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A Healthy Lifestyle and the Association Between VOC Exposure and Cardiovascular Disease in US Adults

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Abstract

Background: Volatile organic compounds (VOCs) are linked to higher cardiovascular disease (CVD) prevalence, and it remains unknown whether a healthy lifestyle modifies this association. **Methods**: This study included 5581 adults from NHANES 2011–2020. We quantified 18 urinary VOC metabolites and constructed a 0–4 healthy lifestyle score based on smoking, alcohol intake, diet and physical activity. Survey-weighted logistic regression and the relative excess risk due to interaction (RERI) were applied. **Results**: Higher VOC levels correlated with elevated CVD prevalence, whereas a higher lifestyle score was associated with lower CVD prevalence (OR = 0.80 per 1-point increment; 95% CI, 0.67–0.95). With the low-exposure/favorable-lifestyle group as the reference, significant additive interactions were found for AAMA (RERI 1.42; 95% CI, 0.63–2.21), 3HPMA (RERI 1.28; 95% CI, 0.62–1.94), and CYMA (RERI 1.33; 95% CI, 0.48–2.18). No significant interactions existed among non-smokers (all $p > 0.10$), with reversed estimates for AAMA and 3HPMA. **Conclusions**: In this cross-sectional analysis, we observed significant additive interactions between a favorable lifestyle and three urinary VOC metabolites (AAMA, 3HPMA, and CYMA) in relation to prevalent CVD. However, this difference was based on small numbers of CVD cases and is largely attributable to the smoking component; there was no evidence of an interaction among non-smokers. These results should be considered preliminary and require prospective validation.

Keywords: volatile organic compounds; healthy lifestyle; cardiovascular disease; NHANES; additive interaction; environmental exposure

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, accounting for 19.2 million deaths and 437 million DALYs in 2023—a 1.4-fold increase since 1990. An estimated 79.6% of this burden is attributable to modifiable risk factors, and CVD etiology

involves complex interactions between genetic, environmental, and behavioral determinants [1–4]. Among environmental risks, exposure to volatile organic compounds (VOCs) has drawn increasing attention due to its potential links to CVD [5,6]. VOCs are released from diverse sources, with human exposure occurring primarily via inhalation, dermal contact, and ingestion [7–9]. Urinary VOC metabolites are reliable biomarkers of recent integrated personal exposure [10]. Specific metabolites (e.g., from acrolein, benzene, and 1,3-butadiene) have been associated with an increased risk of hypertension, metabolic syndrome, and ischemic heart disease [11–13]. Mitigating disease burden from environmental exposures remains a public health challenge; beyond source control, identifying modifiable individual-level protective factors is of substantial value [14].

The World Health Organization and major guidelines emphasize that combined healthy lifestyle behaviors are cost-effective for reducing CVD burden [15,16]. While studies have examined independent associations between lifestyle factors and VOC exposure and CVD risk, important gaps remain. Most prior research examined these factors—such as smoking [17], alcohol consumption [18], diet [19], and physical activity [20]—in isolation, lacking a comprehensive metric. Moreover, whether the association between VOC exposure and CVD differs across levels of a composite healthy lifestyle score remains unclear. Determining whether this association varies by lifestyle category would therefore be informative for the interpretation of joint exposure–behavior patterns.

To address these gaps, we used nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to examine the interaction and joint effects of a healthy lifestyle score and VOC exposure on CVD prevalence, aiming to inform integrated prevention strategies.

2. Materials and Methods

2.1. Study Population

We analyzed NHANES 2011–2020, a serial cross-sectional survey conducted by the National Center for Health Statistics using a stratified, multistage probability sampling design representative of the U.S. civilian non-institutionalized population. The analytic sample comprised 5581 adults (aged ≥ 20 years) with complete data on VOC metabolites, lifestyle, and CVD (Figure S1). The NHANES protocol was approved by the National Center for Health Statistics Research Ethics Review Board, and all participants provided written informed consent. This study was a secondary analysis of publicly available, de-identified data and did not require additional ethical approval. The authors did not have access to information that could identify individual participants during or after data collection.

2.2. Urinary VOC Metabolites

Urinary VOC metabolites are reliable biomarkers of recent exposure, with longer biological half-lives and greater stability than blood measurements [21]. Concentrations of 18 urinary VOC metabolites were quantified using ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-ESI-MS/MS) [22]. Values below the limit of detection (LOD) were imputed as LOD/$\sqrt{2}$. All concentrations were creatinine-corrected and expressed as μg/g Cr. Eighteen urinary VOC metabolites were included in the final analysis (Table S1).

2.3. Lifestyle Factors and Other Covariates

Based on WHO recommendations, a healthy lifestyle score (0–4) was constructed from four modifiable factors: smoking, alcohol consumption, physical activity, and diet [23]. Data were obtained from questionnaires and 24-h dietary recalls. Each healthy behavior scored 1 (Table S2); for diet and physical activity, healthy levels were defined by relative dis-

tributions within the sample rather than by absolute guideline thresholds. The scores were then summed (range: 0–4). This additive score has been validated in large cohorts [24,25]. Although the simple additive lifestyle score has been widely used, it assumes equal weight for each component [26,27]. To improve statistical power, scores 0–1 were combined as "unfavorable," score 2 as "intermediate," and 3–4 as "favorable." Because the simple additive score assumes equal importance of the four lifestyle factors, which may not hold, we additionally constructed a weighted healthy lifestyle score in a sensitivity analysis, weighting each component by the beta-coefficient of its association with prevalent CVD in the regression model [28]. For the interaction analyses, the weighted score was categorized into tertiles based on sample-specific cut-points (low, intermediate, and high). For the non-smoker analysis, the smoking component was removed, yielding a 0–3 score; scores of 0, 1, and 2–3 were classified as unfavorable, intermediate, and favorable, respectively.

Covariates included age, sex, self-reported race/ethnicity, marital status, education, PIR, and self-reported hypertension or diabetes. Race/ethnicity was included as covariates, not as biological constructs. BMI was calculated from examination data. In a sensitivity analysis (Model 7), log-transformed serum cotinine was additionally included as a covariate to account for tobacco smoke exposure.

2.4. Cardiovascular Disease

CVD was defined as a positive self-reported medical diagnosis of any of the following conditions: congestive heart failure, coronary heart disease, angina, heart attack, or stroke. Data were collected via in-home interviews conducted by trained staff using a Computer-Assisted Personal Interview (CAPI) system to enhance accuracy and reliability.

2.5. Statistical Analysis

All analyses accounted for NHANES's complex survey design using cycle-specific weights (WTSA2YR for 2011–2016; WTSAPRP for 2017–2020) with pooled weights for multi-cycle analyses [29]. Missing covariates (<10%) were imputed using chained equations [30]. Continuous variables are presented as weighted means with 95% Cis, and categorical variables are presented as unweighted N with weighted percentages. Group comparisons were performed using linear regression (continuous) and the Rao–Scott chi-square test (categorical).

A progressive strategy was employed to evaluate the VOC–CVD association. Survey-weighted logistic regression was used with sequential adjustment in four models: crude (unadjusted), model 1 (adjusted for age, sex, and race/ethnicity), model 2 (further adjusted for marital status, education, PIR, BMI, and history of hypertension or diabetes), and model 3 (additionally adjusted for healthy lifestyle). Metabolites were retained if they were significantly associated with CVD or were the metabolite most strongly associated with CVD among those derived from the same parent compound. Nonlinearity was tested using restricted cubic splines with 4 knots. VOC concentrations were categorized into quartiles (Q4 = highest) and dichotomized as high (Q4) versus low (Q1–Q3).

The core interaction analysis included the following: First, weighted partial Spearman correlation coefficients between the healthy lifestyle score and each VOC concentration were calculated to evaluate overall correlation. Second, analyses were stratified by VOC exposure level (high/low) to examine the association between the three-category lifestyle variable and CVD prevalence. Third, multiplicative interaction was assessed via the product term (OR and 95% CI). The additive interaction between VOC exposure and lifestyle was quantified using the relative excess risk due to interaction (RERI), with 95% confidence intervals (CIs) estimated via the delta method according to the Hosmer–Lemeshow approach [31]. The joint exposure–lifestyle variable was re-parameterized into a 2 × 3 factorial structure

(2 VOC exposure levels × 3 lifestyle categories), with the stratum combining the lowest VOC exposure category and the most favorable lifestyle category serving as the reference category [32]; this specification was made a priori rather than on the basis of observed risk in these data, and it does not imply that this stratum had the lowest observed risk. With this reference, a positive RERI indicates that the joint association of high exposure and an unfavorable lifestyle exceeds the sum of their separate associations.

Marginal effects analysis was used to visualize the predicted probability of CVD by VOC concentration across lifestyle groups [33]. Finally, to assess joint effects, participants were classified into six groups based on VOC exposure (high/low) and lifestyle (unfavorable/intermediate/favorable). Using the "high VOC exposure & unfavorable lifestyle" group as reference, the odds of CVD for the remaining groups were estimated.

Analyses stratified by sex, race, age, and hypertension/diabetes were performed. In the sensitivity analyses, (1) hypertension/diabetes was excluded; (2) a stricter binge-drinking definition was established [34]; (3) weighted lifestyle scores; were employed (4) individual lifestyle components were used; (5) an additional adjustment for log-transformed serum cotinine was made; and (6) a restriction to non-smokers (serum cotinine < 10 ng/mL) using a smoking-free lifestyle score was applied [35]. In this restricted analysis, the quartile cut-points defining VOC exposure, and hence the threshold for the high-exposure (Q4) category, were recalculated within the non-smoker subsample rather than inherited from the full analytic sample.

All statistical tests involving multiple comparisons were adjusted for the false-discovery rate using the Benjamini–Hochberg method [36]. Analyses used SAS 9.4 and R 4.5.1; two-sided $p < 0.05$ was significant.

3. Results

3.1. Participant Characteristics

Among the 5581 participants, 36.1% were in the low-score group (0–1 points), 34.2% were in the intermediate-score group (2 points), and 29.7% were in the high-score group (3–4 points). Participants with a higher healthy lifestyle score tended to be older, female, and have a higher socioeconomic status, a lower body mass index, and lower prevalences of hypertension and diabetes (Table 1).

Table 1. Baseline Characteristics of Study Participants by Healthy Lifestyle Score Categories.

	Healthy Lifestyle Score			
	Unfavorable (Score = 0, 1)	**Intermediate (Score = 2)**	**Favorable (Score = 3, 4)**	***p* Value**
Characteristics	2004	1929	1648	
Age (year)	46.3 (45.3 to 47.3)	47.7 (46.4 to 48.9)	49.0 (47.7 to 50.3)	<0.001
Sex (%)				<0.001
Male	1212 (58.8%)	970 (49.5%)	722 (42.1%)	
Female	792 (41.2%)	959 (50.5%)	926 (57.9%)	
Race (%)				<0.001
Mexican American	262 (8.8%)	239 (7.8%)	179 (6.4%)	
Other Hispanic	190 (5.6%)	219 (6.7%)	201 (7.3%)	

Table 1. *Cont.*

	Healthy Lifestyle Score			
	Unfavorable (Score = 0, 1)	**Intermediate (Score = 2)**	**Favorable (Score = 3, 4)**	***p* Value**
Non-Hispanic White	878 (68.4%)	715 (66.9%)	560 (65.7%)	
Non-Hispanic Black	477 (10.4%)	498 (11.9%)	390 (11.0%)	
Non-Hispanic Asian	90 (1.8%)	192 (4.3%)	277 (7.5%)	
Other	107 (4.9%)	66 (2.4%)	41 (2.1%)	
Education (%)				<0.001
Less than 9th grade	173 (5.6%)	145 (3.5%)	114 (3.5%)	
9–11th grade	333 (12.7%)	218 (8.4%)	119 (4.2%)	
High school graduate	573 (27.0%)	440 (23.1%)	273 (16.8%)	
Some college or AA degree	651 (34.6%)	618 (33.5%)	492 (28.9%)	
College graduate or above	274 (20.1%)	508 (31.5%)	650 (46.6%)	
PIR	2.7 (2.6 to 2.8)	3.1 (2.9 to 3.2)	3.3 (3.1 to 3.4)	<0.001
Marital Status				0.537
Married/Living with Partner	1140 (60.9%)	1110 (62.1%)	1006 (64.8%)	
Widowed/Divorced/Separated	448 (19.2%)	417 (18.0%)	319 (16.4%)	
Never married	416 (20.0%)	402 (19.9%)	323 (18.8%)	
BMI (kg/m^2)	29.9 (29.4 to 30.3)	29.9 (29.4 to 30.4)	27.9 (27.5 to 28.3)	<0.001
Hypertension (%)				0.033
No	1199 (64.7%)	1190 (67.3%)	1108 (71.2%)	
Yes	805 (35.3%)	739 (32.7%)	540 (28.8%)	
Diabetes (%)				0.057
No	1698 (87.6%)	1615 (88.2%)	1456 (91.2%)	
Yes	306 (12.4%)	314 (11.8%)	192 (8.8%)	

AA degree = Associate of Arts degree; PIR = Poverty–Income Ratio; BMI = body mass index.

In US NHANES, all estimates accounted for complex survey designs, and p values were calculated using analysis of variance adjusting for sampling weights and the Rao–Scott χ^2 test for continuous and categorical variables, respectively. All p values were <0.05, except for marital status ($p = 0.537$) and diabetes ($p = 0.057$).

Compared with participants without CVD ($n = 4973$), those with CVD ($n = 608$) were older, had a higher prevalence of comorbidities, presented a lower proportion with a high lifestyle score, and had a lower mean weighted lifestyle score (Table S3).

Urinary concentrations of multiple VOC metabolites were elevated among participants with less favorable lifestyle scores (Table S4) and among those with prevalent CVD (Table S5).

3.2. Associations Between Urinary VOC Metabolites and Lifestyle and CVD

In fully adjusted models, each 1-point increase in the healthy lifestyle score was associated with an approximately 20% lower prevalence of CVD (OR 0.80, 95% CI 0.67–0.95; $p = 0.012$; Table S6). After further adjustment for this lifestyle score and correction for multiple comparisons, significant positive associations with CVD were observed for multiple

metabolites, while the cyanide metabolite ATCA showed a significant inverse association. The odds ratios for these metabolites were larger in models that did not adjust for the healthy lifestyle score (Figure 1 and Table S7). Restricted cubic spline analyses indicated that the associations of the aforementioned VOC metabolites with CVD did not significantly deviate from linearity (all nonlinear $p > 0.05$; Table S8). Analyses using exposure quartiles revealed monotonic trends for metabolites such as AAMA and CYMA, with the highest quartile (Q4) exhibiting the strongest association with CVD (Table S9). The concentration cutoff defining the high-exposure group (Q4) for most metabolites reached or approached the 75th percentile of the US CDC NHANES reference range (Tables S10 and S11). Compared with the low-exposure group (Q1–Q3), high exposure was associated with a significantly higher prevalence of CVD for most metabolites (Table S12). The exceptions were ATCA, which showed a significant inverse association, and DHBMA, which did not reach significance.

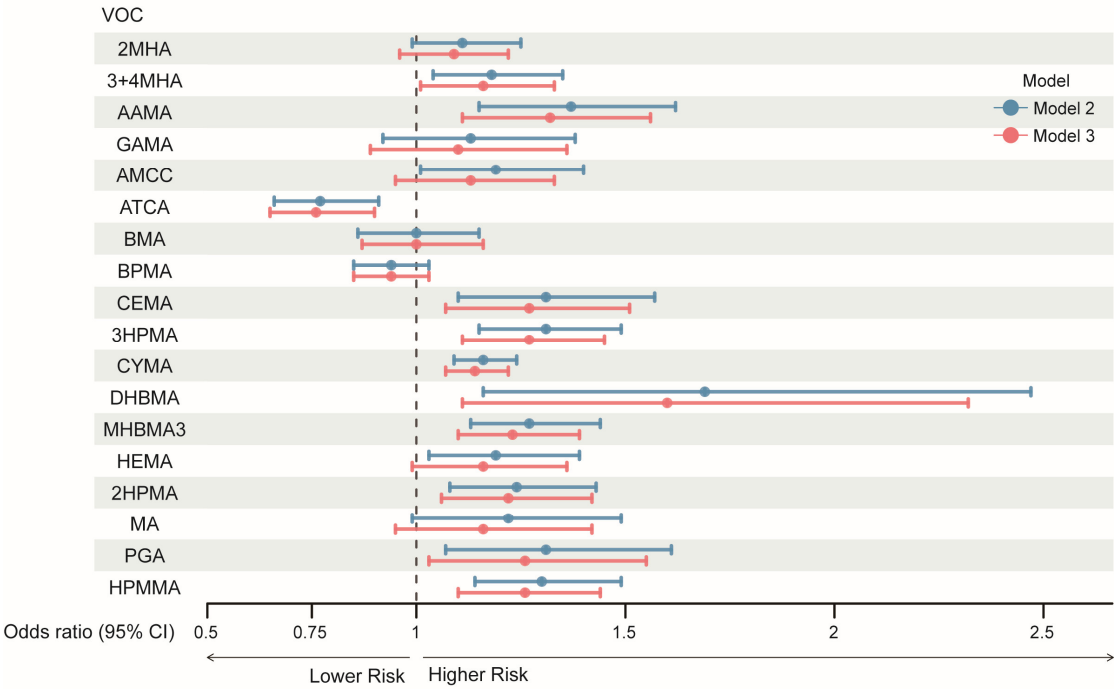


Figure 1. Associations of urinary volatile organic compound (VOC) metabolites with cardiovascular disease (CVD), with and without lifestyle adjustment. Model 2 was adjusted for age, sex, race/ethnicity, marital status, education, poverty-to-income ratio (PIR), body mass index (BMI), and history of hypertension or diabetes; Model 3 further adjusted for healthy lifestyle. Analyses used survey-weighted logistic regression. *p* values were adjusted using the FDR procedure.

3.3. Interaction Analysis of Urinary VOC Metabolites and Lifestyle with CVD

After full adjustment, the healthy lifestyle score showed significant inverse correlations with concentrations of multiple VOC metabolites (all $p < 0.05$), most strongly with CYMA ($\rho = -0.295$), AMCC ($\rho = -0.293$), and 3+4MHA ($\rho = -0.236$; Figure S2 and Table S13). Analysis of multiplicative and additive interactions indicated no statistically significant multiplicative interaction (all product term $p > 0.05$), whereas significant additive interactions were observed for AAMA (RERI 1.42, 95% CI 0.63–2.21; $p = 0.005$), 3HPMA (RERI 1.28, 95% CI 0.62–1.94; $p = 0.002$), and CYMA (RERI 1.33, 95% CI 0.48–2.18; $p = 0.023$; Figures 2 and S3). When lifestyle categories were compared within each exposure stratum (using the unfavorable-lifestyle group as the reference), the pattern differed by exposure level for the three metabolites with significant additive interactions. In the low-exposure stratum, an intermediate lifestyle was associated with lower CVD odds than a favorable lifestyle for AAMA, 3HPMA, and CYMA, whereas in the high-exposure stratum, a favorable lifestyle

was associated with lower odds than an intermediate lifestyle for all three. Several high-exposure/favorable-lifestyle cells contained fewer than 20 CVD cases (Tables S14 and S15, Figure S3). For metabolites such as AAMA and 3HPMA, the marginal-effects curves showed an apparent decrease in predicted probability with increasing exposure within the favorable-lifestyle group. Because this group contained very few CVD cases at high exposure (13, 11 and 9 cases for AAMA, 3HPMA and CYMA, respectively), this apparent decrease is best interpreted as an artefact of small numbers rather than as a genuine exposure–response pattern (Figure S4).

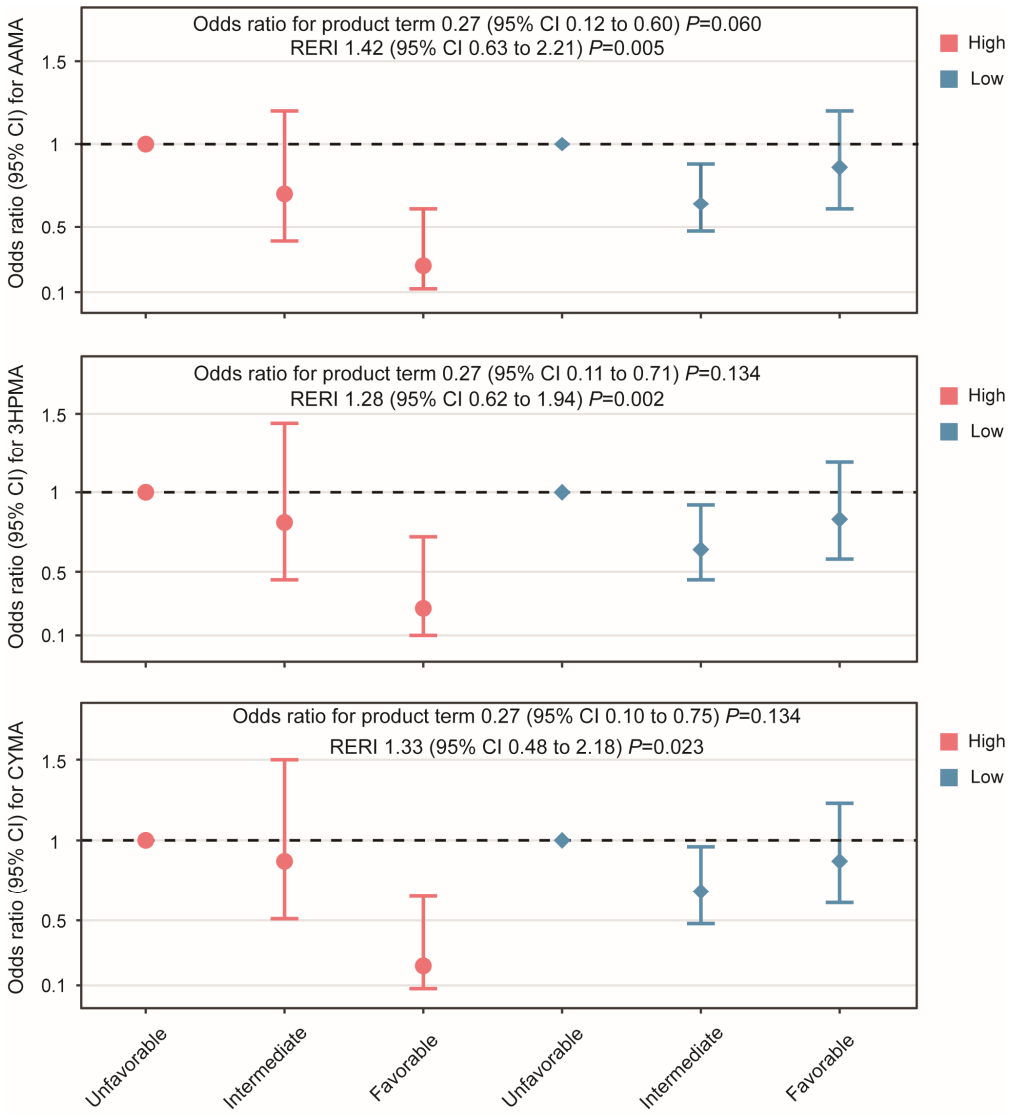


Figure 2. Multiplicative and additive interaction analysis of lifestyle–CVD associations stratified by VOC exposure level: results for selected VOC metabolites. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between three-category lifestyle (Unfavorable/Intermediate/Favorable) and cardiovascular disease (CVD), stratified by VOC exposure level (High/Low) across three VOC metabolites (AAMA, 3HPMA, CYMA). RERI, relative excess risk due to interaction. All models were adjusted for age, sex, race, educational attainment, poverty-to-income ratio (PIR), marital status, body mass index (BMI), hypertension, and diabetes mellitus. Analyses used survey-weighted logistic regression. *p* values were adjusted using the FDR procedure. The stratum-specific ORs used the unfavorable-lifestyle group within each stratum as the reference, whereas the RERI used the low VOC exposure and favorable lifestyle group as the reference. Red circles represent the High VOC exposure stratum, and blue diamonds represent the Low VOC exposure stratum.

In the high-exposure stratum, participants with a favorable lifestyle had a lower CVD prevalence than those with an unfavorable lifestyle. In the low-exposure stratum, the intermediate category generally showed lower odds ratios than the favorable category. In neither stratum, however, was a formal comparison between the intermediate and favorable categories performed, and the corresponding cells contained very few CVD cases; the ordering of these two categories should therefore be regarded as untested and unstable (Figure S5 and Table S16).

To analyze population heterogeneity, we conducted stratified analyses by age, sex, race, and hypertension and diabetes status. Significant multiplicative interactions were identified for certain metabolites (e.g., 3HPMA) in some subgroups, such as younger adults and those without hypertension. The significant additive interactions between the healthy lifestyle score and each of AAMA, CYMA, and 3HPMA persisted in White participants and those without hypertension. A greater number of metabolites exhibited significant additive interactions in younger participants and those without hypertension (Table S17). Analyses within each subgroup showed that the association pattern differed by both exposure stratum and subgroup. Under high VOC exposure, a favorable lifestyle was associated with the lowest odds most consistently among non-White participants, females, and those younger than 60 years; under low VOC exposure, the pattern was less consistent across subgroups (Tables S18–S22).

3.4. Sensitivity Analyses

To assess the robustness of the primary findings, we performed a series of sensitivity analyses. After excluding hypertension and diabetes from the adjustment set, the additive interactions for AAMA ($p = 0.007$), 3HPMA ($p = 0.001$), and CYMA ($p = 0.008$) remained significant (Table S24). When a more stringent definition of binge drinking was applied, none of the three additive interactions reached statistical significance—AAMA ($p = 0.136$), 3HPMA ($p = 0.136$), and CYMA ($p = 0.247$)—and the number of CVD cases was also small in the high-exposure, favorable-lifestyle cells (10 for CYMA, 13 for 3HPMA, and 16 for AAMA; Tables S23 and S24). Using a weighted healthy lifestyle score, the additive interactions remained significant for AAMA ($p = 0.015$) and 3HPMA ($p = 0.015$), but not for CYMA ($p = 0.908$; Table S24).

Analyses of individual lifestyle components showed that smoking was the component most consistently associated with significant additive interactions, including 3HPMA ($p < 0.001$), AMCC ($p = 0.010$), PGA ($p = 0.010$), and HPMMA ($p = 0.009$). The alcohol and diet components showed no significant additive interaction with any metabolite. The physical activity component showed a significant additive interaction only with MHBMA3 ($p = 0.013$; Tables S25 and S27). Given the prominent role of the smoking component in these interactions, we further conducted two analyses focused on the three metabolites that showed significant additive interactions in the primary analysis, in order to assess the extent to which the observed interactions could be attributed to smoking.

First, after additional adjustment for log-transformed serum cotinine, the additive interactions for AAMA (RERI 1.13, 95% CI 0.17–2.08; $p = 0.042$) and 3HPMA (RERI 0.93, 95% CI 0.10–1.76; $p = 0.042$) remained significant, whereas the interaction for CYMA (RERI 1.39, 95% CI −0.22 to 3.00; $p = 0.108$) did not reach statistical significance (Table S29). Subsequently, in an analysis restricted to non-smokers, none of the three additive interactions reached statistical significance—AAMA (RERI −1.71, 95% CI −4.81 to 1.39; $p = 0.280$), 3HPMA (RERI −1.59, 95% CI −3.62 to 0.45; $p = 0.126$), and CYMA (RERI 1.09, 95% CI −1.61 to 3.78; $p = 0.429$; Table S29)—and the point estimates for AAMA and 3HPMA reversed direction. The number of CVD cases in these cells was very small (8, 3, and 9 cases in the

high-exposure, unfavorable-lifestyle cells for AAMA, 3HPMA, and CYMA, respectively; Table S28), and these estimates should therefore be interpreted with caution.

Finally, the observed pattern was reproduced in only some of the sensitivity models for AAMA and 3HPMA, was highly unstable for CYMA, and was not reproduced for any of the three metabolites in the non-smoker analysis (Tables S26 and S30).

4. Discussion

To date, no study has systematically examined the complex relationships between specific internal exposure to VOCs, a composite healthy lifestyle score, and CVD prevalence. The healthy lifestyle score constructed in this study—comprising smoking, alcohol consumption, diet, and physical activity—aligns with the behavioral components of the American Heart Association's "Life's Essential 8" framework [37]. Life's Essential 8 incorporates health factors such as blood pressure, blood glucose, blood lipids, and BMI to construct a comprehensive cardiovascular health metric. In contrast, our lifestyle score was restricted to behavioral factors, and our study focused on whether the association between VOC exposure and CVD differed by lifestyle category, rather than on constructing a holistic health score. This is particularly timely given the U.S. Environmental Protection Agency's identification of VOCs such as acrolein, acrylonitrile, and benzene as priority urban air toxics that pose significant public health threats [38]. Against this background, the main findings can be summarized in three points. First, elevated levels of multiple urinary VOC metabolites were significantly associated with a higher prevalence of CVD. Second, a higher healthy lifestyle score was independently and inversely associated with CVD prevalence. Most critically, we found significant additive interactions between a healthy lifestyle and three specific VOC metabolites (AAMA, CYMA, and 3HPMA) regarding CVD prevalence; however, these interactions were no longer statistically significant among non-smokers, in an analysis in which the smoking component was removed from the lifestyle score, indicating that tobacco exposure contributed substantially to the observed interaction.

Consistent with prior population-based evidence, most urinary VOC metabolites (except ATCA, which showed an inverse association, and DHBMA, which was not significant) were associated with an increased CVD risk [39,40]. Furthermore, VOCs significantly associated with CVD in our study (e.g., acrolein and crotonaldehyde) have been reported in experimental studies to promote atherosclerosis through pathways such as oxidative stress induction, endothelial dysfunction, and reduced circulating angiogenic cells [41–43], which may provide a possible mechanistic explanation for our epidemiological findings. Qian et al. reported positive associations between urinary VOC metabolites and the visceral adiposity index and lipid accumulation product, with CEMA and AMCC as major contributors [44]. This suggests that there is a metabolic pathway linking VOC exposure to CVD risk. Our study further found that the association between VOC exposure and CVD prevalence may differ by lifestyle category, extending these findings from metabolic risk to the public health level.

In recent years, multiple studies have shown that a healthy lifestyle reduces CVD burden [45,46]. In the specific context of air pollution, Hu et al. found that long-term exposure to PM1, PM2.5, PM10, and NO2 was associated with increased CVD risk, with lifestyle partially mediating this association, and that adherence to a healthy lifestyle was associated with reduced CVD incidence among individuals with high pollution exposure [47]. Ogundipe and Obeng-Gyasi found that heavy metal exposure and lifestyle behaviors (smoking and alcohol use) jointly influenced liver health, treating smoking and alcohol as separate exposure variables in their mixture model [48]. However, the former focused on outdoor air pollutants rather than internal VOC exposure and included clinical factors such as blood pressure, glucose, lipids, and BMI in its lifestyle score, whereas the latter treated smoking

and alcohol as separate exposure variables without constructing a composite score or testing effect modification. Our study used urinary VOC metabolites to assess internal exposure, constructed a composite lifestyle score based solely on smoking, alcohol consumption, diet, and physical activity, and examined whether the association between VOC exposure and CVD differed by lifestyle category.

A recent study examined the association between VOC exposure and the Life's Essential 8 score, reporting significant linear associations and mixture effects using BKMR analysis [49]. While that study advanced our understanding of the relationship between environmental pollutants and cardiovascular health, it did not investigate the potential modifying role of lifestyle behaviors. In contrast, our study has two key innovations. First, we focused on lifestyle as an effect modifier rather than as an outcome, providing evidence on whether the association between VOC exposure and CVD prevalence differs by adherence to healthy behaviors. Second, beyond conventional multiplicative interaction analysis, we employed additive interaction analysis using the Relative Excess Risk due to Interaction (RERI). This is methodologically critical because public health interventions are typically evaluated on an additive scale, and the presence of additive interaction—even in the absence of multiplicative interaction—can inform whether the joint effect of two exposures exceeds the sum of their individual effects. Individuals with both high exposure and an unfavorable lifestyle had a higher CVD prevalence than would be expected if the separate associations of the two factors were additive. However, the cross-sectional design precludes causal inference from these estimates, and because several exposure-lifestyle combinations contained very few CVD cases, the corresponding interaction estimates should be regarded as exploratory.

These interaction estimates warrant more specific mention. Among participants with a favorable lifestyle, those with high exposure had fewer CVD cases than those with low exposure, and the OR for high versus low exposure within this group was below 1, a direction opposite to the expected increase in risk with higher exposure. Given the small numbers of participants and CVD cases in these cells (13, 11 and 9 CVD cases in the high-exposure/favorable-lifestyle cells for AAMA, 3HPMA and CYMA, respectively), we regard this pattern as a reflection of imprecision rather than as a substantive finding. It is nevertheless relevant to interpretation, because the interaction estimates are computed from these same cells: part of the apparent joint effect rests on this reversed and imprecise contrast. Adherence to a favorable lifestyle can offset the association with exposure but cannot reverse it, and the observed reversal therefore indicates that these cell estimates carry limited information; the interaction estimates that depend on them are accordingly presented as exploratory.

To further assess the robustness of these estimates, we performed a series of sensitivity analyses. When a more stringent definition of binge drinking was applied, the number of CVD cases in the high-exposure/favorable-lifestyle cells was small, and none of the three additive interactions reached statistical significance. This attenuation may partly reflect the reclassification of a substantial number of participants under the stricter definition, which reduced statistical power, and partly reflect the small number of cases within these cells and the resulting instability of effect estimates. However, the direction of the point estimates remained consistent with the primary analysis. In the weighted-score sensitivity analysis, the AAMA and 3HPMA interactions remained significant. Because the weights were derived from the present sample and are therefore specific to this sample, the primary analysis used the equal-weight score, and the weighted score was used only in sensitivity analyses. Notably, when individual lifestyle components were examined, smoking was the component most consistently associated with significant additive interactions, whereas the alcohol and diet components showed no significant additive interaction with any metabo-

lite; the physical activity component showed a significant additive interaction only with MHBMA3, which was not among the metabolites with significant interactions in the primary analysis. Given the prominent role of the smoking component in the three metabolites of primary interest, we further conducted two analyses focused on the three metabolites that showed significant additive interactions in the primary analysis, in order to assess the extent to which the observed interactions could be attributed to smoking.

Individuals who had smoked ≥ 100 cigarettes in their lifetime—both current and former smokers—were classified as having an unhealthy smoking level, whereas only those who had smoked < 100 cigarettes were classified as healthy, a definition that may classify current smokers below this threshold as healthy. Model 7 retained the full sample and the original quartile cut-points; the smoking component remained in the lifestyle score, and log-transformed serum cotinine was included as a continuous covariate to capture recent tobacco exposure. Under this adjustment, the CYMA RERI was essentially unchanged, whereas its confidence interval widened appreciably and statistical significance was no longer present. A stable point estimate accompanied by a wider interval may reflect variance inflation arising from the close correlation between CYMA—a relatively specific marker of active smoking [50]—and cotinine; these estimates do not permit a conclusion as to whether cotinine adjustment also absorbed part of this interaction. The AAMA and 3HPMA estimates, however, were attenuated while remaining statistically significant, suggesting that part of each joint association overlapped with recent tobacco exposure; the persistence of significance for these two metabolites may reflect their source composition, in that acrylamide derives predominantly from diet [51] and acrolein has extensive environmental sources in addition to tobacco smoke [52]. To assess whether these interactions persisted in the absence of current smoking, we repeated the interaction analysis in a subsample with serum cotinine < 10 ng/mL. Because serum cotinine reflects only recent exposure, this threshold excluded current smokers while retaining former smokers, and the analysis should therefore not be equated with an analysis restricted to never smokers. As urinary metabolite distributions differ in this subsample, the quartile cut-points were re-derived within it, so high exposure corresponds to a lower absolute concentration and a narrower exposure contrast than in the full sample. The subsample was also approximately 25% smaller, and the high-exposure/unfavorable-lifestyle cells contained fewer than 10 CVD cases each for AAMA, 3HPMA, and CYMA. Accordingly, none of the three additive interactions was statistically significant in this analysis. The reversed point estimates for AAMA and 3HPMA may likewise reflect imprecision, whereas the CYMA estimate remained positive but imprecise.

From a biological mechanism perspective, acrylamide, acrylonitrile, and acrolein have each been reported to induce oxidative stress [53–55]. A favorable lifestyle may plausibly attenuate VOC-related cardiovascular risk by helping to maintain the balance of the endogenous antioxidant system; however, because inflammatory and oxidative markers were not measured in the present study, this interpretation remains hypothetical and was not directly tested. Smoking is one of the four components of the lifestyle score, and tobacco smoke is a major source of several of the VOCs examined here (e.g., CYMA [50]); part of the lower urinary VOC metabolite concentrations among individuals with a more favorable lifestyle is therefore expected to reflect lower tobacco exposure. Beyond this, urinary VOC metabolites are eliminated through exhalation or hepatic CYP-mediated metabolism, so their concentrations are jointly determined by external exposure and metabolic clearance [56,57]. If non-tobacco exposure and metabolic clearance were equal, metabolite concentrations would not be expected to be systematically lower in healthier individuals; the lower concentrations observed here may therefore also reflect lower non-tobacco exposure, for example through more active exposure-reduction behaviors or residence in less polluted areas. Because this

was a cross-sectional analysis and external exposure concentrations were not measured, the present study cannot distinguish between these possibilities. Moreover, the additive interaction was more pronounced in younger adults and individuals without hypertension. This is consistent with previous findings on the population heterogeneity of the cardiovascular effects of VOC exposure and further suggests that the association between lifestyle and CVD may vary according to individuals' physiological status, baseline risk, or exposure characteristics [58,59].

From a public health perspective, identifying the subgroups in which lifestyle behaviors are most strongly associated with CVD in the context of environmental exposure is of potential value for prevention, and the additive interaction observed here indicates that this question warrants further investigation. Because these subgroups rest on strata containing very few CVD cases, as discussed above, they should be regarded as provisional.

This study has several limitations. First, the 2017–March 2020 pre-pandemic survey cycles had a low response rate (43.9%), and the cross-sectional design precludes causal inference. Both lifestyle information and cardiovascular disease outcomes were self-reported, which may introduce measurement error and recall bias. Although multiple covariates were adjusted for, residual confounding cannot be ruled out. Moreover, several VOCs included in this study (e.g., benzene, 1,3-butadiene, acrolein, and acrylonitrile) share common sources with well-established cardiovascular pollutants such as particulate matter and nitrogen dioxide; residual confounding by unmeasured ambient air pollution remains possible. Such air pollutants may alter inflammatory and stress-related biomarkers including TNF-α and salivary cortisol, which are relevant to cardiovascular pathogenesis [60]. Second, VOC metabolites were measured in a single spot urine sample. These biomarkers have short half-lives (ranging from hours to approximately one day) and primarily reflect recent exposure rather than long-term cumulative exposure. Third, we used urinary internal biomarkers of VOC exposure instead of ambient concentration measurements, which limits our ability to link findings to specific emission sources or develop targeted source-based exposure control recommendations. Fourth, the healthy lifestyle score assumes equal weighting of its components, and the dichotomous smoking criterion may classify some current smokers as healthy; the non-smoker analysis, in turn, retained former smokers and should therefore not be equated with an analysis restricted to never smokers. The high proportion of CVD participants classified as having healthy alcohol intake also suggests potential reverse causation due to post-diagnosis behavioral changes. Finally, as noted above, several exposure-lifestyle strata contained very few CVD cases, and stratum-specific estimates and RERI values should therefore be interpreted cautiously. Future prospective studies with repeated exposure assessment and detailed tobacco exposure characterization, together with mechanistic investigations, are needed to validate these associations and to determine whether non-smoking lifestyle components modulate VOC-related cardiovascular risk independently of tobacco exposure.

5. Conclusions

In this cross-sectional analysis, we observed significant additive interactions between a favorable lifestyle and three urinary VOC metabolites (AAMA, 3HPMA, and CYMA) in relation to prevalent CVD, with the joint association exceeding the sum of their individual associations. However, this difference was based on small numbers of CVD cases and largely attributable to the smoking component; there was no evidence of an interaction among non-smokers. Given the internal dose measurement and cross-sectional design, these results should be considered preliminary and require prospective validation with comprehensive external exposure assessment and detailed tobacco exposure characterization.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/toxics14111018/s1. Table S1: Volatile Organic Compound (VOC) Metabolites, Their Parent Compounds, Abbreviations, and Limits of Detection (LOD, ng/mL). Table S2: The Score Criteria of Healthy Lifestyle Factors. Table S3: Baseline Characteristics of Participants by Cardiovascular Disease Status. Table S4: Urinary Levels (μg/g Creatinine) of Volatile Organic Compound (VOC) Metabolites in the Study Population. Table S5: Urinary Concentrations (μg/g Creatinine) of Volatile Organic Compound (VOC) Metabolites by Cardiovascular Disease Status. Table S6: Association of Individual and Composite Lifestyle Factors with Prevalent Cardiovascular Disease. Table S7: Multivariable-Adjusted Associations of VOC Metabolites with Cardiovascular Disease Risk. Table S8: Restricted Cubic Spline Analysis of VOC Metabolites and CVD Risk. Table S9: Association Between Cardiovascular Disease Risk and Quartiles of Urinary VOC Metabolite Levels in the Study Population. Table S10: Distribution of VOC Metabolite Concentrations by Exposure Quartile Group. Table S11: US CDC NHANES Reference Ranges for Urinary VOC Metabolite Concentrations (μg/g Creatinine) Across Survey Cycles. Table S12: Odds Ratios for Cardiovascular Disease by Binary VOC Exposure Categories. Table S13: Partial Spearman's Correlation Coefficients Between Healthy Lifestyle Score and Urinary VOC Metabolite Concentrations. Table S14: Unweighted Participant Counts and CVD Cases for Each VOC Exposure–Lifestyle Combination. Table S15: Within-Strata Associations: Lifestyle Categories and Prevalent CVD, Stratified by VOC Exposure Level. Table S16: Risk Levels Across Exposure–Lifestyle Combinations: ORs Using a Common Reference Group. Table S17: Multiplicative and Additive Interaction Analyses Between Lifestyle and VOC Exposure on Prevalent CVD, Across Population Subgroups. Table S18: Association of VOC Metabolite Levels and Lifestyle Score with Cardiovascular Disease, Stratified by Age. Table S19: Association of VOC Metabolite Levels and Lifestyle Score with Cardiovascular Disease, Stratified by Sex. Table S20: Association of VOC Metabolite Levels and Lifestyle Score with Cardiovascular Disease, Stratified by Race. Table S21: Association of VOC Metabolite Levels and Lifestyle Score with Cardiovascular Disease, Stratified by Hypertension. Table S22: Association of VOC Metabolite Levels and Lifestyle Score with Cardiovascular Disease, Stratified by Diabetes. Table S23: Unweighted Numbers of Participants and CVD Cases for Each VOC Exposure–Lifestyle Combination under the Alternative Drinking Definition (Model 5). Table S24: Sensitivity Analysis: Interaction Between VOC Exposure and Lifestyle Score under Different Model Specifications. Table S25: Sensitivity Analysis: Interaction Between VOC Exposure and Individual Lifestyle Factors. Table S26: Sensitivity Analysis: Within-Strata Associations of Lifestyle Score and Prevalent CVD, by VOC Exposure Level. Table S27: Sensitivity Analysis: Association of Individual Lifestyle Factors and Prevalent CVD, by VOC Exposure Level. Table S28: Unweighted Numbers of Participants and CVD Cases for Each VOC Exposure–Lifestyle Combination among Non-Smokers (Model 8). Table S29: Sensitivity Analysis: Interaction Between VOC Exposure and Lifestyle Score on Prevalent CVD by Model Specification: Full Sample and Non-Smoker Analyses. Table S30: Sensitivity Analysis: Within-Strata Associations of Lifestyle Score and Prevalent CVD by VOC Exposure Level: Full Sample and Non-Smoker Analyses. Figure S1: Study Flowchart of Participant Selection. Figure S2: Heatmap of the Adjusted Partial Correlation Matrix Between Healthy Lifestyle Score and Urinary VOC Metabolites. Figure S3: Assessment of Interaction Between Healthy Lifestyle Score and Volatile Organic Compound Metabolite Exposure on Prevalent Cardiovascular Disease. Figure S4: Predicted Probability of Prevalent Cardiovascular Disease by Urinary Volatile Organic Compound Metabolite Concentration and Healthy Lifestyle Score. Figure S5: Comparison of Cardiovascular Disease Risk Across Combinations of VOC Exposure and Lifestyle Score Using a Common Reference Group [61–63].

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. The NHANES protocol was approved by the National Center for Health Statistics Research Ethics Review Board (NCHS IRB/ERB Protocol #2011–17 for the 2011–2016 cycles and Protocol #2018–01 for the 2017–2020 cycles). This study was a secondary analysis of publicly available, de-identified data and did not require additional ethical approval.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the original NHANES survey.

Data Availability Statement: The data presented in this study are available in the NHANES repository at https://www.cdc.gov/nchs/nhanes/ (accessed on 14 August 2025). Further inquiries can be directed to the corresponding author.

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