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# The mediating roles of obesity indicators and serum albumin in the association of DEET exposure with depression and sleep disorders in adults: evidence from NHANES 2007-2016

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## Abstract

**Background** DEET (N, N-diethyl-m-toluamide) is a widely used insect repellent with potential neurotoxic effects. However, its impact on mental health in the general population remains unclear. This study investigates the association between DEET exposure and depression and sleep disorders, exploring the mediating roles of obesity indicators and serum albumin.

**Methods** Data from the National Health and Nutrition Examination Survey (NHANES) 2007–2016 were analyzed. Urinary levels of 3-(diethylaminoformyl) benzoic acid (DCBA), a DEET metabolite, were used as an exposure marker. Depression was defined according to the scores of Patient Health questionnaire-9 (PHQ-9), and sleep disorders were diagnosed according to participants' self-reports. Multivariate logistic regression and restricted cubic spline analysis were employed to assess the associations of DCBA with depression and sleep disorders. Mediating analyses explored the roles of obesity indicators and serum albumin. Subgroup analysis further explored the differences among different populations.

**Results** Higher DCBA levels were positively associated with depression and sleep disorders. Mediating analysis revealed that body mass index (BMI), waist circumference (WC), and serum albumin mediated 11.16%, 12.66%, and 7.04% of the association between DEET exposure and depression, respectively. Subgroup analysis identified increased susceptibility among women and individuals of other races. Sensitivity analysis enhanced the robustness of the results.

**Conclusion** DEET exposure is associated with an increased risk of depression and sleep disorders, mediated by obesity and liver function indicators. These findings highlight the need for public health measures to reduce DEET exposure and further research into its mechanisms of action on mental health.

**Keywords** DEET, Depression, Sleep disorders, NHANES, Obesity, Serum albumin

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## Introduction

DEET (N, N-diethyl-m-toluenamide) stands as a cornerstone in the realm of insecticides, enjoying widespread global usage. Initially engineered by the U.S. Army for military protection, it has since transitioned into civilian applications [1]. The exceptional efficacy of DEET in deterring mosquito bites has cemented its importance in the global public health arena. A plethora of DEET-containing insect repellents populate the market, with over a third of the U.S. population applying these products annually [2]. The widespread use of insect repellents containing DEET components has led to substantial environmental release of DEET [3]. Research has shown that the presence of DEET can be detected in various water bodies worldwide, including surface water, groundwater, streams, and sewage systems [2]. Although DEET was previously considered almost harmless to human health at low exposure levels, with neurotoxic effects and even fatalities associated only with high concentrations, the increasing environmental exposure and detection rates of DEET still sparked concerns [4, 5]. Recent studies have indicated a positive correlation between DEET and its metabolites in the human body and the incidence of cardiovascular disease, hyperuricemia, and obesity [6–8], suggesting that even at safe dosages, chronic DEET exposure might increase the risk of these related ailments. Despite these findings, research in this area remains sparse, necessitating further investigation.

Mental disorders have emerged as a significant burden on global health, exerting profound impacts on public health and economic costs. The cascade of premature aging and accidental deaths attributed to mental disorders poses a grave threat to the physical and psychological well-being of individuals, escalating the financial burden on healthcare systems [9]. Depression and sleep disorders are among the most prevalent mental health issues, and are closely related and often occur together [10]. The World Health Organization (WHO) reports that around 300 million people globally are affected by depression and it is responsible for a significant number of suicides each year, with hundreds of thousands of deaths attributed to it [11]. Consequently, depression has become the primary contributor to global disability. Depression globally has continued to grow in 1990 2019 with a 30-year increase of 0.59% [9]. Of the approximately 18 million Americans with mood disorders found in a U.S. population study, about 10 million have major or clinical depression, and about two-thirds of them are untreated [12]. Modern society is full of factors that interfere with our normal sleep–wake rhythms, such as light pollution, noise, and occupational demands, resulting in an increasing incidence of sleep disorders in the population [13]. Results from the 2022 Centers for Disease Control and Prevention Sleep Survey of all U.S. adults older than 18 years of age showed that 36.8% of respondents reported getting a short amount of sleep (< 7 h), and that people with sleep disorders are more likely to suffer from chronic illnesses, such as cardiovascular disease, endocrine disorders, and renal disease, which severely reduces their quality of life and long-term prognosis [14]. The etiology of mental illnesses such as depression and sleep disorders are multifaceted, encompassing genetic predispositions, psychological stress, and environmental factors [15]. With the progress of industrialization, the potential harm caused by environmental pollution to health has come under the spotlight. Studies have demonstrated that numerous environmental pollutants are linked to an increased incidence of mental disorders [16–18]. As a common environmental pollutant, DEET has been implicated in disrupting neurotransmitter transmission, potentially impacting nervous system function and increasing the risk of mental disorders. However, a positive correlation of DEET exposure with mental disorders has been found only in high-risk populations exposed to substantial doses of DEET, such as Gulf War veterans [19, 20]. The impact of long-term, low-dose environmental DEET exposure on the mental disorders in the general population remains unclear and merits further exploration. Researchers have also identified body mass index (BMI), waist circumference, and liver function indicators such as albumin as pivotal in the pathogenesis of mental disorders, and DEET exposure has been closely linked to obesity and liver function impairment [8, 21–23]. Therefore, obesity and liver function-related indicators may act as mediators in the relationship between DEET exposure and mental disorders, offering crucial insights into their potential mechanisms.

This study leverages the National Health and Nutrition Examination Survey (NHANES) database to exam the association of DEET exposure with depression and sleep disorders in adults, and introduces BMI, waist circumference, and serum albumin as mediating variables to elucidate their potential mechanisms. To ensure the precision of our findings, we opted to use the most sensitive and specific DEET metabolite in urine, 3-(diethylaminoformyl) benzoic acid (DCBA), as a proxy for DEET levels in the human body, eschewing DEET and other metabolites with lower detection rates, such as N,N-diethyl-3-hydroxymethylbenzamide (DHMB) [24]. Our research endeavors to bridge the gap in understanding the long-term environmental impact of DEET on the mental health of the general population and to inform the development of environmental and public health policies with scientific rigor.

## Methods

### Study design and population

The Centers for Disease Control and Prevention (CDC) conducts the National Health and Nutrition Examination Survey (NHANES), a crucial health assessment that provides a comprehensive overview of the health and nutritional status of the U.S. population, including both adults and children. This cross-sectional study serves as a key tool for evaluating the health status and dietary habits of Americans. Extensive health and nutritional data are collected through a multistage probability sampling design and continuous multicycle surveys. The participants were invited to the Mobile Examination Center (EMC) for physical examination and biological sample collection. In addition, the participants also underwent family interviews to collect information about their dietary habits, physical activity, and use of health services. The National Center for Health Statistics' Ethics Review Committee granted approval for the survey. Informed consent was obtained from all individuals who participated in the study. Consequently, further approval by the Institutional Review Board is not necessary for this research.

We collected data from the NHANES from 2007 to 2016, covering five survey cycles, for this study. These cycles recruited a total of 50,588 participants. On the basis of the exclusion criteria in Fig. 1, unqualified participants were excluded from the study: age < 20 years ($N$= 21,387), missing DEET data ($N$= 20,347), and missing depression test and sleep disorders data ($N$= 863). Consequently, the final study population comprised 7,991 participants.

### Definitions of depression and sleep disorders

In the NHANES 2007–2016, we assessed depressive symptoms in adult participants through the administration of the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a well-established tool for screening depression symptoms, aligning with the diagnostic standards set forth by the American Psychiatric Association. By asking patients about their depression symptoms in the past two weeks, doctors can screen, diagnose, and evaluate the effectiveness of treatment for depression symptoms. The PHQ-9 questionnaire consists of 9 items, each representing an aspect of depressive symptoms, covering the core symptoms of depression and its impact on daily life. Each entry adopts a 4-point rating system, with responses ranging from 0 (never) to 3 (nearly every day). The total score range of the PHQ-9 is 0 to 27 points, with higher scores indicating more severe depression. Generally, participants with a cumulative score of 10 or higher on the PHQ-9 are identified as having depressive symptoms [25].

The definition of sleep disorders depends on participants' self-reports: "Have you ever told a doctor or medical professional that you have a sleep disorder?" The participants responded to the questionnaires in four ways: "yes", "no", "refused to answer" and "don't know". The participants who answered "refused" and "don't know" were excluded from the study, as were the participants who did not participate in the questionnaires. The participants who answered "yes" were considered to be suffering from sleep disorders, while the participants who answered "no" were considered to be none.

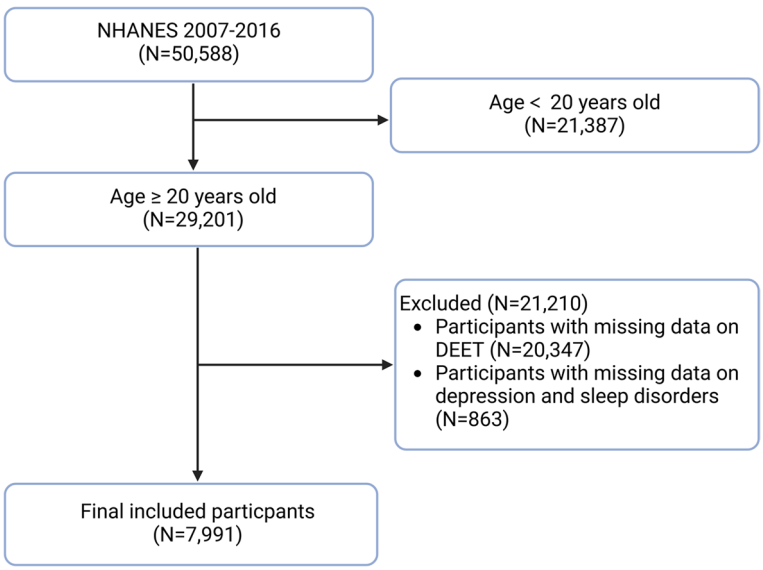


**Fig. 1** The flow chart of inclusion and exclusion criteria in the study. Abbreviations: NHANES, national Health and Nutrition Examination Survey; DEET, N, N-diethyl-m-toluamide

### Measurement of DCBA

DEET is rapidly metabolized within the human body, primarily eliminated through urinary excretion [26]. DCBA, which constitutes 83% of the urine's excreted content of DEET, serves as a definitive biomarker for DEET exposure [8, 27]. The employed technique involves the use of online solid-phase extraction coupled with high-performance liquid chromatography-tandem mass spectrometry (SPE-HPLC–MS/MS) for the quantification of DCBA in 100 μL samples of human urine. Then a series of operations such as decoupling, concentration, chromatographic separation, conversion, filtration, rupture, and refiltration are carried out to extract DCBA, and its concentration is measured. The unit of concentration of DCBA is expressed in ng/mL.

### Potential covariates

The potential covariates considered in this study included demographic characteristics, body measurements, laboratory tests, lifestyle and medical history, which included age, race, education level, marital status, poverty-to-income ratio (PIR), body mass index (BMI, $kg/m^2$), waist circumference (WC, cm), smoking status, drinking status, hypertension, diabetes mellitus, cardiovascular disease (CVD). Poverty was defined as a PIR of less than 1. Smoking status was categorized as never, current and quit using a cut-off of 100 cigarettes to date. Drinking status was considered to be greater than or equal to 12 times drinks in the past 12 months. The diagnosis of hypertension depended on meeting any of the following: self-reported hypertension, currently taking antihypertensive medication, average of systolic blood pressure greater than or equal to 140 mmHg and average of diastolic blood pressure greater than or equal to 90 mmHg after three or four consecutive measurements. Diabetes mellitus was defined by meeting any of the following: self-reported history of diabetes mellitus, currently taking glucose-lowering medication or insulin injections, glycosylated hemoglobin greater than or equal to 6.5%, and fasting plasma glucose $\geq$ 126 mg/dL [28]. If participants report being diagnosed with any of congestive heart failure, ischemic heart disease (including coronary heart disease, angina pectoris, and myocardial infarction), or stroke by a doctor or medical expert, they are considered CVD patients. The laboratory test results included serum albumin (ALB, g/L), alanine aminotransferase (ALT, U/L), serum creatinine (SCR, mg/dL), serum uric acid (SUA, μmol/L) and total cholesterol (TC, mmol/L) levels.

### Statistical analysis

The baseline characteristics of the study participants were delineated on the basis of their DCBA concentration in the urine. Owing to the skewed distribution of DCBA, continuous DCBA was log10-transformed to ensure the robustness of the results. The continuous variables were examined via *Mann–Whitney* U tests and are expressed as medians and quartiles. The categorical variables were compared via the *Chi-square* test and are described as numbers (n) and percentages (%). Some covariates are partially missing, such as WC missing 207(2.6%), ALB missing 339(4.2%), ALT missing 342(4.3%), SCR missing 340(4.3%), SUA missing 343(4.3%), TC missing 321(4.0%), and PIR missing 683 (8.5%), and other covariates with missing data less than 1%. We use the random forest imputation method to fill in the missing covariates.

The multivariate logistic regression analysis was employed to examine the associations of DCBA with depression and sleep disorders across three distinct models, each with a different set of covariates for adjustment. Model 1 was adjusted for no variables. Model 2 incorporates adjustments for gender, age, education level, poverty and marital status. Model 3 was adjusted for gender, age, education level, poverty, marital status, SCR, TC, smoking status, drinking status, diabetes, hypertension, CVD and sleep disorders. The analysis results are presented in terms of the odds ratio (OR) along with its 95% confidence interval (95%CI). The dose–response relationship of DCBA with depression and sleep disorders was depicted via a restricted cubic spline (RCS) curve in the fully adjusted Model 3. The subgroup analysis was conducted to assess potential factors that may affect the associations of DCBA with depression and sleep disorders in Model 3. Several stratified variables including gender, age, race, poverty, BMI, diabetes, hypertension, and CVD, were considered.

The mediating analysis was further applied to determine whether these relationships were partly mediated by ALB, BMI and WC. The purpose of mediation effects analysis is to understand how the independent variable affects the dependent variable through the mediating variable. Specifically, we used the mediate function from the mediation package to implement this analysis. We constructed two main regression models: the mediation model and the outcome model. The mediation model was used to assess the effect of the independent variable on the mediating variable, through which we estimated the direct effect of DCBA on BMI, WC, and ALB (path a). The outcome model was used to assess the joint effect of the independent and mediating variables on the dependent variable, through which we estimated the direct effect of DCBA on depression or sleep disorders (path c') as well as the direct effect of BMI, WC and ALB on depression or sleep disorders (path b). The core of the mediated effects analysis is the estimation of path a, path b and path c'. The path a represents the direct effect of the independent variable on the mediating variable, path b

represents the direct effect of the mediating variable on the dependent variable, and path c'represents the direct effect of the independent variable on the dependent variable after controlling for the mediating variable. The mediating effect, also known as the indirect effect can be estimated by the product of path a and path b, mediating effect = a*b. The total effect is equal to the direct effect c'plus the indirect effect ab, the total effect c = ab + c', and we use the mediate function to calculate the mediating effect, and 1000 times simulations are performed by the self-help method (bootstrapping) in order to obtain the confidence interval of the mediating confidence intervals for the effects, a method that provides more robust statistical inference.

In this study, we utilized the R software environment to carry out the statistical analyses (https://www.r-project.org/; version 4.3.3). The"car"package is used for analyzing multivariate logistic regression and interaction tests, the"broom"package for subgroup analysis, the"forestplotter"and"ggplot2"packages for drawing the forest plots, the"ggrcs"package for plotting RCS curves, and the"mediation"package for conducting mediation effects. A *p*-value of less than 0.05 from a two-tailed test was considered to indicate statistical significance.

#### Sensitivity analysis

To ensure the robustness of the findings and address potential confounding factors, we conducted three sensitivity analyses. The first analysis corrected for the effect of urine creatinine (UCR) levels on DEET exposure by regression predictive adjustment method. The second analysis included UCR as a confounding factor in Model 3. The third analysis included additional lifestyle factors in the regression model, including dietary intake and physical activity.

In studies, we typically use DEET metabolites in urine, such as DCBA, to assess DEET exposure levels. However, the concentration of metabolites in the urine may be affected by the degree to which the urine is diluted. This change is not related to the actual DEET exposure level, but can affect our assessment of the exposure level. UCR is a relatively stable metabolite, and its excretion is mainly related to muscle mass and kidney function, and is less affected by diet and water intake. Therefore, by adjusting UCR, the effect of urine dilution can be corrected to more accurately reflect the level of DEET exposure. To address the potential confounding effect of UCR on DEET exposure levels, we performed the sensitivity analysis using the regression prediction adjustment method and the confounding factor adjustment method. This method is designed to provide a more accurate measure of DEET exposure by correcting UCR levels.

In the first analysis, we established a linear regression model, taking UCR as the independent variable and DCBA concentration as the dependent variable, and obtained a linear regression equation. Substituting urine creatinine into the linear regression equation, each participant will have a new DCBA concentration, which we call the adjusted DCBA. It should be emphasized that this adjusted DCBA level was adjusted by urine creatinine. In the subsequent analysis, these adjusted DCBA were used as indicators of DEET exposure instead of the original DCBA concentration. This method directly corrected the effect of urine creatinine on the concentration of DCBA, enabling the concentration of DCBA to better reflect the true exposure level of DEET. We examined the association between the adjusted DCBA levels and the risk of developing depression and sleep disorders in the current three multivariate logistic regression models.

In the second analysis, UCR was included as a confounding factor in the model, while other potential confounding factors were adjusted in the multivariate logistic regression model. By adjusting for urine creatinine and other confounding factors, the independent association between DCBA concentration and the research results can be directly evaluated. This method directly adjusts the influence of urine creatinine in the model and simultaneously adjusts multiple confounding factors to provide a more comprehensive analysis. We consider this method to be a reliable way to adjust the effect of urine creatinine.

In the third analysis, we incorporated additional lifestyle factors into Model 3 to further ensure the robustness of our findings. Specifically, we adjusted for daily energy intake and physical activity levels to assess the relationship between DEET exposure and mental health outcomes. The energy intake was measured in kilocalories per day (kcal/day), reflecting the total energy consumed from food and beverages. Physical activity can be divided into no physical activity, moderate physical activity and vigorous physical activity. Moderate physical activity is defined as performing any moderate-intensity exercise, fitness, or recreational activity that causes a slight increase in breathing or heart rate for at least 10 min continuously over a 1-week period. Vigorous physical activity is defined as any vigorous exercise, fitness or recreational activity that causes a substantial increase in breathing or heart rate for at least 10 consecutive minutes during the week. The expanded Model 3 includes the following confounding factors: gender, age, education level, poverty, marital status, SCR, TC, smoking status, drinking status, diabetes, hypertension, CVD, sleep disorders, energy intake and physical activity. In the expanded Model 3, the relationship between DEET exposure and mental health outcomes was re-evaluated.

## Results

### Baseline characteristics

After rigorous screening, a total of 7,991 participants were included in the study. Among them, 2,052 (25.68%) had sleep disorders, and 733 (9.17%) had depression. The median age was 49 years, with women comprising 51.08% of the cohort. In terms of race, white were the majority at 42.86%. Regarding education, 53.44% had received education beyond high school. Poverty status was noted in 20.62%, while 58.87% were married or living with a partner. Smoking and drinking habits revealed that 55.29% had never smoked, and 71.48% were drinkers. In terms of medical history, 16.38% had diabetes, 42.67% had hypertension, and 10.64% had cardiovascular disease. Participants were divided into four groups based on their log-transformed DCBA quartiles (Q1-Q4). Table 1 presents the baseline characteristics of participants grouped by quartile. Compared to the lowest quartile, those in the highest quartile were generally younger, more likely to be male, white, have lower education levels, be classified as poor, and be married or living with a partner. This group also exhibited higher levels of BMI, WC, ALT, SCR and SUA. They were more likely to be current smokers and drinkers, yet less likely to have a history of diabetes, hypertension, or CVD. Significantly, they had a higher prevalence of depression and sleep disorders.

### Association of DCBA with depression and sleep disorders in adults

A multivariate logistic regression analysis was conducted to explore the association between DCBA exposure, expressed both continuously and in quartiles, and the prevalence of depression and sleep disorders among adults (Table 2). The continuous analysis showed that, in Model 1 without any adjustment, a positive correlation was observed between log10-transformed DCBA levels and depression prevalence, with a 14% increase in depression risk for each 1 ng/ml increment in the natural logarithm of DCBA (OR = 1.14, 95%CI:1.04–1.26, p = 0.005). No significant association was found between log10-transformed DCBA and sleep disorders (OR = 1.04, 95%CI:0.98–1.11, p = 0.205). In the fully adjusted Model 3, a significant positive correlation was found between log10-transformed DCBA and both depression and sleep disorders. Specifically, a 1 ng/ml increase in the natural logarithm of DCBA was associated with a 13% increase in depression prevalence (OR = 1.13, 95%CI:1.02–1.25, p = 0.021) and a 7% increase in sleep disorders prevalence (OR = 1.07, 95%CI:1.01–1.15, p = 0.038). The categorical analysis shows that in Model 3, the third quartile (Q3) of log10-transformed DCBA was linked to a higher prevalence of depression compared to the lowest quartile (Q1) (OR = 1.27, 95%CI:1.00–1.60, p = 0.048), and the highest quartile (Q4) was linked to a higher prevalence of sleep disorders (OR = 1.18, 95%CI:1.02–1.37, p = 0.031). An increase in the quartiles of log10-transformed DCBA was significantly associated with an increased prevalence of depression (p for trend = 0.029) and sleep disorders (p for trend = 0.016). In Model 3, the RCS analysis was performed to assess the dose–response relationship between DCBA and the two disorders in adults, as depicted in Fig. 2. The analysis demonstrated a significant linear association (p-values for nonlinearity were 0.605 and 0.179, respectively).

### Subgroup analyses

Subgroup analyses and interaction tests were performed across various demographic and health-related factors, including gender, age, race, poverty, BMI, diabetes, hypertension, and CVD. The findings from these analyses are depicted in Fig. 3. The correlation between DCBA exposure and the prevalence of depression is still positive in female, less than 50 years old, other race, non-poor, BMI less than 30 $kg/m^2$, without diabetes, without hypertension and without CVD individuals. The correlation between DCBA exposure and the prevalence of sleep disorders remains positive in males, black individuals, and non-CVD individuals. Notably, there were interactions only for female (p for interaction = 0.047) and other race (p for interaction = 0.040) in the relationship between DCBA exposure and depression.

### Mediating analysis

In the mediating analysis, we investigated whether serum albumin, BMI and WC mediate the relationship of DCBA with depression and sleep disorders (Tables 3 and 4). We found a significant positive correlation between DCBA and depression in Model 3 (total effect = 0.00995, 95%CI: 0.00205–0.01784; $p = 0.014$). DCBA indirectly increases the risk of depression by increasing BMI (indirect effect = 0.00111, 95%CI: 0.00053–0.00191; $p < 0.001$) and WC (indirect effect = 0.00126, 95%CI: 0.00067–0.00209; $p < 0.001$), and reducing ALB (indirect effect = 0.00070, 95%CI: 0.00025–0.00138; $p = 0.004$). The direct effect of DCBA exposure on depression remained significant, after controlling for the effects of BMI, WC, and ALB separately. Therefore, the proportion of mediating effects of BMI, WC, and ALB is 11.16%, 12.66%, and 7.04%, respectively (Fig. 4). Furthermore, we did not find any mediating effects of BMI, WC, and ALB in the relationship between DCBA exposure and sleep disorders. There was a significant positive correlation between DCBA and sleep disorders in Model 3 (total effect = 0.01241, 95%CI: 0.00030–0.02453; $p = 0.045$). However, after controlling for the effects of BMI, WC, and ALB separately,

**Table 1** Baseline characteristics of participants according to DCBA exposure

| Variables | Total participants | log10-transformed DCBA, ng/mL | | | | *p*-value |
|---|---|---|---|---|---|---|
| | | Q1 (≤ −0.176) | Q2 (−0.176 ~ 0.303) | Q3 (0.303 ~ 0.862) | Q4 (≥ 0.862) | |
| **Count** | 7991 | 1995 | 1998 | 2000 | 1998 | |
| **Age, years** | 49.00 (34.00,64.00) | 54.00 (39.00,66.00) | 49.00 (34.00,64.00) | 47.00 (33.00,63.00) | 47.00 (34.00,62.00) | < 0.001 |
| **Gender, n (%)** | | | | | | < 0.001 |
| Female | 4082 (51.08) | 1113 (55.79) | 1064 (53.25) | 982 (49.10) | 923 (46.20) | |
| Male | 3909 (48.92) | 882 (44.21) | 934 (46.75) | 1018 (50.90) | 1075 (53.80) | |
| **Race, n (%)** | | | | | | < 0.001 |
| Mexican American | 1214 (15.19) | 336 (16.84) | 270 (13.51) | 292 (14.60) | 316 (15.82) | |
| Non-Hispanic White | 3425 (42.86) | 852 (42.71) | 843 (42.19) | 827 (41.35) | 903 (45.20) | |
| Non-Hispanic Black | 1673 (20.94) | 262 (13.13) | 470 (23.52) | 489 (24.45) | 452 (22.62) | |
| Other Race | 1679 (21.01) | 545 (27.32) | 415 (20.77) | 392 (19.60) | 327 (16.37) | |
| **Education level, n (%)** | | | | | | 0.006 |
| High school or below | 3721 (46.56) | 882 (44.21) | 919 (46.00) | 928 (46.40) | 992 (49.65) | |
| Above high school | 4270 (53.44) | 1113 (55.79) | 1079 (54.00) | 1072 (53.60) | 1006 (50.35) | |
| **poverty,n(%)** | | | | | | < 0.001 |
| No | 6343 (79.38) | 1653 (82.86) | 1578 (78.98) | 1541 (77.05) | 1571 (78.63) | |
| Yes | 1648 (20.62) | 342 (17.14) | 420 (21.02) | 459 (22.95) | 427 (21.37) | |
| **Marital status, n (%)** | | | | | | < 0.001 |
| Married/living with partner | 4704 (58.87) | 1185 (59.40) | 1146 (57.36) | 1115 (55.75) | 1258 (62.96) | |
| Widowed/ divorced/separated | 1769 (22.14) | 484 (24.26) | 451 (22.57) | 467 (23.35) | 367 (18.37) | |
| Never married | 1518 (19.00) | 326 (16.34) | 401 (20.07) | 418 (20.90) | 373 (18.67) | |
| **BMI, kg/m$^2$** | 28.17 (24.36,32.60) | 27.20 (23.90,31.60) | 28.20 (24.30,32.52) | 28.60 (24.70,33.10) | 28.81 (24.70,33.30) | < 0.001 |
| **WC, cm** | 98.30 (87.90,109.10) | 96.40 (86.60,107.00) | 98.00 (87.60,109.10) | 99.10 (88.80,109.60) | 99.90 (88.90,111.00) | < 0.001 |
| **Smoke, n (%)** | | | | | | < 0.001 |
| Never | 4418 (55.29) | 1179 (59.10) | 1147 (57.41) | 1100 (55.00) | 992 (49.65) | |
| Current | 1685 (21.09) | 331 (16.59) | 390 (19.52) | 454 (22.70) | 510 (25.53) | |
| Quit | 1888 (23.63) | 485 (24.31) | 461 (23.07) | 446 (22.30) | 496 (24.82) | |
| **Drink,n(%)** | | | | | | < 0.001 |
| No | 2279 (28.52) | 650 (32.58) | 58 5(29.28) | 567 (28.35) | 477 (23.87) | |
| Yes | 5712 (71.48) | 1345 (67.42) | 1413 (70.72) | 1433 (71.65) | 1521 (76.13) | |
| **Diabetes, n (%)** | | | | | | 0.427 |
| No | 6682 (83.62) | 1660 (83.21) | 1653 (82.73) | 1690 (84.50) | 1679 (84.03) | |
| Yes | 1309 (16.38) | 335 (16.79) | 345 (17.27) | 310 (15.50) | 319 (15.97) | |
| **Hypertension, n (%)** | | | | | | 0.373 |
| No | 4581 (57.33) | 1113 (55.79) | 1143 (57.21) | 1167 (58.35) | 1158 (57.96) | |
| Yes | 3410 (42.67) | 882 (44.21) | 855 (42.79) | 833 (41.65) | 840 (42.04) | |
| **CVD, n (%)** | | | | | | 0.573 |
| No | 7141 (89.36) | 1775 (88.97) | 1775 (88.84) | 1801 (90.05) | 1790 (89.59) | |
| Yes | 850 (10.64) | 220 (11.03) | 223 (11.16) | 199 (9.95) | 208 (10.41) | |
| **Sleep, n (%)** | | | | | | 0.471 |
| No | 5939 (74.32) | 1503 (75.34) | 1494 (74.77) | 1476 (73.80) | 1466 (73.37) | |
| Yes | 2052 (25.68) | 492 (24.66) | 504 (25.23) | 524 (26.20) | 532 (26.63) | |
| **Depression, n (%)** | | | | | | 0.017 |
| No | 7258 (90.83) | 1842 (92.33) | 1823 (91.24) | 1798 (89.90) | 1795 (89.84) | |
| Yes | 733 (9.17) | 153 (7.67) | 175 (8.76) | 202 (10.10) | 203 (10.16) | |

**Table 1** (continued)

| Variables | Total participants | log10-transformed DCBA, ng/mL | | | | *p*-value |
|---|---|---|---|---|---|---|
| | | Q1 (≤ −0.176) | Q2 (−0.176 ~ 0.303) | Q3 (0.303 ~ 0.862) | Q4 (≥ 0.862) | |
| **ALB, g/L** | 43.00 (40.97,45.00) | 43.00 (41.00,45.00) | 42.00 (40.00,45.00) | 43.00 (40.00,45.00) | 43.00 (41.00,45.00) | < 0.001 |
| **ALT, U/L** | 21.00 (16.00,28.00) | 21.00 (16.00,27.00) | 20.00 (16.00,27.00) | 21.00 (16.00,28.00) | 21.00 (17.00,29.00) | < 0.001 |
| **SCR, mg/dL** | 0.85 (0.72,1.00) | 0.82 (0.69,0.97) | 0.84 (0.72,1.00) | 0.86 (0.72,1.02) | 0.88 (0.73,1.02) | < 0.001 |
| **SUA, μmol/L** | 321.20 (261.70,374.70) | 309.30 (255.80,362.80) | 315.20 (261.70,374.70) | 321.91 (267.70,374.70) | 333.10 (273.60,392.60) | < 0.001 |
| **TC, mmol/L** | 4.94 (4.27,5.64) | 5.00 (4.34,5.69) | 4.91 (4.27,5.59) | 4.89 (4.22,5.61) | 4.96 (4.27,5.64) | 0.008 |

The continuous variables were expressed as median and quartiles, and the categorical variables were expressed as number and percentage

*Abbreviations*: *DCBA*, 3-(diethylcarbamoyl) benzoic acid, *BMI* body mass index, *WC* waist circumference, *CVD* cardiovascular disease, *ALB* albumin, *ALT* alanine aminotransferase, *SCR* serum creatinine, *SUA* serum uric acid, *TC* total cholesterol

**Table 2** Multivariable logistic regression between DCBA and depression and sleep disorders in adults

| log10-transformed DCBA and depression | | | | | | |
|---|---|---|---|---|---|---|
| DCBA, ng/mL | Model 1 | | Model 2 | | Model 3 | |
| | OR (95%CI) | *p*-value | OR (95%CI) | *p*-value | OR (95%CI) | *p*-value |
| Continuous | 1.14 (1.04,1.26) | 0.005 | 1.17 (1.06,1.29) | 0.001 | 1.13 (1.02,1.25) | 0.021 |
| Quartiles | | | | | | |
| Q1 | Reference | | Reference | | Reference | |
| Q2 | 1.16 (0.92,1.45) | 0.210 | 1.13 (0.90,1.43) | 0.290 | 1.10 (0.87,1.40) | 0.426 |
| Q3 | 1.35 (1.09,1.69) | 0.007 | 1.34 (1.07,1.67) | 0.012 | 1.27 (1.00,1.60) | 0.048 |
| Q4 | 1.36 (1.09,1.70) | 0.006 | 1.39 (1.11,1.75) | 0.004 | 1.26 (1.00,1.59) | 0.054 |
| p for trend | 0.002 | | 0.001 | | 0.029 | |
| log10-transformed DCBA and Sleep disorders | | | | | | |
| DCBA, ng/mL | Model 1 | | Model 2 | | Model 3 | |
| | OR (95%CI) | *p*-value | OR (95%CI) | *p*-value | OR (95%CI) | *p*-value |
| Continuous | 1.04 (0.98,1.11) | 0.205 | 1.10 (1.03,1.17) | 0.005 | 1.07 (1.01,1.15) | 0.038 |
| Quartiles | | | | | | |
| Q1 | Reference | | Reference | | Reference | |
| Q2 | 1.03 (0.89,1.19) | 0.681 | 1.09 (0.94,1.26) | 0.252 | 1.06 (0.91,1.23) | 0.470 |
| Q3 | 1.09 (0.94,1.25) | 0.264 | 1.19 (1.03,1.37) | 0.021 | 1.16 (1.00,1.34) | 0.056 |
| Q4 | 1.11 (0.96,1.28) | 0.155 | 1.25 (1.08,1.45) | 0.002 | 1.18 (1.02,1.37) | 0.031 |
| p for trend | 0.116 | | 0.001 | | 0.016 | |

Model 1 adjusted for no variables. Model 2 adjusted for gender, age, education level, poverty and marital status. Model 3 adjusted for gender, age, education level, poverty, marital status, SCR, TC, smoking status, drinking status, diabetes, hypertension, CVD and sleep disorders

DCBA exposure has no significant direct effect on sleep disorders.

### Sensitivity analysis

In order to increase the feasibility of the results and the robustness of the regression model, we conducted a sensitivity analysis.

The results show that under the current regression model, the relationship between the adjusted DCBA concentration and the risk of depression and sleep disorders is basically consistent with the previous results (Table S1). In the new model 3 that included urine creatinine, the relationship between DEET exposure and mental disorders still maintained strong robustness (Table S2). We extend the confounders in the current model 3 to increase energy intake and physical activity. In expanded Model 3, we found that urinary DCBA remained positively associated with the incidence of depression and sleep disorders (Table S3).

## Discussion

This study is the first to explore the relationship between environmental DEET exposure and the risk of mental disorders in the general population. The results indicate a significant positive correlation between DEET levels and the risk of depression and sleep disorders among the general U.S. population in the NHANES database from 2007 to 2016. Furthermore, to delve into the underlying

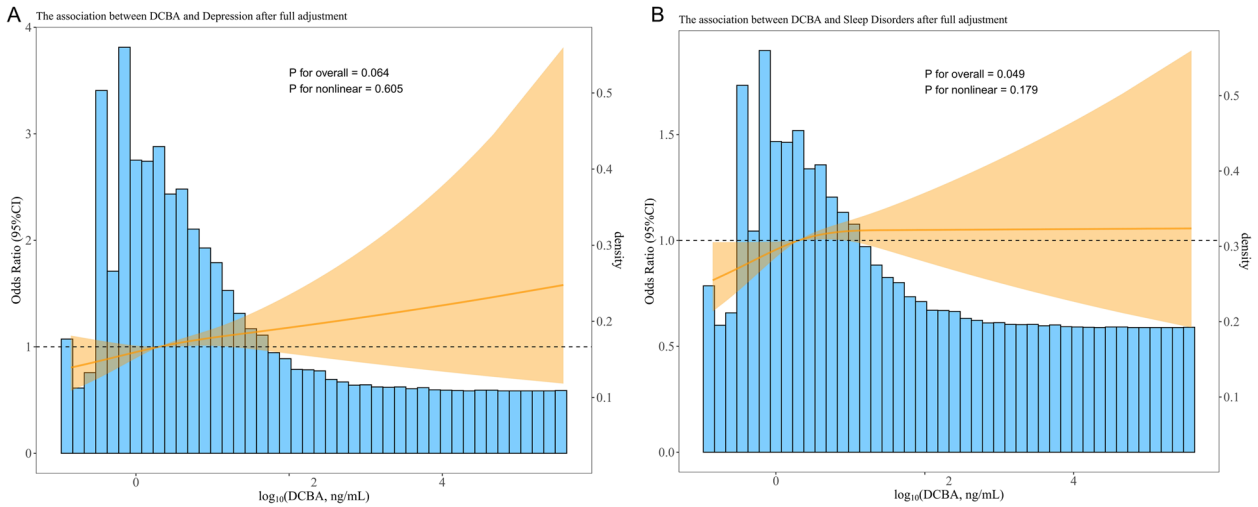


**Fig. 2** The dose–response relationship of DCBA with depression (**A**) and sleep disorders (**B**) in adults. The OR (orange solid lines) and 95%CI (orange shaded areas) in the RCS was adjusted for gender, age, education level, poverty, marital status, SCR, TC, smoking status, drinking status, diabetes, hypertension, CVD and sleep disorders

**A**

| Subgroups | Count | Depression, n(%) | OR (95% CI) | p-value | p for interaction |
|---|---|---|---|---|---|
| Overall | 7991 | 733(9.17%) | | | |
| Gender | | | | | 0.047 |
| Female | 4082 | 469(11.49%) | 1.17 (1.02 to 1.33) | 0.023 | |
| Male | 3909 | 264(6.75%) | 1.07 (0.90 to 1.26) | 0.423 | |
| Age, years | | | | | 0.506 |
| < 50 | 4016 | 359(8.94%) | 1.17 (1.01 to 1.35) | 0.038 | |
| >= 50 | 3975 | 374(9.41%) | 1.10 (0.95 to 1.27) | 0.195 | |
| Race | | | | | 0.040 |
| Mexican American | 1214 | 105(8.65%) | 1.06 (0.79 to 1.41) | 0.672 | |
| Non-Hispanic White | 3425 | 302(8.82%) | 1.04 (0.89 to 1.22) | 0.613 | |
| Non-Hispanic Black | 1673 | 174(10.40%) | 1.12 (0.88 to 1.40) | 0.347 | |
| Other Race | 1679 | 152(9.05%) | 1.40 (1.13 to 1.73) | 0.002 | |
| Poverty | | | | | 0.919 |
| No | 6343 | 455(7.17%) | 1.16 (1.02 to 1.31) | 0.018 | |
| Yes | 1648 | 278(16.87%) | 1.07 (0.89 to 1.28) | 0.471 | |
| Marital status | | | | | 0.101 |
| Married/living with partner | 4704 | 315(6.70%) | 1.06 (0.90 to 1.23) | 0.468 | |
| Widowed/divorced/separated | 1769 | 271(15.32%) | 1.17 (0.98 to 1.39) | 0.080 | |
| Never married | 1518 | 147(9.68%) | 1.20 (0.96 to 1.50) | 0.109 | |
| BMI, Kg/m2 | | | | | 0.951 |
| < 30 | 4901 | 354(7.22%) | 1.16 (1.00 to 1.34) | 0.043 | |
| >= 30 | 3090 | 379(12.27%) | 1.07 (0.92 to 1.24) | 0.357 | |
| Diabetes | | | | | 0.584 |
| No | 6682 | 561(8.40%) | 1.13 (1.00 to 1.26) | 0.043 | |
| Yes | 1309 | 172(13.14%) | 1.15 (0.91 to 1.46) | 0.238 | |
| Hypertension | | | | | 0.864 |
| No | 4581 | 346(7.55%) | 1.19 (1.03 to 1.36) | 0.018 | |
| Yes | 3410 | 387(11.35%) | 1.06 (0.91 to 1.23) | 0.424 | |
| CVD | | | | | 0.622 |
| No | 7141 | 590(8.26%) | 1.16 (1.04 to 1.30) | 0.008 | |
| Yes | 850 | 143(16.82%) | 0.94 (0.72 to 1.22) | 0.642 | |

**B**

| Subgroups | Count | Sleep Disorders, n(%) | OR (95% CI) | p-value | p for interaction |
|---|---|---|---|---|---|
| Overall | 7991 | 2052(25.68%) | | | |
| Gender | | | | | 0.469 |
| Female | 4082 | 1201(29.42%) | 1.04 (0.95 to 1.14) | 0.432 | |
| Male | 3909 | 851(21.77%) | 1.11 (1.01 to 1.22) | 0.029 | |
| Age, years | | | | | 0.749 |
| < 50 | 4016 | 845(21.04%) | 1.08 (0.97 to 1.19) | 0.148 | |
| >= 50 | 3975 | 1207(30.36%) | 1.06 (0.97 to 1.16) | 0.230 | |
| Race | | | | | 0.072 |
| Mexican American | 1214 | 208(17.13%) | 1.00 (0.80 to 1.23) | 0.978 | |
| Non-Hispanic White | 3425 | 1084(31.65%) | 0.96 (0.88 to 1.06) | 0.450 | |
| Non-Hispanic Black | 1673 | 418(24.99%) | 1.24 (1.06 to 1.45) | 0.008 | |
| Other Race | 1679 | 342(20.37%) | 1.15 (0.99 to 1.35) | 0.071 | |
| Poverty | | | | | 0.204 |
| No | 6343 | 1582(24.94%) | 1.05 (0.98 to 1.13) | 0.171 | |
| Yes | 1648 | 470(28.52%) | 1.13 (0.97 to 1.32) | 0.103 | |
| Marital status | | | | | 0.642 |
| Married/living with partner | 4704 | 1125(23.92%) | 1.05 (0.96 to 1.14) | 0.271 | |
| Widowed/divorced/separated | 1769 | 581(32.84%) | 1.13 (0.99 to 1.30) | 0.078 | |
| Never married | 1518 | 346(22.79%) | 1.00 (0.85 to 1.19) | 0.971 | |
| BMI, Kg/m2 | | | | | 0.925 |
| < 30 | 4901 | 1100(22.44%) | 1.06 (0.97 to 1.16) | 0.164 | |
| >= 30 | 3090 | 952(30.81%) | 1.06 (0.96 to 1.18) | 0.258 | |
| Diabetes | | | | | 0.329 |
| No | 6682 | 1577(23.60%) | 1.06 (0.98 to 1.14) | 0.122 | |
| Yes | 1309 | 475(36.29%) | 1.12 (0.95 to 1.32) | 0.180 | |
| Hypertension | | | | | 0.835 |
| No | 4581 | 926(20.21%) | 1.10 (1.00 to 1.20) | 0.052 | |
| Yes | 3410 | 1126(33.02%) | 1.04 (0.94 to 1.14) | 0.484 | |
| CVD | | | | | 0.939 |
| No | 7141 | 1705(23.88%) | 1.08 (1.01 to 1.16) | 0.035 | |
| Yes | 850 | 347(40.82%) | 1.03 (0.85 to 1.25) | 0.753 | |

**Fig. 3** Each subgroup analysis was adjusted for gender, age, education level, poverty, marital status, SCR, TC, smoking status, drinking status, diabetes, hypertension, CVD and sleep disorders, except for stratified variables

mechanisms, we conducted mediation analyses and found that BMI, waist circumference (WC), and ALB are potential mediating factors for this positive correlation. Subsequent subgroup analyses revealed significant interactions between DEET exposure and depression across gender and racial subgroups. Specifically, the occurrence of depression is more susceptible to the influence of DEET exposure in women and individuals of other races, providing a novel perspective on the field of research into the health impacts of environmental DEET exposure. In addition, the results of sensitivity analysis showed that the relationship between UCR-adjusted DCBA concentrations and the risk of depression and sleep disorders was generally consistent with previous results. In the expanded model 3, which newly included energy intake and physical activity, the positive association between DCBA and the incidence of depression and sleep disorders remained robust.

**Table 3** Mediating effects in the association between the DCBA and depression in adults

| Mediating effects | Coefficient | Standard error | 95 % CI | *p*-value |
|---|---|---|---|---|
| BMI ~ X | 0.58533 | 0.09532 | (0.39848,0.77218) | < 0.001 |
| Y ~ BMI | 0.00197 | 0.00047 | (0.00104,0.00289) | 0.00003 |
| Total | 0.00995 | 0.00403 | (0.00205,0.01784) | 0.01354 |
| Direct | 0.00884 | 0.00403 | (0.00093,0.01674) | 0.02846 |
| Indirect | 0.00111 | 0.00037 | (0.00053,0.00191) | < 0.001 |
| Waist ~ X | 1.39560 | 0.22213 | (0.96016,1.83104) | < 0.001 |
| Y ~ Waist | 0.00093 | 0.00020 | (0.00054,0.00133) | < 0.001 |
| Total | 0.00995 | 0.00403 | (0.00205,0.01784) | 0.01354 |
| Direct | 0.00869 | 0.00403 | (0.00078,0.01659) | 0.03122 |
| Indirect | 0.00126 | 0.00037 | (0.00067,0.00209) | < 0.001 |
| ALB ~ X | −0.21174 | 0.04561 | (−0.30115,−0.12234) | < 0.001 |
| Y ~ ALB | −0.00341 | 0.00099 | (−0.00534,−0.00147) | 0.00056 |
| Total | 0.00995 | 0.00403 | (0.00205,0.01784) | 0.01354 |
| Direct | 0.00925 | 0.00403 | (0.00135,0.01715) | 0.02174 |
| Indirect | 0.00070 | 0.00028 | (0.00025,0.00138) | 0.00400 |

The mediating analysis adjusted for gender, age, education level, poverty, marital status, SCR, TC, smoking status, drinking status, diabetes, hypertension, CVD and sleep disorders. X represents DCBA and Y represents depression

**Table 4** Mediating effects in the association between the DCBA and sleep disorders in adults

| Mediating effects | Coefficient | Standard error | 95 % CI | *p*-value |
|---|---|---|---|---|
| BMI ~ X | 0.59898 | 0.09553 | (0.41172,0.78624) | < 0.001 |
| Y ~ BMI | 0.00468 | 0.00072 | (0.00327,0.00610) | < 0.001 |
| Total | 0.01241 | 0.00618 | (0.00030,0.02453) | 0.04464 |
| Direct | 0.00966 | 0.00618 | (−0.00246,0.02177) | **0.11826** |
| Indirect | 0.00276 | 0.00059 | (0.00168,0.00403) | < 0.001 |
| Waist ~ X | 1.43171 | 0.22279 | (0.99499,1.86843) | < 0.001 |
| Y ~ Waist | 0.00227 | 0.00031 | (0.00167,0.00288) | < 0.001 |
| Total | 0.01241 | 0.00618 | (0.00030,0.02453) | 0.04464 |
| Direct | 0.00921 | 0.00618 | (−0.00290,0.02132) | **0.13609** |
| Indirect | 0.00321 | 0.00068 | (0.00213,0.00478) | < 0.001 |
| ALB ~ X | −0.21439 | 0.04561 | (−0.30381,−0.12498) | < 0.001 |
| Y ~ ALB | −0.00407 | 0.00151 | (−0.00704,−0.00110) | 0.00724 |
| Total | 0.01241 | 0.00618 | (0.00030,0.02453) | 0.04464 |
| Direct | 0.01157 | 0.00619 | (−0.00056,0.02370) | **0.06145** |
| Indirect | 0.00084 | 0.00039 | (0.00021,0.00172) | 0.00800 |

The mediating analysis adjusted for gender, age, education level, poverty, marital status, SCR, TC, smoking status, drinking status, diabetes, hypertension, CVD and sleep disorders. X represents DCBA and Y represents sleep disorders

Existing research on the relationship between DEET environmental exposure and mental disorders such as depression and sleep disorders are scarce, particularly in the general population. Previous studies primarily found a positive correlation between DEET exposure and a range of diseases including neurological and mental disorders among Gulf War veterans, collectively referred to as "Gulf War Syndrome" [29]. These veterans were exposed to a significant amount of environmental pollutants like DEET in the war environment, leading to a marked increase in the incidence of depression and sleep disorders [30, 31]. DEET exposure has been associated with an increased risk of depression in multiple human and animal studies, primarily through mechanisms affecting hippocampal neurons and the cholinergic system [32].

Firstly, DEET exposure may inhibit the growth and survival of hippocampal neurons. In animal experiments,

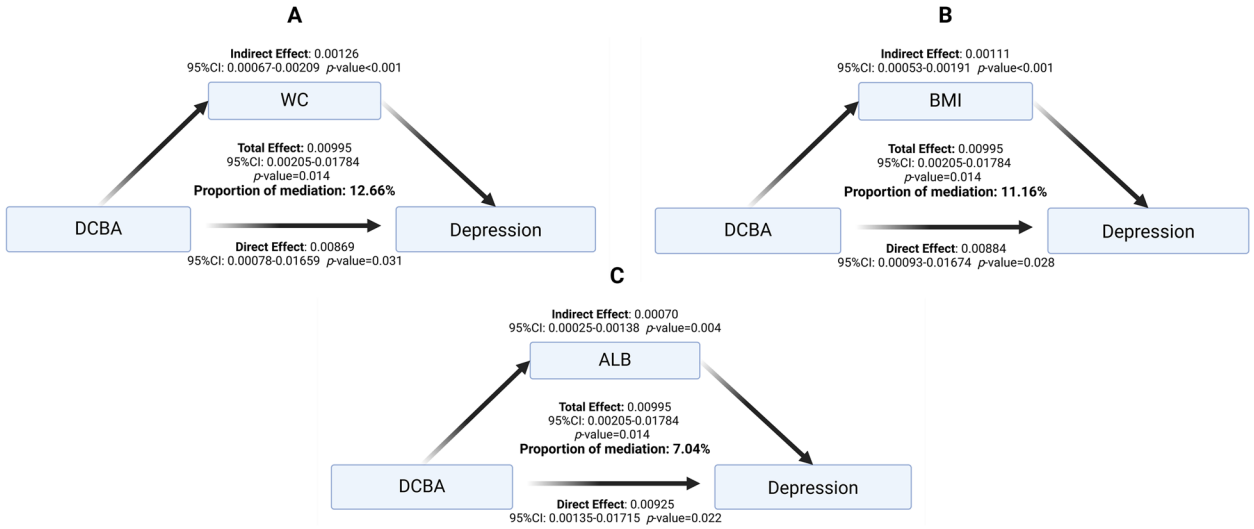


**Fig. 4** The mediating effects of WC, BMI and ALB on the relationship between DCBA and depression. Abbreviations: DCBA, 3-(diethylcarbamoyl) benzoic acid; WC, waist circumference; BMI, body mass index; ALB, albumin; TE: total effect; DE: direct effect; IE: indirect effect. The mediating analysis adjusted for gender, age, education level, poverty, marital status, SCR, TC, smoking status, drinking status, diabetes, hypertension, CVD and sleep disorders

researchers observed a loss of hippocampal neurons and a significant reduction in neurogenesis, even at physiological concentrations of DEET exposure, accompanied by a marked increase in the hypertrophy rates of astrocytes and microglia [20, 32]. This phenomenon may function through the regulation of immediate early genes (IEGs) such as Arc, Egr1, and Nr4a1, which play a crucial role in the interaction between the environment and epigenetics, determining the occurrence of depression under environmental pollution exposure [33, 34]. After DEET exposure, the downregulation of Arc, Egr1, and Nr4a1 was most significant, which may lead to impaired hippocampal neuron growth, reduced neurogenesis in the hippocampus, and loss of presynaptic vesicles [33, 35]. Additionally, the Arc gene is highly expressed in glutamatergic neurons, participating in synaptic remodeling and potentiation; its downregulation may lead to impaired synaptic function, affecting mood regulation and ultimately leading to depression [36, 37]. Studies have shown that long-term treatment with antidepressants can increase Arc expression in the hippocampus and prefrontal cortex of patients with depression, thereby improving depressive symptoms [38, 39]. Therefore, DEET exposure, by downregulating these key genes related to hippocampal neuron generation, may exacerbate the progression of depression. Secondly, the interference of DEET with the cholinergic system is also an important mechanism for its depressive effects. DEET has been found in animal models to inhibit the activity of acetylcholinesterase (AChE) and enhance the activity of other AChE inhibitors, disrupting the homeostasis of the cholinergic system and thereby affecting mood [40]. AChE is an enzyme responsible for the hydrolysis of acetylcholine, and its activity regulates the level of acetylcholine in synapses. Dysfunction of the cholinergic system, especially in the basal forebrain-cortical pathway, has been proven to be closely related to depression and cognitive disorders [40]. DEET may lead to the accumulation of acetylcholine by reducing AChE activity, thereby activating M1 and M2 muscarinic acetylcholine receptors related to mood regulation [41]. Ultimately, the adaptive changes in these receptors under long-term DEET exposure lead to the occurrence of depression. DEET also contributes to depression by activating an oxidative stress response that may be activated by mitochondrial dysfunction and inflammation. In their experiments, the researchers observed that DEET-exposed animals developed mutations that led to mitochondrial dysfunction and oxidative DNA damage, both of which upregulated the expression of oxidative stress-related genes [42, 43]. Excessive oxidative stress has long been recognized as a major etiological factor in depression, which demonstrates the bridging role of oxidative stress in the positive correlation between DEET and the incidence of depression, and fortunately, the recently FDA-approved drug, Epidiolex, is able to ameliorate mood disorders, such as depression, by ameliorating oxidative stress and thus improving the mood disorders in people with high exposure to DEET [44, 45]. Lastly, studies have found that long-term exposure to DEET leads to low-grade persistent systemic inflammation, with significantly elevated levels of plasma inflammatory biomarkers [46, 47]. DEET exposure may activate

neuroinflammatory pathways, leading to the overactivation and dysregulation of microglia and astrocytes, which are markers of neuroinflammation [46, 48]. The overactivation of microglia and astrocytes may cause them to lose their original ability to provide nutritional support for neuronal cells, turning instead to accelerate neuronal cell death and becoming neurotoxic, ultimately leading to depression [49]. The gut microbiota can play an important role in regulating mental health through brain gut axis [50–52]. DEET may destroy the structure of gut microbiota. Recent studies have shown that gut microbiota may be an important factor between environmental toxicants and mental health [53]. Animal studies have shown that other pesticides (such as organophosphorus) can significantly reduce intestinal microbial diversity, reduce anti-inflammatory bacteria, and increase pro-inflammatory bacteria, thereby increasing the incidence of anxiety and depression in mice [54]. The intestinal flora imbalance may increase intestinal permeability, trigger systemic inflammation and lead to neuroinflammation and blood–brain barrier damage, which is a key cause of depression and sleep disorders [55]. Although there is no direct study on the effect of DEET on intestinal flora. However, it may indirectly change the intestinal brain signal transduction by inhibiting the neurotoxicity of cholinesterase. Future studies should focus on verifying whether DEET can interfere with gut liver brain axis function and its potential mechanism. Similarly, DEET exposure can also lead to sleep disorders by affecting the cholinergic nervous system. Acetylcholine is an important neurotransmitter in sleep regulation, playing a key role in nocturnal sleep and the regulation of sleep circadian rhythms [56, 57]. DEET, by affecting the cholinergic system, may reduce deep sleep at night and disrupt sleep rhythms, leading to sleep disorders. Researchers have also found that DEET interferes with respiratory function, which itself can affect the quality of sleep in humans, and that deterioration of respiratory function is one of the main causes of sleep disorders [58]. Excessive exposure to DEET can inhibit respiratory function by interfering with central respiratory control centers and respiratory muscle function [59]. Inhibition of respiratory function was also found in animal experiments to potentially lead to depressive symptoms and even death in mice, a mechanism that is common to DEET-induced sleep disorders and depression (Severe toxic reactions and death following the ingestion of diethyltoluamide-containing insect repellents). Sleep disorders themselves are key regulators of mood, affecting emotional stability and reducing restorative rest, further accelerating the worsening of depressive symptoms [60, 61].

Although the direct impact of DEET on the nervous system may explain its association with depression and sleep disorders, recent studies have also suggested that environmental chemicals may indirectly affect mental health through metabolic disorders (such as obesity) or chronic low-grade inflammation (such as hypoalbuminemia). To elucidate potential mechanistic pathways, this study assessed whether obesity indicators and serum albumin mediate the association between DEET exposure and increased risks of depression and sleep disorders. The results suggest that DEET exposure can increase the risk of depression in the U.S. population by increasing obesity-related factors such as BMI and waist circumference, and can also increase the risk of depression by reducing serum albumin levels. DEET exposure may lead to obesity through multiple biological pathways, particularly by inducing the accumulation of visceral fat, leading to central obesity and exacerbating the occurrence of depression [8, 23]. The accumulation of visceral fat may be due to increased chronic inflammation and oxidative stress caused by DEET exposure, which are major factors leading to lipid metabolism disorders and obesity-related pathological injuries [22, 62]. Another potential pathway to obesity is based on DEET exposure damaging liver function, which is often accompanied by lipid metabolism disorders and insulin resistance, both of which are high-risk factors for obesity [63, 64]. Studies have also shown that the cholinergic system disorder caused by DEET exposure may have a toxic effect on neurons, and long-term exposure to neurotoxins may lead to a preference for high-fat diets, which can also accelerate the occurrence of obesity [65]. Obesity itself has been proven to have a close relationship with depression, with long-term obese individuals having significant chronic inflammation, increased secretion of adipokines, and neuroendocrine changes, thereby exacerbating the occurrence of depressive symptoms. These findings can provide an explanation for obesity being a potential mediating factor between DEET exposure and the positive correlation with depression. In addition, mediation analysis also found that albumin, an important biomarker for assessing liver function and nutritional status, plays a significant mediating role between DEET exposure and depression. Albumin is mainly synthesized in the liver, and DEET exposure-induced liver dysfunction can affect albumin production and reduce serum albumin levels [63, 66, 67]. Albumin itself has antioxidant stress effects in the body, capable of clearing oxygen free radicals and reducing oxidative stress levels [68, 69]. Hypoalbuminemia exacerbates oxidative stress and neuroinflammation, especially in the brain, affecting the balance of various neurotransmitters and ultimately leading to emotional disorders such as depression [70, 71]. In patients with depression, researchers often find lower levels of albumin, and the level of albumin is negatively correlated

with the severity and duration of depressive symptoms [72, 73]. After receiving drug treatment, the level of albumin in patients with depression can increase, further confirming that the decrease in albumin levels may play an important biological bridging role between DEET exposure and depression [69]. In patients with liver disease or malnutrition, DEET exposure may aggravate the risk of depression by further reducing the already low serum albumin level. In addition, liver disease itself may affect mental health through a variety of mechanisms, and malnutrition itself may also affect the development and function of the nervous system. These effects have a synergistic effect with DEET exposure, which further aggravates the occurrence of mental health disorders.

In subgroup analyses, the study found that the relationship between DEET and depression has significant interactions with gender and race. Specifically, this correlation has gender and racial differences, with DEET having a more significant risk effect on the occurrence of depression in women and individuals of other races. This may be closely related to the hormonal fluctuations unique to women, who experience more intense estrogen fluctuations during life stages such as puberty, menstrual cycles, and pregnancy [74]. This makes women more sensitive to environmental pollutant exposure such as DEET compared to men. Studies have shown that environmental exposure to estrogen endocrine disruptors may affect the endocrine system of women, promote sexual precocity, and have long-term effects on mood, psychology, and neurophysiology [75, 76]. In addition, in a longitudinal observational study of anxiety and depression in adolescents, researchers found that women are more prone to depression and have a worse course progression compared to male patients with depression [77]. This may infer that women are more likely to suffer from depression when exposed to certain depressive exposure factors [78]. However, there is currently a lack of research on the role of racial factors in the relationship between DEET and depression. In another article describing DEET environmental exposure in the NHANES database, it was mentioned that non-Hispanic whites have the highest DEET exposure in the summer, possibly three times that of non-Hispanic blacks [79]. This difference may be due to non-Hispanic whites using both sunscreen and DEET-containing insect repellents, leading to increased skin permeability and increased DEET exposure [80]. However, in this study, we did not observe a more significant correlation between DEET and depression in non-Hispanic whites, only observing this effect in other races. The specific reasons for this racial difference require further exploration in the future. Women and other races are susceptible to DEET exposure. The government can carry out special health education activities for these groups in order to improve their awareness of the potential risks of DEET and their living environment and health status.

In view of the significant association between DEET exposure and depression and sleep disorders revealed in this study, its importance to public health is self-evident. Some comprehensive measures should be advocated to reduce the health risk of DEET exposure to depression and sleep disorders. First, for patients with depression and sleep disorders, especially women, it is recommended to reduce the frequency of use of DEET insect repellent or choose low concentration products through public health publicity. Secondly, in view of the potential health risks of DEET, the development and promotion of safer alternatives to insect repellents, such as natural plant extracts, should be encouraged. Finally, the widespread use of DEET has led to its widespread presence in the environment, which has increased the risk of public exposure and may have a negative impact on the ecosystem. Therefore, a long-term environmental monitoring mechanism should be established to regularly assess the concentration of DEET in the environment and its impact on ecosystem and public health, and adjust relevant policies and management measures accordingly. In conclusion, we believe that these measures can better protect the health of patients with depression and sleep disorders, reduce the impact on the environment, provide a scientific basis for public health policies, and make public health efforts more targeted and effective.

This study is the first to demonstrate a correlation between environmental DEET exposure and the prevalence of depression and sleep disorders in the general population, and it proposes that BMI, WC, and albumin are potential mediating factors between DEET and depression, with this positive correlation interacting with gender and race. Sensitivity analysis enhanced the feasibility and robustness of the results. However, the study also has significant limitations. Firstly, despite our efforts to include more cycles of data, the sample size used in the study is still small due to the detection rate of DEET, and all are U.S. populations. The study design is cross-sectional, and the causal relationship between DEET and depression or sleep disorders cannot be determined. Future studies should use larger multicenter longitudinal studies or Mendelian randomization studies in more countries to further verify the long-term effects and causal effects of DEET exposure on depression and sleep disorders in the general population. Secondly, this paper only explores the potential mechanisms between DEET and depression and sleep disorders from the perspective of mediation analysis, without exploring the specific mechanisms in basic experiments in terms of targets or pathways. More basic experiments should be conducted

in the future to explore the specific mechanisms by which DEET increases the incidence of mental disorders such as depression and sleep disorders. Thirdly, DEET insect repellent used in daily life is often used with other chemical insecticides such as pyrethroids. The correlation analysis between single DEET exposure and disease cannot fully represent the potential hazards of the insect control methods used by the public. We can explore the mixed effects of multiple insect control chemicals on human health in the future to gain a more comprehensive understanding of the potential hazards of insect control chemicals. Finally, in addition to the accumulation of DEET exposure in aquatic ecosystems, the amount of DEET exposure from insect repellents used daily has a seasonal nature, generally peaking in the hot summer. This study cannot consider the potential bias caused by season and temperature on the results, and future studies need to verify our conclusions in data with more complete variables.

## Conclusion

This study reveals a significant correlation between DEET exposure and the prevalence of depression and sleep disorders in the general population, with BMI, waist circumference, and serum albumin acting as potential mediating factors. The findings highlight the need for targeted public health measures, especially considering the increased susceptibility observed in women and individuals of other races. Future research should address the limitations of this cross-sectional study by employing longitudinal designs and exploring a broader range of potential relationship to provide a more comprehensive understanding of the mechanisms underlying DEET's impact on mental health.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22880-4.

Supplementary Material 1.

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**Authors' contributions**
HZ: wrote the main manuscript text, data sorting and make tables. RT: prepared figures. QY and MY: study design. QF and YZ: wrote and review the main manuscript text and data analysis. All authors reviewed the manuscript.

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**Data availability**
The datasets used in this study were extracted from the NHANES (http://wwwn.cdc.gov/nchs/nhanes/).

## Declarations

**Ethics approval and consent to participate**
The research design and implementation of NHANES follow the ethical principles outlined in the Helsinki Declaration. This study utilized data from NHANES project that were publicly available and approved by National Center for Health Statistics (NCHS) Ethics Review Board (ERB). NHANES requires informed consent from participants and ensures their privacy and information security.

**Consent to Publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's Note