, and individuals with high exposure levels may have stronger health adaptation capabilities (survivor effect) thereby reducing risks[50,51]. Although the overall effect of 2HPMA was non-significant, the significant nonlinear trend of 2HPMA suggested that the potential effect deserves further exploration. Future studies can focus on exploring the physiological and pathological mechanisms of the linear and nonlinear relationships between various mVOCs and sarcopenia.

Considering that aging, malnutrition, lack of physical activity, and concurrent chronic illnesses are prevalent factors contributing to sarcopenia, we conducted a subgroup analysis stratified by various demographic and health-related variables. Our findings revealed a stronger association between mVOCs and sarcopenia in females and individuals with obesity. The underlying mechanism remains uncertain; however, it is posited that women employed in the cosmetics service sector may be particularly vulnerable to volatile organic compound exposure. Louis et al. discovered a higher level of mVOCs in the urine of female hair salon workers compared to non-salon workers[52]. Furthermore, obesity triggers the activation of macrophages, mast cells, and T lymphocytes, leading to a state of low-grade inflammation in the body that contributes to increased fat mass and decreased

muscle mass[53]. This inflammatory response, combined with exposure to mVOCs, may contribute to muscle mass loss. Further study is needed to clarify the regulatory mechanisms of gender and BMI in relation to VOCs and sarcopenia.

Our research possesses numerous strengths. Primarily, this study is believed to be the initial exploration of the correlation between exposure to VOCs mixture and sarcopenia. We incorporated a substantial sample from the NHANES and employed various statistical models to systematically elucidate the association between exposure to individual VOCs and combinations of VOCs with sarcopenia. Additionally, we identified several components of mVOCs with the highest contribution weights. Furthermore, we controlled for numerous covariates and conducted stratified analysis to mitigate the influence of confounding variables. Utilizing creatinine-corrected and logarithmized urine mVOCs concentrations as proxies for VOC exposure levels bolstered the methodological robustness of our study. The findings have the potential to enhance public health awareness and offer novel strategies for sarcopenia prevention.

Nevertheless, it is important to acknowledge the limitations of our study. Firstly, as a cross-sectional observational study, causal relationships cannot be inferred. This limitation raises the possibility of reverse causation, whereby individuals with sarcopenia may engage in behaviors or environments that result in higher VOC exposure. Secondly, reliance on self-reported variables may introduce subjective bias into the data. Third, due to the variety of pollutant components in the air, other pollutants that were not included in the study, such as PM2.5 and solid fuels, may also affects the prevalence of sarcopenia, which may bring confounding effects. Finally, since NHANES is data from the American population, extrapolating the research conclusions to different populations requires caution. More large-sample cross-regional prospective studies are still needed in the future to overcome the above limitations.

Conclusions

In conclusion, our study demonstrated that mixed exposure to VOCs was associated with an increased risk of sarcopenia, with DHBMA, 3HPMA, ATCA and 3,4MHA identified as the primary metabolic components driving this association. Furthermore, inflammation and oxidative stress were found to partially mediate the observed positive relationship between VOC exposure and increased risk of sarcopenia. These findings offer novel perspectives on the potential risks of sarcopenia stemming from environmental pollution, and further prospective investigations should be conducted in the future to validate our findings.

Data availability

The datasets used for these analyses are publicly available (https://www.cdc.gov/nchs/nhanes/index.htm).

Received: 5 August 2024; Accepted: 17 March 2025
Published online: 28 March 2025

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Acknowledgements

The authors thank to Chengyuan Tang (The second Xiangya Hospital) for his work in nhanes R package, makes it easier for us to explore the NHANES databases.

Author contributions

Conceptualization and Writing—original draft: W.T.; Formal analysis and Visualization: T.T.C.; Software and Data curation: Z.X.L; Supervision and Writing—review and editing: J.X.C. All authors have read and agreed to the published version of the manuscript. All authors reviewed the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-94622-w.

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