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Anhedonia, a hallmark of depression, is associated with environmental exposure to volatile organic compounds in U.S. adults from NHANES

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ABSTRACT

Background and Aim: Environmental exposure to volatile organic compounds (VOCs) is linked to depressive disorder, examined as a unitary outcome. Symptom-specific observations are scarce. Anhedonia, a representative phenotype in depression, has unique biology from negative valences. Here, we aim to investigate associations between urinary metabolites of VOCs (UVOCs) and anhedonia. **Methods:** We analyzed 5,084 adults from five cycles of National Health and Nutrition Examination Survey (NHANES) over a decade. Anhedonia was assessed by the first item of the Patient Health Questionnaire-9. Fifteen UVOCs included were selected based on their importance by multivariate logistic regression, elastic net, and random forest models. Dose-response relationships were examined by generalized additive models and restricted cubic splines. Mixed exposure was evaluated by environmental risk score and weighted quantile sum regression. Mechanisms were explored by mediation analysis. **Results:** We found six UVOCs with strong links to anhedonia: four positive (MHBMA3, DHBMA, MA, 3HPMA) and two inverse (2MHA, 2HPMA). Positively associated UVOCs exhibited J-shaped dose-response relationships with anhedonia, while inversely associated ones showed reverse patterns. Mixed exposure was positively connected to anhedonia, with DHBMA (metabolite of 1,3-butadiene) still contributing the most. A nomogram was developed for risk estimation based on UVOC concentrations. Mechanistically, white blood cells and neutrophils acted as detrimental mediators, lymphocytes and monocytes as protective ones, whereas albumin showed suppression effects. **Conclusions:** We report the symptom-specific associations between certain VOC exposure and anhedonia. These findings may propose environmental predictors of anhedonia and advance precision approaches in psychiatric epidemiology.

Introduction

Volatile organic compounds (VOCs) are ubiquitous in the environment, mostly from industrial processes, vehicle emissions and building materials [1][2]. These lipophilic chemicals, represented by unsaturated hydrocarbons and their derivatives, readily cross the blood-brain barrier (BBB), accumulate in the brains, and exert neurotoxicity [3]. Urinary metabolites of volatile organic compounds (UVOCs), serving as non-invasive biomarkers of integrated exposure across all routes, offer a complementary measurement of VOCs alongside exhaled breath and blood testing [4]. Many studies using UVOC data have validated the link between VOC exposure and neurological disorders, such as anxiety [5], sleep abnormality [6], cognitive impairment [7], and depression [8][9][10].

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Mechanistically, inflammatory overactivation and oxidative stress are key medicators to explain the VOC-linked outcomes [11][12].

Depression affects over 280 million individuals worldwide [13] and represents a leading cause of disability [14][15]. While traditional research has focused on this disorder as a unitary construct, emerging evidence demonstrates that specific symptoms may exhibit distinct neurobiological substrates and clinical trajectories [16][17]. Among these, anhedonia, the diminished ability to experience pleasure or enjoyment, is present in about 70% of individuals with depression [18] and predicts treatment resistance, suicidality, and poor functional outcomes independently from the unitary measure [19][20]. Unlike other symptoms that largely involve negative valences, anhedonia is particularly related to the disruption of reward systems—dopaminergic pathways, for instance [21][22]. This specificity underlies differential risk factors and epidemiological causes [23], which, however, are understood poorly due to the lack of population-based studies that treat it as a separate outcome.

Here, we analyzed over a decade of National Health and Nutrition Examination Survey (NHANES) data to explore the associations between UVOCs and anhedonia in U.S. adults. We systematically identified significant UVOCs linked to anhedonia, examined their individual and mixed patterns of exposure, revealed the immune-related mechanisms as potential mediators, and developed a nomogram for risk estimation. This work provides symptom-specific evidence on environmental contributions to mental health and underscores the need for precision management in public psychiatry [24].

2. Methods

2.1 Data source

NHANES is a complex, multi-stage program to assess the health and nutritional status of Americans. All its processes, including written consent, are supervised by the Ethics Review Board of the National Center for Health Statistics [25]. This study pooled 5 cycles of NHANES data (2005-2006 and 2011-March 2020) accessed from https://wwwn.cdc.gov/nchs/nhanes/, equivalent to 11.2 years in total.

2.2 Assessment of anhedonia

Depressive severity was assessed by Patient Health Questionnaire (PHQ-9), a 9-item self-rating scale on frequent symptoms of depression over the past two weeks [26]. Each item is scored 0 (Not at all), 1 (Several days), 2 (More than half the days), or 3 (Nearly every day). A sum score $\geqslant$10 indicates clinically relevant depression [27][28][29]; higher scores indicate greater severity [30]. We used the first item (DPQ010) of PHQ-9, "Over the last 2 weeks, how often have you been bothered by little interest or pleasure in doing things", to identify anhedonia [31]. Participants scoring 2 or 3 were classified as present with anhedonia [26]. Only adults >20 years were included.

2.3 Detection of UVOCs

We collected data of 18 UVOCs that were shared across involved cycles of NHANES. UVOCs were quantified using ultra performance liquid chromatography coupled with electrospray tandem mass spectrometry (UPLC-ESI/MSMS) [4]. Concentrations below the lower limit of detection (LLOD) were imputed as LLOD/$\sqrt{2}$. UVOCs with detection rates <70% or abnormal distributions were excluded. Eventually, we included 15 metabolites for analysis.

UVOCs (ng/mL) were corrected by urine creatinine (mg/dL), reported in μg/(g creatinine). Prior to analysis and modeling, they were further ln-transformed [9].

2.4 Covariates

We included several confounders to adjust the models [32][33]. They were grouped into three categories. 1) Demographics: age, sex, race/ethnicity, education level, marital status, and family poverty income ratio (PIR). 2) Risk factors: smoking, alcohol use, body mass index (BMI), hypertension, diabetes, and kidney conditions. 3) Laboratory tests: white blood cell (WBC), lymphocyte, monocyte, segmented neutrophil, urine albumin, and urine creatinine.

2.5 Statistics

Analysis was performed in R (The R Foundation) or Python (The Python Software Foundation). Survey design was taken into account wherever appropriate [34]. Continuous variables were described by mean and standard deviation (SD), assessed by t-tests. Categorical variables were described by frequency (N) and weighted percentage (%), assessed by chi-square tests.

We used three machine learning approaches to examine associations and screen significant exposures from the 15 UVOCs. We established multivariate logistic regression models, elastic net (ENET) models with L1/L2-balanced regularization [35], and random forest models with 50 decision trees [36]. Coefficients from the three models were normalized by min-max scaling. Area under the curve (AUC) of receiver operating characteristic (ROC) curves was used to evaluate model performance [36]. Finally, we ranked UVOCs by their performance scores calculated as the AUC-weighted sum of the three normalized coefficients.

To investigate the dose-response relationships between individual UVOCs and anhedonia, we transformed UVOC concentrations into four ordinal classes based on quartiles and fitted logistic regression analysis. To further reveal nonlinear associations, we constructed generalized additive models (GAM) to observe the general characteristics, which incorporated smooth terms for continuous variables with 2nd-order splines and parametric terms for categorical covariates [37]. Similarly, we established restricted cubic spline (RCS) models to characterize these associations more precisely, which were fitted based on weighted logistic regression. Nonlinearity was assessed by likelihood ratio tests comparing nonlinear models against linear ones.

To explore the mixed exposure, we constructed an environmental risk score (ERS) based on the ENET coefficient-weighted sum of UVOC concentrations [38]. Additionally, we used weighted quantile sum (WQS) regression to evaluate the mixture while weighting the contribution of each UVOC in the mixture, which both analyzed the positive and negative effects [39]. Finally, a nomogram for risk prediction was created.

Mediation analysis was performed to reveal the potential mechanisms. The total effect (TE) of UVOCs on anhedonia was decomposed into direct effect (DE) and indirect effect (IE) through immune-related mediators, with the proportion of IE to TE indicating mediation efficacy.

Sensitivity analysis was based on logistic regression models, and particularly, subgroup analysis was performed on subcohorts from stratification by categorical covariates.

3. Results

3.1 Baseline characteristics

This study included 5,084 individuals (Figure 1) with balanced sexes and an average age of 46.43 years, among whom 5.7% were detected present with anhedonia and were more likely to exhibit clinically relevant depression as well (Table 1). Participants with anhedonia tended to be non-Hispanic White, married, living in poverty, less educated, smokers, alcohol consumers, hypertensive, with a higher BMI, and elevated inflammatory levels. Eight of the 15 UVOCs showed increased levels in the anhedonia population, two showed decreased levels, and five showed insignificant changes.

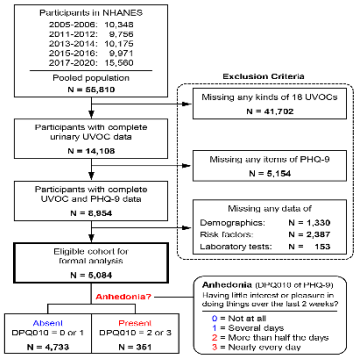


Fig. 1 - Participant inclusion and cohort composition.

Table 1 - Characteristics of the eligible cohort stratified by anhedonia status.

Characteristics	Total	Anhedonia		P value
		Absent	Present	
	N = 5,084	N = 4,733	N = 351	
PHQ-9 score, Mean (SD)	3.02 (4.04)	2.40 (3.08)	11.28 (5.85)	< 0.001
Depression status, N (%)				< 0.001
Yes	385 (7.0%)	190 (3.7%)	195 (3.3%)	
No	4,699 (93.0%)	4,543 (90.6%)	156 (2.4%)	
Demographics				
Age (year), Mean (SD)	46.43 (16.92)	46.51 (17.00)	45.40 (15.85)	0.239
Sex, N (%)				0.111
Male	2,685 (50.7%)	2,514 (48.1%)	171 (2.7%)	
Female	2,399 (49.3%)	2,219 (46.2%)	180 (3.0%)	
Race/Ethnicity, N (%)				< 0.001
Mexican American	708 (7.8%)	671 (7.4%)	37 (0.4%)	
Other Hispanic	413 (5.3%)	367 (4.8%)	46 (0.5%)	
Non-Hispanic White	2,232 (70.2%)	2,108 (66.8%)	124 (3.4%)	
Non-Hispanic Black	1,138 (9.9%)	1,030 (9.0%)	108 (1.0%)	
Other Race (Including Multi-Racial)	593 (6.8%)	557 (6.4%)	36 (0.4%)	
Education level, N (%)				< 0.001
Less than 9th grade	300 (2.8%)	266 (2.5%)	34 (0.3%)	
9-11th grade (Includes 12th grade with no diploma)	540 (7.2%)	479 (6.4%)	61 (0.9%)	
High school graduate/GED or equivalent	1,159 (22.8%)	1,065 (20.9%)	94 (1.9%)	
Some college or AA degree	1,667 (32.8%)	1,549 (31.0%)	118 (1.8%)	
College graduate or above	1,418 (34.4%)	1,374 (33.5%)	44 (0.8%)	
Marital status, N (%)				< 0.001
Married	2,746 (58.4%)	2,601 (56.0%)	145 (2.5%)	
Widowed	490 (8.7%)	449 (7.9%)	41 (0.8%)	
Divorced	640 (12.2%)	583 (11.3%)	57 (0.8%)	
Separated	99 (1.3%)	83 (1.1%)	16 (0.2%)	
Never married	761 (13.3%)	698 (12.2%)	63 (1.0%)	
Living with partner	348 (6.2%)	319 (5.7%)	29 (0.4%)	
Family PIR, Mean (SD)	2.79 (1.65)	2.84 (1.65)	2.11 (1.55)	< 0.001
Risk factors				

Smoking, N (%)				< 0.001
Yes	2,465 (46.3%)	2,254 (42.8%)	211 (3.6%)	
No	2,619 (53.7%)	2,479 (51.6%)	140 (2.1%)	
Alcohol use (drink/day), Mean (SD)	2.70 (2.47)	2.68 (2.45)	3.05 (2.66)	0.006
BMI (kg/m2), Mean (SD)	29.28 (7.05)	29.19 (6.92)	30.58 (8.54)	< 0.001
Hypertension, N (%)				< 0.001
Yes	1,632 (29.9%)	1,482 (27.4%)	150 (2.5%)	
No	3,452 (70.1%)	3,251 (66.9%)	201 (3.2%)	
Diabetes, N (%)				0.303
Yes	531 (8.7%)	486 (8.1%)	45 (0.6%)	
No	4,447 (89.4%)	4,149 (84.4%)	298 (5.0%)	
Borderline	106 (1.9%)	98 (1.8%)	8 (0.1%)	
Kidney conditions, N (%)				0.055
Yes	114 (2.1%)	101 (1.9%)	13 (0.2%)	
No	4,970 (97.9%)	4,632 (92.4%)	338 (5.5%)	
Laboratory tests				
WBC (1000 cells/μL), Mean (SD)	7.24 (2.12)	7.23 (2.10)	7.49 (2.37)	0.024
Lymphocyte (1000 cells/μL), Mean (SD)	2.15 (0.73)	2.15 (0.73)	2.17 (0.73)	0.607
Monocyte (1000 cells/μL), Mean (SD)	0.56 (0.19)	0.56 (0.19)	0.57 (0.20)	0.649
Segmented neutrophil (1000 cells/μL), Mean (SD)	4.28 (1.71)	4.26 (1.69)	4.48 (1.94)	0.019
Urine albumin (mg/L), Mean (SD)	39.27 (303.47)	36.78 (293.10)	72.89 (418.06)	0.031
Urine creatinine (mg/dL), Mean (SD)	124.04 (80.12)	123.02 (79.67)	137.78 (84.98)	0.002
UVOC				
CEMA, Mean (SD)	1.41 (1.58)	1.39 (1.57)	1.68 (1.72)	< 0.001
3HPMA, Mean (SD)	4.94 (7.49)	4.84 (7.38)	6.30 (8.67)	< 0.001
AAMA, Mean (SD)	0.81 (0.82)	0.80 (0.82)	0.93 (0.91)	0.017
BPMA, Mean (SD)	0.12 (0.26)	0.12 (0.27)	0.10 (0.20)	0.014
DHBMA, Mean (SD)	3.33 (1.69)	3.31 (1.63)	3.57 (2.31)	0.047
MHBMA3, Mean (SD)	0.12 (0.21)	0.12 (0.20)	0.17 (0.23)	< 0.001
HPMMA, Mean (SD)	4.90 (7.48)	4.80 (7.43)	6.27 (8.02)	< 0.001
ATCA, Mean (SD)	1.64 (1.72)	1.63 (1.71)	1.81 (1.81)	0.158
AMCC, Mean (SD)	2.30 (2.50)	2.27 (2.47)	2.74 (2.87)	0.003
PGA, Mean (SD)	2.47 (8.30)	2.46 (8.58)	2.61 (2.25)	0.060
2HPMA, Mean (SD)	0.72 (4.30)	0.73 (4.45)	0.58 (0.99)	0.729
MA, Mean (SD)	1.92 (4.99)	1.90 (5.14)	2.19 (2.05)	< 0.001
BMA, Mean (SD)	0.14 (1.05)	0.14 (1.07)	0.15 (0.56)	0.282
2MHA, Mean (SD)	0.70 (5.39)	0.70 (5.58)	0.70 (0.93)	0.092
34MHA, Mean (SD)	4.72 (51.88)	4.74 (53.74)	4.49 (6.03)	0.020

3.2 Feature selection of UVOCs strongly associated with anhedonia

We used a machine learning approach to identify the most significant exposures among the 15 UVOCs. Briefly, a logistic regression model was employed to evaluate the direction and magnitude of associations (Figure 2A), an ENET model was established to further select UVOCs through regularization (Figure 2B), and a random forest model was trained to calculate feature importance scores (Figure 2C). Six UVOCs suggested by the overall models as strongly linked to anhedonia were chosen for subsequent analyses (Figure 2D): four showing positive associations (MHBMA3, DHBMA, MA, 3HPMA) and two showing inverse associations (2MHA, 2HPMA).

3.3 Associations between individual UVOCs and anhedonia

To explore the dose-response relationship of selected UVOCs, we performed logistic regression analyses with UVOC concentrations binned into quartiles (Q1-Q4), using the lowest quartile (Q1) as the reference (Figure 3A). MHBMA3 (Q4 vs. Q1: OR = 1.423, 95% CI: 1.004-2.016, P = 0.048)

and MA (Q4 vs. Q1: OR = 1.508, 95% CI: 1.083-2.101, P = 0.015) were positively associated with anhedonia.

ORs did not change monotonically across quartiles for most UVOCs, typically showing a slight decrease in Q3. Therefore, we conducted nonlinear analyses using GAM and RCS (Figure 3B-G) to better characterize these relationships. Consistently, UVOCs with previously positive associations exhibited J-shaped nonlinear patterns with anhedonia, while those with inverse associations revealed vertically symmetrical ones.

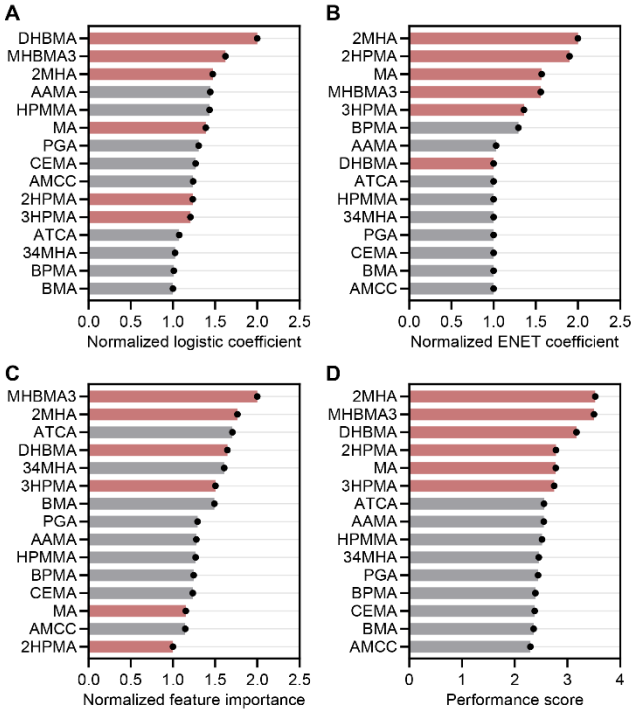


Fig. 2 - Feature selection of significant UVOCs.

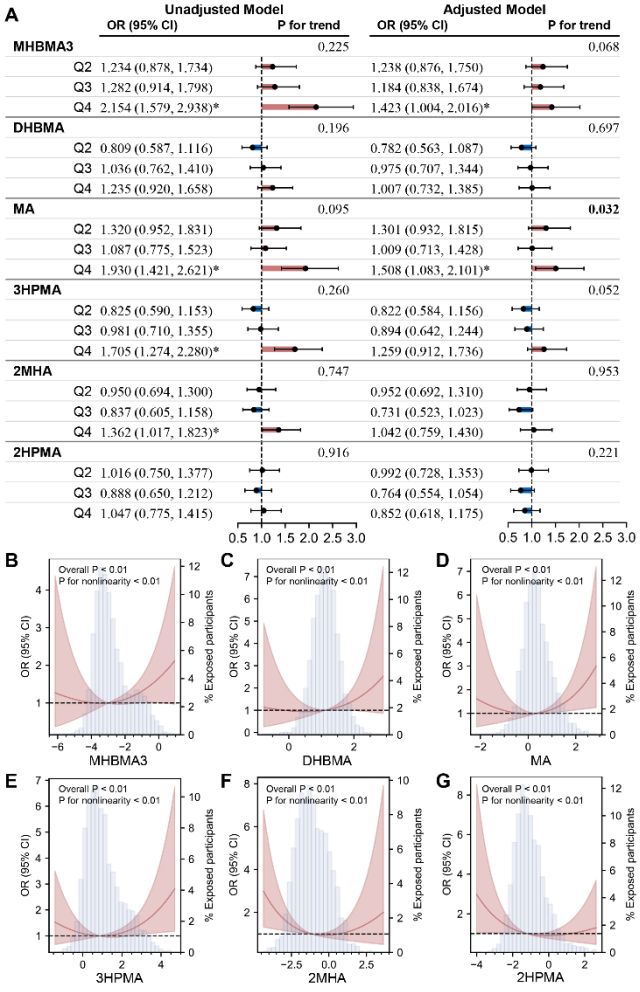
(A) Logistic regression, (B) ENET, and (C) random forest models were used to evaluate UVOCs with important contributions to anhedonia. Coefficients were min-max scaled. Models were adjusted for covariates including demographics and risk factors. (D) Performance scores of each UVOC across the three models. The top six UVOCs were selected and colored red.

3.4 Associations between mixed UVOCs and anhedonia

In the real world, multiple VOCs coexist and may produce intertwined effects, as evidenced by the strong correlations observed between nearly all UVOC pairs. To quantify such patterns of exposure, we constructed an ERS from the six UVOCs to evaluate its associations with anhedonia. Logistic regression indicated strong positive associations (continuous: OR = 1.395, 95% CI: 1.191-1.635, P < 0.001; quartile binned: Q4 vs. Q1, OR = 2.342, 95% CI: 1.415-3.876, P = 0.002) (Figure 4A).

We further applied WQS regression to evaluate the mixture while determining the relative contribution of individual UVOCs in the mixture (Figure 4B-F). In the positive direction, the model found a positive association between the WQS index and anhedonia (OR = 1.180, 95% CI: 1.010-1.380, P = 0.041), with DHBMA (weight = 0.358) as the top contributor. In the negative direction, no significant association was found.

The above findings altogether suggest that VOC exposure is overall linked to a higher prevalence of anhedonia. To facilitate clinical and environmental management, we developed a nomogram for fast, quantitative risk estimation of anhedonia based on the regression coefficients from a single logistic model incorporating the six UVOCs (Figure 5). In this nomogram, each UVOC concentration value is mapped to a corresponding point, and



the summed point is converted to the predicted probability of anhedonia.

Fig. 3 - Associations between individual UVOCs and anhedonia.

(A) Quartile-binned logistic regression between selected UVOCs and anhedonia, with Q1 as reference. Trend tests used quartile median values. * P < 0.05. (B-G) RCS models further characterized nonlinear associations. Red lines show the estimation of OR; red shadings show the 95% CI. Blue histograms show the distribution of participants. Models were adjusted for covariates including demographics and risk factors.

3.5 Immune components differentially mediate the associations of UVOCs with anhedonia

We examined immune mediators potentially involved in the associations of different UVOCs with anhedonia, and identified distinct modulatory patterns that showed low but highly significant proportions of mediation (Table S7). Compared to the direct pathways, WBC and neutrophils as mediators increased the risk of anhedonia, whereas lymphocytes and monocytes diminished the risk. Interestingly, albumin was found to suppress the direct pathways. These findings suggest that acute inflammatory cells serve as

detrimental mediators while other immune subpopulations may partially act as protective mediators in the associations of UVOCs and anhedonia.

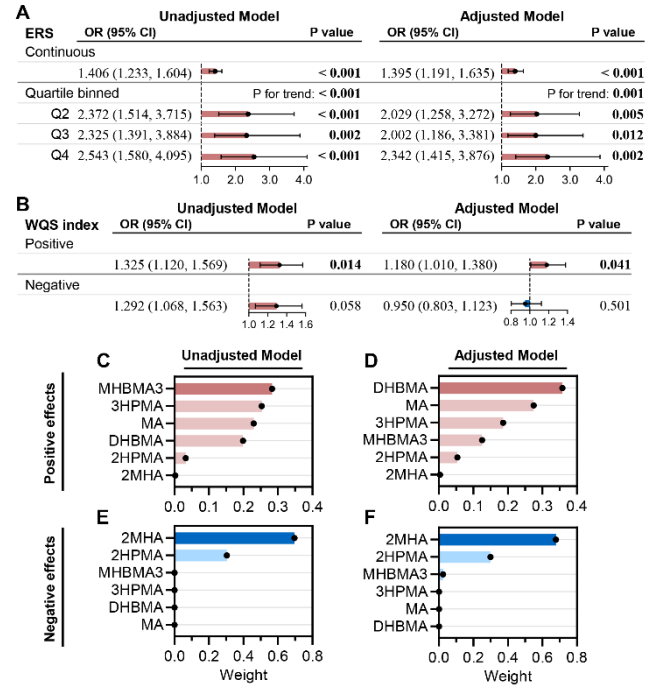


Fig. 4 - Associations between mixed UVOCs and anhedonia.
(A) Logistic regression between ERS and anhedonia; both the continuous analysis and quartile-binned one (with Q1 as reference) were conducted. Trend tests used quartile median values. (B) WQS regression, both in the positive (C & D) and negative (E & F) directions, validated these associations and identified key UVOCs contributing most to the mixture effects. Models were adjusted for covariates including demographics and risk factors. Error bars show the 95% CI.

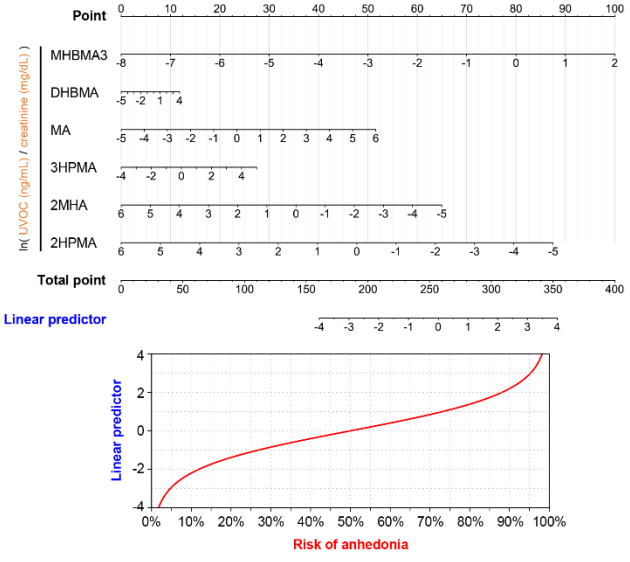


Fig. 5 - Nomogram for fast estimation of anhedonia risk.

3.6 Sensitivity analysis

First, we performed subgroup analysis and found that neither the positive associations (MHBMA3, DHBMA, ERS) nor inverse associations (2MHA, 2HPMA) varied across different groups of participants. Second, we supplementally included urine creatinine as a covariate and found that the six UVOCs retained previously detected associations with anhedonia. Third, we excluded samples with extremely dilute or concentrated urine (urine creatine < 30 mg/dL or > 300 mg/dL) [35] and found consistent results. These findings suggest VOC exposure is robustly linked to anhedonia.
However, when incorporating other eight items of PHQ-9, depression status, or PHQ-9 score as covariates in three respective models, these associations were no longer significant, suggesting that UVOCs may influence a broad spectrum of depressive symptoms besides anhedonia.

4. Discussion

We conducted the first systematic, cross-sectional investigation of the relationship between VOC exposure and anhedonia, one of the most prevalent symptoms in depressive disorders, on 5,084 participants from NHANES 2005-2020. Combining machine learning and regression analysis, we identified six out of fifteen UVOCs with significant links to anhedonia. Both linear and nonlinear models characterized four of them (MHBMA3, DHBMA, MA, 3HPMA) showing positive associations and two (2MHA, 2HPMA) showing inverse patterns. Accordingly, 1,3-butadiene, acrolein, and styrene are concluded as risk exposures of anhedonia, whereas metabolites of xylene and propylene oxide are likely protective predictors.
Comprehensive research has established links between VOC exposure and adverse outcomes involving the cardiovascular [40][41], urinary [42][43], and musculoskeletal systems [44][45][46]. Previous studies using PHQ-9 sum scores have also found that depression is closely associated with the exposure to benzene and ethylbenzene [8] and with exposure to acrylonitrile, toluene, and styrene [9]. To refine these disorder-level observations [47], one approach is to treat depressive symptoms as individual outcomes separated from the unitary concept of depression, which enables a more precise risk prediction while reducing the cumulative instability of self-report data. This design has been practiced and successfully identified acrylamide as the specific exposure that predicts suicidal ideation [35], another depressive symptom that brings about enormous social burden [48]. Inspired, we here further identified 1,3-butadiene as a risk predictor of anhedonia, and even proposed propylene oxide as an opposite. These VOC exposures identified, with nearly unshared composition and properties, motivate us to move forward this symptom-centered paradigm, which is expected to unveil more link patterns and possibly discover novel biomarkers.
Benzene and its derivatives, including styrene, represent a broad class of VOCs and are involved in neurological impairments, such as cognitive disorder and depression [8][9][49][50][51]. Styrene can interfere with neurotransmitters, such as dopamine and serotonin, responsible for reward processing [52][53]. In our analysis, styrene consistently acted as a contributor to increased anhedonia risk; however, xylene was found linked with decreased risk. We hypothesize that the observed outcomes of these disorders, as a whole, reflect the cumulated risks of their individual symptoms, each of which may show differential or even contradictory associations with VOC exposure. This can be validated in future analyses following a similar symptom-centered design.

1,3-Butadiene, as another VOC, is widely used in the production of synthetic rubbers, resins, and nylon. Environmental sources of 1,3-butadiene include industrial emissions, vehicle exhaust, and tobacco smoke [54]. Upon inhalation, it readily accumulates in the brain, forming reactive epoxides, DNA adducts, and protein conjugates that exert mutagenic and carcinogenic effects [55]. These biotransformation processes trigger oxidative stress, partly through glutathione depletion [56], and impair mitochondrial respiratory complexes [57]. Consequently, it causes damage to the central nervous system, inducing symptoms like headaches, blurred vision, hearing loss, and autism [58][59]. However, the implications of 1,3-butadiene exposure for emotional and cognitive regulation remain largely unexplored. A study conducted in a small population has identified its strong association with depression [10]. Future research may focus on neurotransmitter metabolism, such as monoamine synthesis, and dopaminergic projections to elucidate its effects on the reward system [60].

Intriguingly, we revealed that propylene oxide showed a remarkably negative association with anhedonia. To our knowledge, propylene oxide has never been reported to benefit mental health; instead, existing literature has clearly identified it as a direct-acting carcinogen due to its alkylating reactivity [61]. Primates chronically exposed to propylene oxide have been shown to develop axonal dystrophy in the medulla oblongata, coupled with somatic symptoms like incoordination and fatigue [62]. More broadly, a few studies have also found that certain metabolites, whose parent VOCs are well established to be detrimental, are associated with lower risk of depression, such as phenylglyoxylic acid (a metabolite of ethylbenzene and styrene) [63]. One possible explanation for such paradoxical findings is that elevated UVOC levels serve as biomarkers of an enhanced detoxification capacity. Individuals with robust metabolic function may more efficiently convert parent VOCs into their urinary metabolites, thereby reducing toxic burden and health consequences [64]. Nevertheless, we still expect direct evidence to either prove or disprove the seemingly protective associations with anhedonia, possibly building on behavioral paradigms, such as sucrose preference, that specifically reflect the pleasure experience and reward processing in animals [65]. Upon validated, these economical, industrialized compounds have the potential of being a new class of fast antidepressants upon structural modification to avoid toxigenic side effects.

Mechanistically, we identified three distinct patterns of mediation effects through different immune components to explain part of the associations between VOC exposure and anhedonia. First, WBC and neutrophils always increased the risk. Leukocyte infiltration and cytokine secretion create a sustained pro-inflammatory environment [66][67][68], which may compromise BBB integrity and trigger microglial activation [69][70]. This immune mobilization represents the primary inflammatory pathway linking VOC exposure to mental illness [11][71]. Second, lymphocytes and monocytes always decreased the risk. Among them, we propose it is the regulatory T cells and M2-polarized macrophages (differentiated from monocytes) that actually provide protection against VOCs [72][73]. Low-level, chronic VOC exposure may promote their release of anti-inflammatory and neurotrophic factors that improve toxin tolerance [74]. Third, albumin demonstrated a suppression mediation pattern. We consider it as a protective regulator that can buffer VOC toxicity. Some volatile compounds can bind to human serum albumin through van der Waals force and hydrophobic interactions, providing direct evidence that albumin may capture and sequester VOCs [75]. As a result, albumin acts as a limiting factor in toxin passage across biological membranes due to the high molecular mass of the complex formed, thus reducing VOC bioavailability [76].

Finally, we developed a nomogram for rapid, quantitative estimation of anhedonia risk with non-invasive urinary test data. Based on the regression coefficients, UVOC concentrations are together converted to a predicted probability of anhedonia. This tool, with its simple operability and reproducibility, is expected to support large-scale epidemiological screening and offer an adjunctive measure for depression diagnosis [77]. Notably, this study did not perform necessary real-world validation. Future research should evaluate its specificity and sensitivity before use, and possibly conduct calibrations addressing demographic, regional, and individual susceptibility differences [47]. Nevertheless, we have provided proof of concept for developing clinical tools that link chemical exposure to anhedonia risk.

This study has several limitations. First, the definition of anhedonia was rather brief and underspecified, because the PHQ-9 scale is not prepared for a comprehensive characterization of anhedonia. Some specifically designed measures [78][79] can provide more accurate assessments by differentiating anticipatory and consummatory pleasure in social and physical activities. Second, UVOCs only represent acute exposure to VOCs and may be influenced by individual metabolic capacity [4]. Third, putative causal relationships need longitudinal validation. Importantly, the protective associations identified for some exposures should be understood cautiously. Their validity, side effects, and chronic toxicity remain unclear. Additionally, we may overlook some unincluded covariates, given the complexity of emotional experiences and the diversity of air pollutants.

5. Conclusions

We provide the first symptom-specific evidence of bidirectional links between environmental VOC exposure and anhedonia prevalence in a nationally representative population. We propose a reevaluation of the intuition that all kinds of VOC exposure are detrimental, and demonstrate the significance of precision phenotyping in psychiatric epidemiology.

Declaration

A.1. Data availability

We used public data from the NHANES program supervised by the Ethics Review Board (ERB) of the National Center for Health Statistics (NCHS), with all participants having completed the written consent. Relevant information is available at https://www.cdc.gov/nchs/nhanes/about/erb.htm

-l. No newly enrolled human subjects are involved in this study.

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A.3. Authors' contributions

Bingxuan Huang: Conceptualization, Investigation, Formal analysis, Methodology, Software, Data curation, Writing - original draft, Writing - review and editing, Visualization, Supervision; Yuan Ning: Conceptualization, Investigation, Formal analysis, Methodology, Software, Data curation, Writing - review and editing, Visualization, Supervision; Xiangtong Li: In-

vestigation, Formal analysis, Software, Visualization. Mingyi Han: Investigation, Formal analysis, Software, Visualization. All authors approved this manuscript.

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