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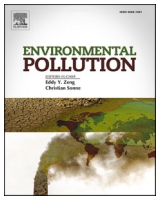

# Association between organophosphorus pesticide exposure and depression risk in adults: A cross-sectional study with NHANES data☆

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ABSTRACT

Organophosphorus pesticides (OPPs) are widely used pesticides, and previous studies showed that OPPs can increase the risk of central nervous system disorders (e.g., Parkinson's and Alzheimer's disease). However, few studies have comprehensively explored their association with depression in general adults. We analyzed data from 5206 participants aged 20 years or more based on four National Health and Nutrition Examination Survey (NHANES) cycles. OPPs exposure was estimated using measures of urinary concentrations for six OPPs metabolites. Survey-weighted generalized linear regression model (SWGLM) was used to explore the association of OPPs metabolites with depression. Subgroup analyses were performed by age (≦60 years and >60 years) and gender. The weighted quantile sum (WQS) regression model was used to explore the overall association of six OPPs metabolites with depression. In addition, The Bayesian kernel machine regression (BKMR) model was applied to investigate the interaction and joint effects of multiple OPPs metabolites with depression. The SWGLM showed that dimethyl phosphate (DMP) and dimethyl thiophosphate (DMTP), whether taken as continuous or quartile variables, had a positive correlation with depression. Diethyl phosphate (DEP) and dimethyl dithiophosphate (DMDTP) in the highest quartile were positively associated with depression compared to the lowest quartile. In subgroup analysis, we found that the effects of the above chemicals on depression existed in the male and young middle-aged population, while DMP was present in the female. There was a significant combined overall effect of six OPPs metabolites with depression [OR = 1.232, 95%CI: (1.011, 1.504)] in WQS. Furthermore, the BKMR model also showed a positive trend in the overall effect of six OPPs metabolites with depression. In conclusion, our results suggest that exposure to OPPs may increase the risk of depression in US adults. Men and young and middle-aged populations are more vulnerable to OPPs and the mixture of OPPs metabolites may induce depression.

*Abbreviations:* AChE, Acetylcholinesterase; DMTP, Dimethyl thiophosphate; AIC, Akaike information criterion; EPA, Environmental Protection Agency; BDNF, Brain-derived neurotrophic factor; FBG, Fasting blood glucose; BKMR, Bayesian kernel machine regression model; FIR, Family income to poverty ratio; BMI, Body Mass Index; HbA1c, Glycosylated hemoglobin level; CDC, Centers for Disease Control and Prevention; MEC, Mobile Examination Center; CI, Confidence interval; NCHS, National Center for Health Statistics; CVD, Cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; DAPs, Dialkyl phosphates; OPPs, Organophosphorus pesticides; DBP, Diastolic blood pressure; OR, Odds ratio; GLM, Generalized linear model; PHQ-9, Patient Health Questionnaire; DEP, Diethyl phosphate; SBP, Systolic blood pressure; DEDT, Diethyl dithiophosphate; SWGLM, Survey-weighted generalized linear regression model; DETP, Diethyl thiophosphate; VIFs, Variance inflation factors; DMDTP, Dimethyl dithiophosphate; WQS, Weighted quantile sum regression model; DMP, Dimethyl phosphate.

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## 1. Introduction

Depression is a common mental disorder that is characterized by persistent feelings of sadness (World Health Organization, depression). The number of deaths due to depression is also rising sharply each year (Malhi and Mann, 2018). A recent Lancet study shows that the global prevalence of depression has increased 0.6 times in the last 30 years and is expected to become the number one global disease burden by 2030 (Diseases and Injuries, 2020; Malhi and Mann, 2018). In addition, the disease burden of depression appears to be more severe in developed countries and regions (Collaborators, 2022). Depression not only causes serious physical and psychological harm to the patients themselves but also brings huge production losses and medical burdens to their families and society (Bai et al., 2020; Greenberg and Birnbaum, 2005; Guo et al., 2019; Tian et al., 2005). Currently, there is still a great challenge to completely cure depression, and medication generally has strong side effects (Tian et al., 2022). Therefore, prevention of the disease is the most feasible and crucial measure. Depression is a disorder caused by a combination of genetic and environmental factors, and genetic factors explain less than 40% of major depressive disorders (Penner-Goeke and Binder, 2019; Sullivan et al., 2000). With the increase in global environmental pollution, environmental factors have become particularly important in the development of the disease (Liu et al., 2021).

Pesticides play an important role in life and production processes by preventing pathogen infection and killing insect pests (Tudi et al., 2021). Global pesticide production is reported to be increasing at a rate of 11% per year, with approximately 3 billion kilograms of pesticides being used in environmental operations each year (Carvalho, 2017). Only 1% of them play an effective role and the rest are left in the environmental medium (Bernardes et al., 2015). Due to the low price, effectiveness, and ease of decomposition of organophosphorus pesticides (OPPs), they have been widely used in agriculture, horticulture, and households in recent decades, and have largely replaced organochlorine pesticides as the basic pesticides. In 2001, the use of OPPs in the United States accounted for 70% of all pesticides, since then there has been a decline but the proportion remains at 30–40% (van den Dries et al., 2020; EPA, 2017). OPPs not only kill pests in the environment, but they can also harm human health by exposing people to them in a variety of routes, such as inhalation, ingestion, and direct skin contact (Farahat et al., 2010; Yoshida et al., 2022). Short-term exposure to large doses of OPPs can lead to overstimulation of muscarinic and nicotinic receptors, which can involve the nervous and respiratory systems and even death if timely and effective measures are not taken (Peter et al., 2014; Robb and Baker, 2022). Since the implementation of the Food Quality Protection Act in 1996, the United States has gradually restricted the household use of OPPs, yet metabolites of OPPs can still be detected in the urine of the general population (Clune et al., 2012; Guo et al., 2022b). Therefore, there is currently more concern about the health risks of long-term, low-dose exposure to OPPs. In recent years, more and more scholars have become concerned about the mental health effects of OPPs. OPPs have neurotoxic effects due to their irreversible binding to the catalytic site of acetylcholinesterase (AChE) and inhibition of key enzymes involved in neurotransmission, which is essential to ensure proper nervous system function (Burke et al., 2017; Flaskos, 2012). Several studies have found the relationship between OPPs and central nervous systems, such as Parkinson's disease and Alzheimer's disease (Ali and Rajini, 2016; Hayden et al., 2010; Manthripragada et al., 2010). However, there are few studies on the association between OPPs exposure and depression. In addition, most of the relevant studies are mainly on people in direct contact with OPPs such as agricultural and OPPs production workers (Beard et al., 2014; Fghihi--Zarandi et al., 2022; Malekirad et al., 2013), which limits the generalization of the findings to the general population. And these studies assessed OPPs exposure via questionnaire and did not take a quantitative approach, which may have produced a misclassification bias. Given the widespread use of OPPs in daily life and agricultural production, it is necessary to conduct studies on the general population to further clarify the relationship between OPPs and depression by quantifying OPPs exposure. To this end, this study aimed to explore the association between urinary metabolites of six OPPs and depression by three statistical models (generalized linear model (GLM), weighted quantile sum (WQS) model, and Bayesian kernel machine regression (BKMR) model) using data from the US National Health and Nutrition Examination Survey. Subgroup analyses were conducted in different sex and age groups to estimate the health hazards of OPPs and provide more scientific and comprehensive evidence for policymakers to prevent and control the occurrence of depression.

## 2. Methods

### 2.1. Study design and population

The National Nutrition and Health Examination (NHANES) is a nationwide health nutrition assessment cross-sectional survey conducted by the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC) to assess the nutritional and health status of adults and children throughout the United States (Wu et al., 2020; Xu et al., 2021). The project was divided into three main parts, starting with a basic information questionnaire within the household and followed by a physical examination and biological sample collection at the Mobile Examination Center (MEC) and subsequent sample analysis in the laboratory. NHANES uses a complex, stratified, multi-stage sampling probability design to select a representative population over a two-year sampling cycle (CDC, sample design). Since 1999, the survey became a continuous program that publishes new data every two years. The dataset is public data and can be accessed as a free download at the following website (https://www.cdc.gov/nchs/nhanes/index.htm).

Since the cycles containing OPPs data were 2003–2004, 2005–2006, 2007–2008, 2011–2012, and 2015–2016, and the cycles for depression scores were 2005 and later, adults aged 20 years and older in the four cycles of 2005–2006, 2007–2008, 2011–2012, and 2015–2016 were selected for this study. Initially, 40224 study subjects were included, we further excluded those under the age of 20 years and those who did not test for metabolites of OPPs and did not assess depression scores, followed by the exclusion of those with missing covariates, and finally, 5206 study subjects were included. The detailed inclusion-exclusion process is shown in Fig. 1. The NHANES research project was approved by the NCHS Research Ethics Review Committee and all study participants provided written informed consent at the time of recruitment.

### 2.2. Exposure assessment

People can be exposed to OPPs through a variety of routes (such as dermal contact, respiratory and digestive tracts, etc.) and are eventually excreted in the urine as the non-specific metabolites dialkyl phosphates (DAPs) after metabolism in the body (Berman et al., 2013; Cequier et al., 2016). Therefore, DAPs are the most commonly used biomarkers to measure the level of OPPs exposure in humans and play an important role in the assessment of OPPs exposure and health (Guo et al., 2022a; Ock et al., 2020). A total of six DAPs [dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), diethyl phosphate (DEP), diethyl thiophosphate (DETP), and diethyl dithiophosphate (DEDTP)] were measured in this study, and these six metabolites covered almost the majority of OPPs registered by the U.S. Environmental Protection Agency (EPA) (Bravo et al., 2004) (Which specific organophosphorus pesticides can be represented by DAPs, see Appendix 1 in the supplementary material). DAPs were analyzed using gas chromatography-tandem mass spectrometry (GC-MS/MS) with isotope dilution. Detailed instructions for sample collection and analysis can be found in CDC Laboratory Procedures Manual (CDC, laboratory).

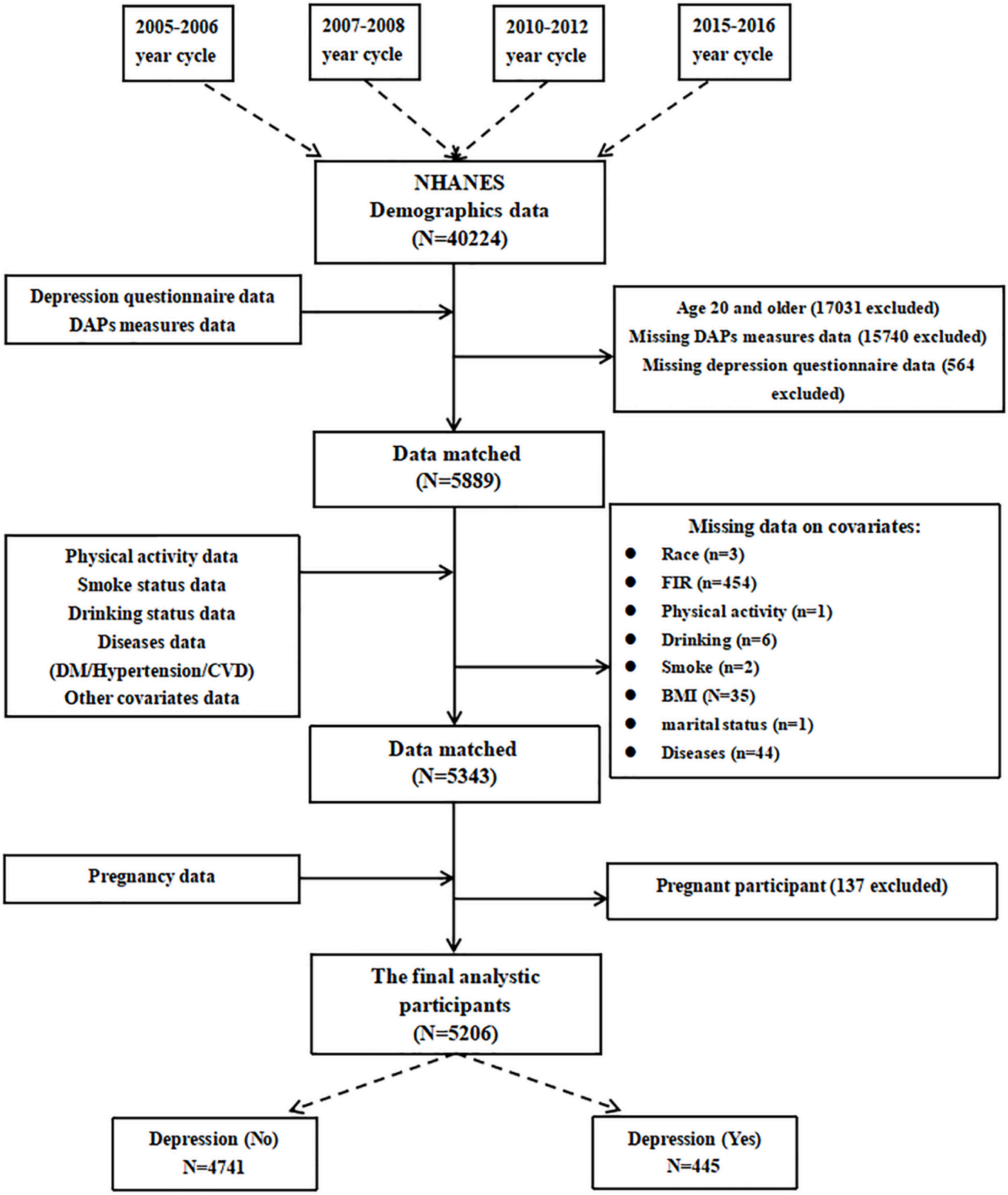


**Fig. 1.** Flow chart of the participants' selection. Notes: DAPs: metabolites dialkyl phosphates; FIR: Family income to poverty ratio. BMI: Body Mass Index, DM: diabetes, CVD: cardiovascular diseases.

### 2.3. Depression assessment

NHANES used the Patient Health Questionnaire (PHQ-9) to assess depression in the past two weeks of depressive status of study participants (Kroenke et al., 2010). The questionnaire contains a total of 9 questions, each with a score ranging from 0 (not at all) to 3 (nearly every day), with a total score ranging from 0 to 27. When the PHQ-9 score was 10 and above (PHQ-9 score ≥10), we considered the study subjects to be suffering from depression (Manea et al., 2012, 2015). PHQ-9 has a high internal consistency and good sensitivity and specificity in identifying depression (sensitivity 81.3%, specificity 85.3%) (Kroenke et al., 2001; Manea et al., 2015). In addition, to further improve the quality of the PHQ-9 questionnaire, only participants who answered 8 questions and above were included in this study.

### 2.4. Assessment of covariates

Information on socio-demographics, lifestyle, and health status was collected during the NHANES household interviews through the use of individual and household demographic questionnaires. The following covariates were included in this study. Age, gender (Male, Female), race (Mexican American, Non-Hispanic White, Non-Hispanic Black, other races)、educational level (below high school, high school, and above high school), Family income to poverty ratio ( FIR ) (≦1.3, 1.31–3.5, >3.5), Body Mass Index (BMI) (<25 kg/m2, 25 to <30 kg/m2, ≥30 kg/m2), Marital Status (married/living with a partner, widowed/divorced/separated, never married), Smoking status (never smoker, former smoker, and current smoker), Drinking status (having at least 12 alcohol drinks per year or not), Physical Activity (vigorous、moderate or other), Cardiovascular disease (yes or no), Diabetes (self-reported physician diagnosis or glycosylated hemoglobin level (HbA1c) ≥6.5% or fasting blood glucose (FBG) ≥7.0 mmol/L or taking hypoglycemic drugs to lower blood sugar), Hypertension (self-reported physician diagnosis or systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg or taking medications for hypertension currently) and the NHANES cycle.

Smoking is defined according to two questions, “Smoking at least 100 cigarettes in your life?” and “Do you now smoke cigarettes?”. Study participants were considered non-smokers if they had smoked less than 100 cigarettes in their lifetime, former smokers if they had smoked more than 100 cigarettes in their lifetime but were now non-smokers, and current smokers if they had smoked more than 100 cigarettes in their lifetime and were still smoking (Xiao et al., 2022; Zhu et al., 2021). the dichotomous outcome variable CVD (cardiovascular disease) was defined using self-reporting congestive heart failure, coronary heart disease, angina, heart attack, or stroke. In addition, considering that urine dilutes the concentration of DAPs, we used a urinary creatinine correction to reduce the interference with the measurements (O’Brien et al., 2016), as described in previous studies (Guo et al., 2020; Guo et al., 2022a).

### 2.5. Statistical analysis

Considering the complex multistage sampling design of NHANES, we used appropriate sample weights, strata, and clustering variables for the main analyses. Since our data contain four survey periods (8 years), for this reason, we calculated 8-year weights for subsequent data weighting analyses using weights for each OPPs-related subgroup (2-year weights) according to official NHANES guidance (https://wwwn.cdc.gov/nchs/nhanes/tutorials/Module3.aspx). Urinary creatinine-corrected metabolite concentrations of DAPs were natural log (ln) transformed [Ln-transformed (continuous)] due to skewed distributions and categorized into four quartiles (Q1, Q2, Q3, and Q4) (Zhang et al., 2019). The continuous variables were expressed in weighted mean ± standard error (SE), and categorical variables were described by number and weighted percentage (%). We used weighted Chi-square tests and t-tests to assess the baseline characteristics of the participants by depression status. Pearson correlation coefficients were calculated to evaluate the correlations among levels of all six studied DAPs.

We constructed the following three survey-weighted generalized linear regression models (SWGLMs) to assess the relationship between each DAPs exposure and the risk of depression based on covariate adjustment: Model I adjusted for age, sex, race, education, FIR, marital status, NHANES cycle, and BMI. Model II adjusted for physical activity, alcohol consumption, and smoking status based on Model I. Model III adjusted for hypertension, diabetes, and cardiovascular disease based on Model II. In addition, the trend test across increasing exposure groups was calculated in multivariable models using integer values (0, 1, 2, and 3).

Subgroup analysis was stratified by age (middle-aged group (20 ≤ Age ≦60) and the elderly group (Age >60) and sex. Meanwhile, we also carried out the trend test.

The WQS regression model is a mixed-effects strategy that is commonly used to explore the relationship between multiple chemical exposures and outcomes (Czarnota et al., 2015). The model assesses the relationship between multiple exposures and outcomes by calculating a weighted index and calculating a relative contribution for each exposure. The weight values for each exposure ranged from 0 to 1, and the weights were summed to 1. In our study, the WQS model was used to assess the relationship between six OPPs metabolites and depression and adjust for all mentioned covariates. We randomly divided the original data into 40% of the training set and the remaining 60% of the validation set to estimate weight values for each OPPs metabolite by the bootstrap method (n = 3000).

Given the possible non-linear and non-additive relationship between mixture exposures and depression, we fitted BKMR models to see the association between the combined 6 OPPs metabolites and depression. The BKMR model is a nonparametric Bayesian variable selection framework that combines Bayesian and statistical learning methods. It can estimate the overall health effects of mixtures and assess potential interaction effects and nonlinear associations between multiple exposures (Bobb et al., 2015; Bobb et al., 2018). In this study, a Markov chain Monte Carlo algorithm was used for 10,000 iterations to fit the BKMR model. The overall effect of all OPPs metabolites on depression was estimated by comparing the value of the exposure-response function when all exposures are at a particular quantile as compared to when all of them are at their median value. Exposure-response relationships between the six OPPs metabolites and depression were determined by fixing the exposure levels of the remaining OPPs metabolites at median levels. We then explored the interaction between the chemicals, the remaining chemicals were fixed at the median to explore the dose-response relationship between a chemical and depression when another chemical level was at the 10th, 50th, and 90th.

We performed some sensitivity analysis to assess the robustness of our results. Firstly, we excluded those who did not answer all questions on the depression questionnaire to obtain a more accurate evaluation of results. Secondly, to assess the impact of excluding observations with missing values, we kept the missing covariates and used the "other" category to replace the missing part of the FIR variables (since missingness amounted to 8.7%), while the remaining missing covariates were analyzed using the random proportional replacement method (according to the proportion of the variable’s classification) due to the small number of missing covariates. Finally, we excluded covariates with large variance inflation factors in the sensitivity analysis to determine if excluding variables with the highest VIF would result in a better fitted model (ie, if including these variables resulted in overfitting the model).

All statistical analyses were performed in R software (R 4.1.1) using the "survey", "gWQS", and "bkmr" packages. Two-sided $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Characteristics of participants

As shown in Table 1, a total of 5206 study participants (male: 2601; female: 2605) were included in the final study, of which 445 (8.5%) were considered depressed. The weighted mean age was 47.06 ± 0.45 years, 42.95% of the study participants were non-Hispanic white and 38.55% were participants whose BMI was greater or equal to 30. In addition, we also found significant differences between depressed and non-depressed in terms of gender, race, education level, FIR, BMI, marital status, physical activity, smoking, diabetes, and CVD. The weighted distributions of participants' characteristics and other covariates according to depression situation also are presented in Table 1. The distribution of the six DAPs in different populations is shown in Table S1. Pearson correlation results showed moderately strong correlations between DMP and DMTP ($r = 0.61$, $P < 0.05$) and between DMTP and DMDTP ($r = 0.71$, $P < 0.05$) among 5206 subjects (Fig. 2).

### 3.2. Survey-weighted generalized linear regression analysis

Table 2 showed us the results of weighted generalized linear regression models adjusting for different covariates to assess the association between a single DAP (continuous) and the risk of depression. In the model I, we found no significant correlation between any of the six DAPs and depression. After further adjustment for behaviors and lifestyles (model II) and disease conditions (model III), we found significant correlations between DMP and DMTP and depression. In addition, there was almost a significant association between DEP and DMDTP and depression in model III. We performed multicollinearity analysis between each of the exposures and covariates for different models. Almost all the variance inflation factors (VIFs) in the multivariable linear regression model were lower than 10 (Table S2), which meant there was little multicollinearity between the chemical and covariates (Zhang et al., 2019). In addition, we also compared different models by using the Akaike information criterion (AIC) and found that the fully adjusted model (model III) was more reasonable (The smaller the value of AIC, the more parsimonious and reasonable the model is.) (See Table S3), so we followed the covariates controlled in model III in the subsequent analyses.

Table 3 presents the results from the analysis on association between DAP exposure, expressed as a continuous variable and as a categorical (quartiles) variable, and depression. The results between the two operationalizations of the exposure variables are basically consistent. When taking the lowest quartile (Q1 [OR = 1]) as reference, we found significant positive associations between DMP in the second quartile [OR = 1.60, 95%CI: (1.11, 2.30)] and fourth quartile [1.76 (1.26, 2.44)], DEP in the fourth quartile [1.64 (1.12, 2.41)], DMDTP in the fourth quartile [1.70 (1.09, 2.65)], and DMTP in the second [1.51 (1.04, 2.20)], third [1.47 (1.00, 2.15)], and fourth quartiles [1.58 (1.08, 2.30)] with depression. Subsequently, trend tests were performed for the quartile groups and we found a significant linear trend between DMP, DEP, DMTP, and DMDTP and depression (*P* for trend <0.05). In the sensitivity analysis, the main results did not change substantially (Tables S4–S6).

### 3.3. Subgroup analysis

Table 4 showed the results of the subgroup analysis between different DAPs and depression. In middle-aged (20≦Age (years)≦60) group, a growing risk of depression for the highest quartile of exposure (versus Q1) was found in DMP [2.04 (1.41, 2.94)], DEP [1.99 (1.29, 3.07)] and DMTP [1.95 (1.26, 3.00)], and DMDTP [2.27 (1.41, 3.65)]. Moreover, with increasing quantiles of DMP, DEP, DMTP, DMDTP, and DEDTP, the risk of depression was increased in a dose-dependent manner (all *P* for trend <0.05). However, this association was not found in the elderly (Age (years) > 60) group. Additionally, among the

**Table 1**
Weighted characteristics of the study population (Age≧20 years) with and without depressive symptoms, NHANES, USA.

| Characteristics | Total participants | depression situation | | *P* value |
|---|---|---|---|---|
| | | Yes | No | |
| **N** | 5206 | 445 (8.55%) | 4761 (91.45%) | |
| **Age**, year | 47.06 ± 0.45 | 46.00 ± 0.89 | 47.14 ± 0.48 | 0.451 |
| **Gender** | | | | <0.001 |
| Male | 2601 (49.97%) | 164 (36.86%) | 2437 (48.81%) | |
| Female | 2605 (50.03%) | 281 (63.14%) | 2324 (51.19%) | |
| **Ethnicity** | | | | 0.001 |
| Mexican American | 832 (15.98%) | 59 (13.26%) | 773 (16.24%) | |
| Non-Hispanic black | 1192 (22.90%) | 122 (27.42%) | 1070 (22.47%) | |
| Non-Hispanic white | 2236 (42.95%) | 172 (38.65%) | 2064 (43.35%) | |
| Other | 945 (18.17%) | 92 (20.67%) | 854 (17.94%) | |
| **Educational level** | | | | <0.001 |
| Below high school | 1291 (24.80%) | 173 (38.88%) | 1118 (23.48%) | |
| High school | 1169 (22.46%) | 105 (23.60%) | 1064 (22.35%) | |
| Above high school | 2746 (52.74%) | 167 (37.52%) | 2579 (54.17%) | |
| **Family income-to-poverty ratio** | | | | <0.001 |
| ≦ 1.30 | 1603 (30.79%) | 231 (51.91%) | 1372 (28.82%) | |
| 1.31–3.5 | 1941 (37.28%) | 158 (35.51%) | 1783 (37.45%) | |
| >3.5 | 1662 (31.93%) | 56 (12.58%) | 1606 (33.73%) | |
| **Body mass index (kg/m$^2$)** | | | | 0.003 |
| <25 | 1461 (28.06%) | 107 (20.05%) | 1354 (28.45%) | |
| 25 to <30 | 1738 (33.39%) | 114 (25.62%) | 1624 (34.11%) | |
| ≧ 30 | 2007 (38.55%) | 224 (50.33%) | 1783 (37.45%) | |
| **Marital status** | | | | <0.001 |
| Married/Living with partner | 3062 (58.82%) | 190 (42.70%) | 2872 (60.32%) | |
| Widowed/Divorced/ Separated | 1169 (22.46%) | 161 (36.18%) | 1008 (21.17%) | |
| Never Married | 975 (18.72%) | 94 (21.12%) | 881 (18.51%) | |
| **physical activity** | | | | <0.001 |
| Vigorous | 1772 (34.04%) | 211 (47.42%) | 1561 (32.79%) | |
| Moderate | 1602 (30.77%) | 125 (28.09%) | 1477 (21.02%) | |
| Other | 1832 (35.19%) | 109 (24.49%) | 1723 (36.19%) | |
| **Smoke** | | | | <0.001 |
| Never | 2817 (54.11%) | 155 (34.83%) | 2662 (55.91%) | |
| Former | 1247 (23.95%) | 102 (22.92%) | 1145 (24.05%) | |
| Now | 1142 (21.94%) | 188 (42.25%) | 954 (20.04%) | |
| **Drinking** | | | | 0.627 |
| No | 1479 (28.41%) | 119 (26.74%) | 1360 (28.56%) | |
| Yes | 3727 (71.59%) | 326 (73.26%) | 3401 (71.44%) | |
| **Hypertension** | | | | 0.074 |
| No | 2394 (45.99%) | 193 (43.37%) | 2201 (46.23%) | |
| Yes | 2812 (54.01%) | 252 (56.63%) | 2560 (53.77%) | |
| **Diabetes** | | | | 0.003 |

(*continued on next page*)

**Table 1** (*continued*)

| Characteristics | Total participants | depression situation | | *P* value |
|---|---|---|---|---|
| | | Yes | No | |
| No | 4262 (81.87%) | 335 (75.28%) | 3927 (82.48%) | |
| Yes | 944 (18.13%) | 110 (24.72%) | 834 (24.72%) | |
| **CVD** | | | | <0.001 |
| No | 4657 (89.45%) | 354 (79.55%) | 4303 (90.38%) | |
| Yes | 549 (10.55%) | 91 (20.45%) | 458 (9.62%) | |
| **Cycle** | | | | 0.329 |
| **1** | 1170 (22.47%) | 86 (19.33%) | 1084 (22.77%) | |
| **2** | 1472 (28.28%) | 154 (34.61%) | 1318 (27.68%) | |
| **3** | 1238 (23.78%) | 116 (26.06%) | 1122 (23.57%) | |
| 4 | 1326 (25.47%) | 86 (20.00%) | 1237 (25.98%) | |
| **Exposures (μg/L)** | | | | |
| DMP | 1.20 (0.33–4.58) | 1.49 (0.33–5.25) | 1.19 (0.33–4.55) | 0.184 |
| DEP | 1.11 (0.26–3.62) | 1.23 (0.26–4.05) | 1.10 (0.26–3.58) | 0.204 |
| DMTP | 1.31 (0.39–3.97) | 1.30 (0.41–3.72) | 1.31 (0.39–3.99) | 0.763 |
| DETP | 0.40 (0.18–0.66) | 0.40 (0.19–0.62) | 0.40 (0.18–0.66) | 0.666 |
| DMDTP | 0.36 (0.11–0.36) | 0.36 (0.14–0.36) | 0.36 (0.10–0.36) | 0.353 |
| DEDTP | 0.07 (0.07–0.28) | 0.28 (0.07–0.28) | 0.07 (0.07–0.28) | 0.897 |

Note: FIR: Family income-to-poverty ratio; BMI: Body mass index; Continuous variables were presented as mean ± SD or median (interquartile range); Categorical variables were presented as n (%).

male group, compared to the lowest quartile group, DEP in the fourth quartile [2.59 (1.41, 4.74), *P* for trend = 0.002], DMTP in the third quartile [2.24 (1.24, 4.04), *P* for trend = 0.031], and DMDTP in the fourth quartile group [2.71 (1.37, 5.36), *P* for trend = 0.017] had significant association and linear trend with depression. Nevertheless, in the female group, we only found a significant association and linear trend (*P* for trend = 0.011) between DMP in the fourth quartile [1.95 (1.25, 3.04)], in the third quartile [1.74 (1.03, 2.94)] and depression compared to the lowest quartile group. The details are shown in Table 4 or Fig. S1.

### 3.4. Weighted quantile sum regression analysis

The results of the association between the WQS index and depression are shown in Table S7. In the model I adjusted for basic information, we did not find a significant association between the WQS index and depression ($P = 0.098$). In model II, which further adjusted for behavior and lifestyle, the WQS index was significantly associated with depression (OR: 1.235, 95% CI: 1.012–1.508). In the fully adjusted WQS model (model III), the WQS index was significantly associated with depression (OR: 1.232, 95% CI: 1.011–1.504). The estimated chemical weights for each WQS index are shown in Supplementary Material Table S8 and Fig. 3. The chemical with the highest weight in Model III is DEP (weight of 0.307), followed by DMDTP, DEDTP, DMTP, and BPS (weights of 0.264, 0.195, 0.135, and 0.085, respectively), and DETP is assigned the lightest weight (weight of 0.014).

### 3.5. Bayesian kernel machine regression analysis

From the results of the BKMR model, we found that DMP, DEP, DMTP, DMDTP, and DEDTP showed a positive relationship with depression when all other chemicals were at median levels, whereas DETP showed an inverse relationship. The trends of exposure-response for these six chemicals are shown in Fig. 4. We then explored the interaction between the chemicals, the remaining chemicals were fixed at the median to explore the dose-response relationship between a chemical and depression when another chemical level was at the 10th, 50th, and 90th. From Fig. S2, we found that the slope of the dose-response relationship between DMDTP and depression was different when DMTP was at different levels (10th, 50th, and 90th percentiles), suggesting a possible interaction between DMDTP and DMTP. Similarly, there may be interactions between DEP and DMTP, DMP and DETP. We also analyzed the overall effect of DAPs on depression, which tended to increase when all chemicals were at or above the 60th percentile, compared with the 50th percentile (Fig. 5).

## 4. Discussion

A recent study indicates that depression remains a significant public health problem in the United States (Greenberg et al., 2021). In addition, some studies have reported that OPPs are very potent neurotoxins, producing neurotoxicity in both acute and chronic exposure (Jokanović, 2018; Naughton and Terry, 2018). To the best of our knowledge, this is the first large-scale epidemiological study to use different statistical models to explore the single and joint effects of multiple OPPs metabolites on depression.

In this study, we provided novel findings on the complicated associations of OPPs metabolites with depression risk in adults in the U.S. By survey-weighted logistic regression models, we found a significant positive association between DMP and DMTP and depression. The highest quartile of DEP and DMDTP were significantly positively associated with depression compared to the lowest quartile. In subgroup analyses, most metabolites of OPPs were associated with depression in men and young and middle-aged adults compared to women and older adults. DEP, DMTP, and DMDTP were associated with depression in men, however, only DMP was significantly associated with depression in women. We also found that DMP, DEP, DMTP, and DMDTP were associated with depression in young and middle-aged adults, but not in older adults. Notably, we found mixed OPPs metabolites had a positive correlation with depression risk, and emphasized DEP, DMDTP, DEDTP, and DMTP as the strongest risk factor for the outcome in the WQS analysis. Moreover, In the BKMR model results, we also found a positive trend in the overall effect of mixtures of OPPs metabolites with depression. From the results of three statistical models, we were able to find that the DAPs mixture as a whole may be harmful to depression. Even though only two DAPs were found to be statistically significant in the SWGLM model, all DAPs had OR values greater than 1 for the association with depression, and this consistency of direction can suggest that DAPs overall can increase the risk of depression. Also, it is noteworthy that in the subgroup analysis, the vast majority of the association OR values between DAPs and depression were greater than 1.

In studies related to environmental epidemiology, generalized linear regression models usually provide us with a simple relationship between individual exposures and outcomes and do not take into account other chemical exposures. WQS models can initially explore the association between mixtures as a whole and outcomes and provide specific risk values. The BKMR model can explore the dose-response relationship for each chemical by fixing other chemicals at a certain level, in addition to the interaction between any two exposed substances and the trend in the overall hazard to the outcome of the chemical mixture at different exposure levels. Therefore, each of these three models has its advantages and can compensate each other to make the results richer and more reliable.

Previous cross-sectional and cohort studies have shown that farmers who work with OPPs are at higher risk of developing major depression (Beseler and Stallones, 2008; Malekirad et al., 2013), which is consistent with the findings of this study. Animal studies have similarly found that exposure to OPPs can increase the risk of depression-like conditions by inhibiting the action of acetylcholinesterase in rats and mice (Aliomrani


**Fig. 2.** Pearson correlations between ln-transformed concentrations of six urinary creatinine-corrected organophosphorus pesticides Metabolites (N = 5206), NHANES, USA.

**Table 2**
Comparison between different models of the weighted relationship between organophosphorus pesticide metabolites in urine and risk of depression, NHANES, USA (n = 5206).

| Chemicals (μg/L) | Model I | | Model II | | Model III | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *P* | OR (95%CI) | *P* | OR (95%CI) | *P* |
| DMP | 1.088 (1.001,1.183) | 0.054 | 1.114 (1.026,1.210) | 0.014 | 1.118 (1.029,1.215) | 0.012 |
| DEP | 1.081 (0.984,1.188) | 0.110 | 1.092 (0.997,1.196) | 0.066 | 1.095 (0.999,1.199) | 0.060 |
| DMTP | 1.069 (0.973,1.173) | 0.170 | 1.121 (1.020,1.232) | 0.023 | 1.123 (1.020,1.235) | 0.023 |
| DETP | 0.994 (0.875,1.129) | 0.928 | 1.037 (0.914,1.175) | 0.579 | 1.042 (0.917,1.184) | 0.535 |
| DMDTP | 1.074 (0.949,1.215) | 0.264 | 1.126 (0.995,1.276) | 0.068 | 1.133 (0.999,1.284) | 0.059 |
| DEDTP | 1.095 (0.738,1.627) | 0.654 | 1.118 (0.725,1.722) | 0.617 | 1.124 (0.733,1.724) | 0.596 |

Notes: DMP: dimethyl phosphate; DMTP: dimethyl thiophosphate; DMDTP: dimethyl dithiophosphate; DEP: diethyl phosphate; DETP: diethyl thiophosphate, and DEDTP: diethyl dithiophosphate; OR: Odds ratio; 95%CI: 95% Confidence interval; Q, quartile.
Model I: Adjusting for age, gender, race, educational level, FIR, BMI, marital status, and NHANES cycle.
Model II: Model I + adjusted for physical activity, drinking, and smoking.
Model III: Model II + adjusted for hypertension, diabetes, and cardiovascular diseases.

et al., 2021; Savall et al., 2020). Moreover, an animal experiment found that in adult male and female Wistar rats treated with the same dose of malathion (250 mg/kg), the decrease in acetylcholinesterase activity in the hippocampus was more pronounced in males leading to depression-like behavior (Maris et al., 2010), which is consistent with the findings of this study. Notably, in the age subgroup analysis, we found that the young and middle-aged population was more prone to depression-like symptoms when exposed to OPPs than the older population, and the mechanisms involved are not yet clear.

The biological mechanisms by which OPPs exposure causes depression are not fully understood. The mechanism can be broadly divided into two aspects, one is the effect on cholinergic receptors. OPPs exposure can cause the downregulation of postsynaptic acetylcholine receptors in the body and thus inhibit the release of acetylcholine in the postsynaptic ganglion (Aliomrani et al., 2021; Ivanović et al., 2016; Karimani et al., 2021) and further leading to depressed mood. On the other hand, there is a non-cholinergic-related mechanism. Some animal experiments have found that exposure to OPPs (e.g., malathion) can increase Trkβ levels and decrease brain-derived neurotrophic factor (BDNF) levels in the prefrontal cortex of rats (Dorri et al., 2015; Savall et al., 2020), thereby blocking the BDNF-Trkβ pathway, those factors that have been shown to be associated with depression (Dorri et al., 2015; Qiao et al., 2017). The OPPs exposure may also cause depression-like changes in the body by affecting oxidative stress, systemic inflammation, and apoptosis (Androutsopoulos et al., 2013; Farkhondeh et al., 2020). For example, animal studies found that exposure of rats to chlorpyrifos and monocrotophos increased malondialdehyde and reactive oxygen species levels in the body, which consequently

**Table 3**
Weighted association of single organophosphorus pesticide metabolites with risk of depression, NHANES, USA (n = 5206).

| Chemicals (μg/L) | Continuous | Q1 | Q2 | Q3 | Q4 | *P* for trend |
|---|---|---|---|---|---|---|
| | OR (95%CI) | Reference | OR (95%CI) | OR (95%CI) | OR (95%CI) | |
| DMP | | | | | | **0.009** |
| dep/non-dep | 445/4761 | 99/1203 | 125/1176 | 102/1199 | 119/1183 | |
| Model | **1.118(1.029,1.215)** | 1 | **1.60(1.11,2.30)** | 1.52 (0.95,2.42) | **1.76(1.26,2.44)** | |
| DEP | | | | | | **0.042** |
| dep/non-dep | 445/4761 | 99/1203 | 116/1185 | 100/120 | 130/1172 | |
| Model | 1.095 (0.999,1.199) | 1 | 1.41 (0.96,2.08) | 1.13 (0.70,1.82) | **1.64(1.12,2.41)** | |
| DMTP | | | | | | **0.036** |
| dep/non-dep | 445/4761 | 101/1201 | 125/1176 | 112/1189 | 107/1195 | |
| Model | **1.123(1.020,1.235)** | 1 | **1.51(1.04,2.20)** | **1.47(1.00,2.15)** | **1.58(1.08,2.30)** | |
| DETP | | | | | | 0.189 |
| dep/non-dep | 445/4761 | 109/1193 | 97/1204 | 128/1173 | 111/1191 | |
| Model | 1.042 (0.917,1.184) | 1 | 0.96 (0.53,1.72) | 1.29 (0.73,2.27) | 1.23 (0.74,2.06) | |
| DMDTP | | | | | | **0.032** |
| dep/non-dep | 445/4761 | 99/1203 | 114/1187 | 111/1190 | 121/1181 | |
| Model | 1.133 (0.999,1.284) | 1 | 1.46 (0.83,2.58) | 1.28 (0.76,2.16) | **1.70(1.09,2.65)** | |
| DEDTP | | | | | | 0.103 |
| dep/non-dep | 445/4761 | 97/1205 | 114/1187 | 97/1204 | 137/1165 | |
| Model | 1.124 (0.733,1.724) | 1 | 1.33 (0.84,2.10) | 0.78 (0.41,1.50) | 1.11 (0.57,2.15) | |

Notes: dep: depression; non-dep: non-depression; OR: Odds ratio; 95%CI: 95% Confidence interval; Q, quartile. Model adjusting for age, gender, race, educational level, FIR, BMI, marital status, NHANES cycle, physical activity, drinking, smoking, hypertension, diabetes, and cardiovascular diseases.

**Table 4**
Weighted associations of urinary organophosphorus pesticide metabolites with depression risk stratified by age and gender, NHANES, USA.

| Chemicals (μg/L) | Continuous | Q1 | Q2 | Q3 | Q4 | *P* for trend |
|---|---|---|---|---|---|---|
| | OR (95%CI) | Reference | OR (95%CI) | OR (95%CI) | OR (95%CI) | |
| **DMP** | | | | | | |
| Male | 1.10 (0.96, 1.26) | 1.00 | 1.72 (0.87,3.43) | 1.23 (0.56,2.70) | 1.64 (0.86,3.14) | 0.212 |
| Female | **1.15(1.03, 1.27)** | 1.00 | 1.56 (0.98,2.49) | **1.74(1.03,2.94)** | **1.95(1.25,3.04)** | **0.011** |
| 20≤Age (years)≤60 | **1.16(1.06, 1.28)** | 1.00 | **1.66(1.14,2.42)** | **1.80(1.06,3.04)** | **2.04(1.41,2.94)** | **0.002** |
| Age (years) > 60 | 0.98 (0.76, 1.26) | 1.00 | 1.45 (0.52, 4.06) | 0.83 (0.32, 2.14) | 1.02 (0.38, 2.72) | 0.650 |
| **DEP** | | | | | | |
| Male | **1.22(1.09, 1.35)** | 1.00 | 1.48 (0.79,2.76) | 1.31 (0.61,2.84) | **2.59(1.41,4.74)** | **0.002** |
| Female | 1.03 (0.91, 1.17) | 1.00 | 1.42 (0.91,2.21) | 1.02 (0.61,1.69) | 1.30 (0.81,2.08) | 0.560 |
| 20≤Age (years)≤60 | **1.15(1.03, 1.27)** | 1.00 | 1.43 (0.94,2.19) | 1.35 (0.78,2.32) | **1.99(1.29,3.07)** | **0.007** |
| Age (years) > 60 | 0.88 (0.73, 1.05) | 1.00 | 1.42 (0.58, 3.45) | 0.55 (0.23, 1.31) | 0.68 (0.31, 1.49) | 0.105 |
| **DMTP** | | | | | | |
| Male | **1.20(1.01, 1.44)** | 1.00 | 1.39 (0.69,2.78) | **2.24(1.24,4.04)** | 1.92 (0.87,4.24) | **0.031** |
| Female | 1.09 (0.97, 1.22) | 1.00 | 1.57 (0.96,2.56) | 1.09 (0.68,1.76) | 1.45 (0.87,2.40) | 0.356 |
| 20≤Age (years)≤60 | **1.17(1.05, 1.30)** | 1.00 | **1.81(1.17,2.83)** | **1.73(1.10,2.72)** | **1.95(1.26,3.00)** | **0.010** |
| Age (years) > 60 | 0.99 (0.77, 1.29) | 1.00 | 0.66 (0.32, 1.38) | 0.80 (0.42, 1.53) | 0.73 (0.27, 1.98) | 0.589 |
| **DETP** | | | | | | |
| Male | 1.11 (0.92, 1.34) | 1.00 | 1.04 (0.42,2.55) | 1.42 (0.68,2.97) | 1.56 (0.71,3.42) | 0.165 |
| Female | 1.01 (0.83, 1.24) | 1.00 | 0.90 (0.41,1.99) | 1.23 (0.57,2.67) | 1.07 (0.53,2.19) | 0.577 |
| 20≤Age (years)≤60 | 1.09 (0.93, 1.26) | 1.00 | 1.08 (0.53,2.19) | 1.48 (0.76,2.88) | 1.48 (0.80,2.73) | 0.075 |
| Age (years) > 60 | 0.84 (0.67,1.07) | 1.00 | 0.57 (0.26, 1.25) | 0.70 (0.30, 1.67) | 0.57 (0.30, 1.10) | 0.219 |
| **DMDTP** | | | | | | |
| Male | **1.26(1.02, 1.56)** | 1.00 | 1.56 (0.84,2.90) | 1.56 (0.74,3.26) | **2.71(1.37,5.36)** | **0.017** |
| Female | 1.07 (0.90, 1.26) | 1.00 | 1.43 (0.70,2.90) | 1.12 (0.58,2.18) | 1.37 (0.76,2.47) | 0.404 |
| 20≤Age (years)≤60 | **1.20(1.05, 1.36)** | 1.00 | **1.94(1.04,3.63)** | **1.83(1.03,3.25)** | **2.27(1.41,3.65)** | 0.004 |
| Age (years) > 60 | 0.92 (0.62, 1.38) | 1.00 | 0.56 (0.21, 1.50) | 0.22 (0.08, 0.62) | 0.63 (0.20, 2.01) | 0.512 |
| **DEDTP** | | | | | | |
| Male | 1.28 (0.81, 2.02) | 1.00 | 1.29 (0.66,2.51) | 0.62 (0.24,1.62) | 1.02 (0.29,3.52) | 0.274 |
| Female | 0.99 (0.54, 1.82) | 1.00 | 1.34 (0.72,2.50) | 0.90 (0.36,2.24) | 1.15 (0.51,2.59) | 0.264 |
| 20≤Age (years)≤60 | 1.38 (0.90, 2.12) | 1.00 | **1.76(1.03,3.01)** | 0.90 (0.41,1.99) | 1.39 (0.64,3.06) | **0.016** |
| Age (years) > 60 | 0.26 (0.04,1.77) | 1.00 | 0.38 (0.15, 0.95) | 0.29 (0.05, 1.56) | 0.26 (0.05, 1.41) | 0.081 |

Notes: OR: Odds ratio; 95%CI: 95% Confidence interval; Q, quartile. Model adjusting for age, gender, race, educational level, FIR, BMI, marital status, NHANES cycle, physical activity, drinking, smoking, hypertension, diabetes, and cardiovascular diseases.

decreased acetylcholinesterase activity (Karumuri et al., 2019; Ambali et al., 2010). In addition, animal experiments have also found that OPPs can alter the monoamine system in adult male rats, which has the function of controlling motivation, emotion, and reward (Abd El-Moneim Ibrahim et al., 2020; Moreno et al., 2008). Further leading to decreased function of the 5-hydroxytryptamine system is a marker of mood disorders such as depression (Chen et al., 2011; Oquendo and Mann, 2000).

The main strength of this study is the use of three models to quantify and visualize the single and combined exposure effects of OPPs metabolites on depression. In addition, the large and nationally representative sample size of this study allows for good generalization of the findings to populations with similar characteristics. This study also has several limitations. First, the design of this study was cross-sectional and did not confirm a causal relationship between OPPs metabolites and depression risk. Second, although we used multiple DAPs, each metabolite was a mixture of one or more OPPs, so we were unable to infer an association between specific pesticides and depression. Third, since the study

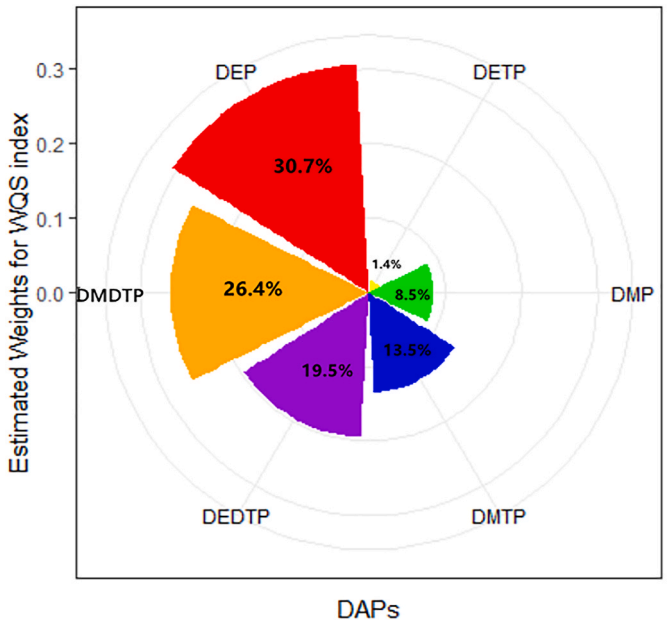


**Fig. 3.** WQS model regression index weights for depression. The model was adjusted for age, gender, race, educational level, FIR, BMI, marital status, NHANES cycle, physical activity, drinking, smoking, hypertension, diabetes, and cardiovascular diseases.

participants were only tested once for urinary DAPs, this does not reflect OPPs exposure levels very accurately due to the body's metabolism, this misclassification may discount the power of the association. In addition, individuals exposed to OPPs are also more likely to be exposed to other non-OPPs, which also may lead to misclassification of exposure. Finally, it is worth noting that the use of fixed values to replace the levels of some DAPs below the detection limit may also slightly underestimate the association effect (Hargarten and Wheeler, 2020). Therefore, the present study is an exploratory study and future prospective cohort studies are needed to further validate this association.

## 5. Conclusion

Our study found that exposure to organophosphorus pesticides may increase the risk of depression in U.S. adults. Also, the joint exposure model better confirms this idea. Men and young and middle-aged groups may be more vulnerable to the effects of OPPs. In the future, we should conduct more similar cohort studies and use advanced statistical models to further confirm that single and combined exposure to organophosphorus pesticides can increase the risk of depression and provide reliable evidence for policy development related to organophosphorus pesticides and mental health.

## Credit authors statement

**Yudong Wu**: Data curation, Writing - original draft & editing; **Jian Song**: Conceptualization, Data curation; **Qin Zhang**: Data curation, Software; **Shuangshuang Yan**: Methodology, Software; **Xiaoni Sun**: Data curation, Resources; **Weizhuo Yi**: Validation, Data curation; **Rubing Pan**: Software, Validation; **Jian Cheng**: Methodology; **Zhiwei Xu**: Data curation, Resources, and Conceptualization; **Hong Su**: Conceptualization and Supervision. Resources, Funding acquisition,

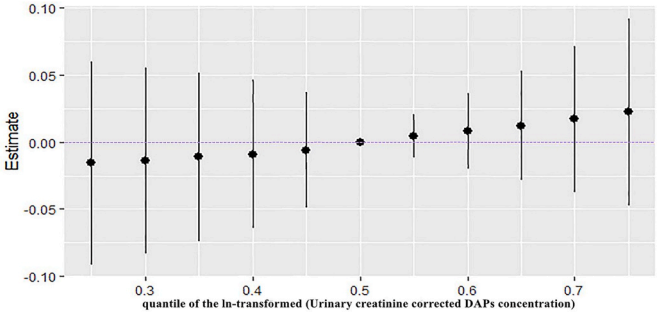


**Fig. 5.** Joint effect (95% CI) of the DAPs on depression when all the chemicals at particular percentiles were compared to all the chemicals at their 50th percentile. The model was adjusted for age, gender, race, educational level, FIR, BMI, marital status, NHANES cycle, physical activity, drinking, smoking, hypertension, diabetes, and cardiovascular diseases.

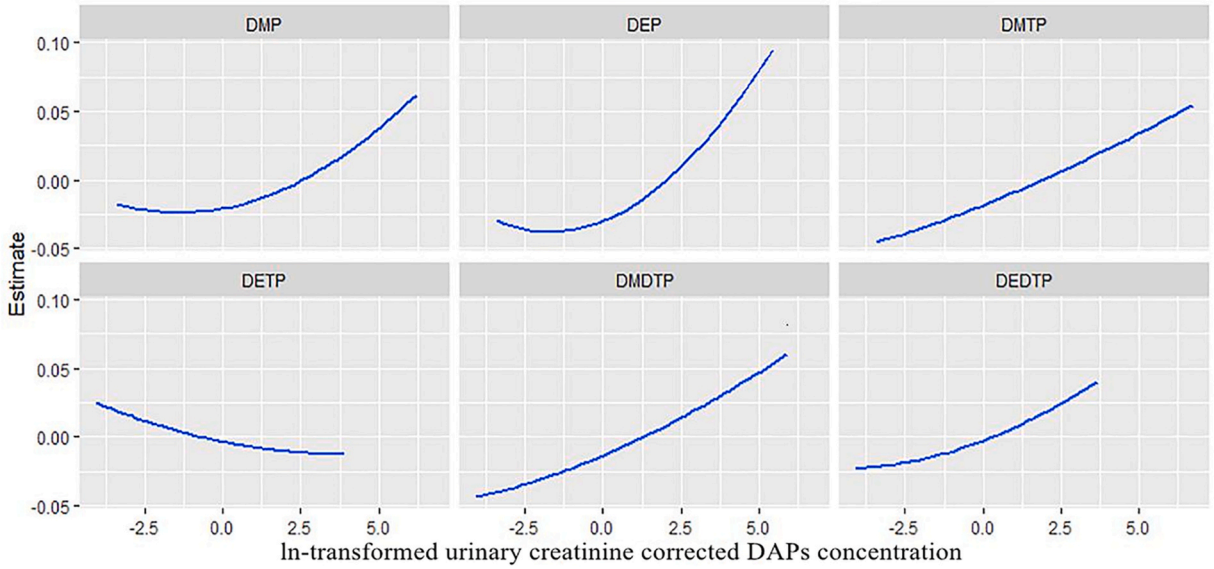


**Fig. 4.** Univariate exposure-response relationships (95% CI) between selected urine creatinine corrected ln-transformed organophosphorus pesticides Metabolites concentrations and depression while fixing at the median for other urine creatinine corrected ln-transformed DAPs concentrations. The results were assessed by the BKMR model adjusted for age, gender, race, educational level, FIR, BMI, marital status, NHANES cycle, physical activity, drinking, smoking, hypertension, diabetes, and cardiovascular diseases.

Project administration, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2022.120445.

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