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ORIGINAL RESEARCH

Association Between Urinary Glyphosate Concentrations and Chronic Obstructive Pulmonary Disease in USA Participants: Evidence from NHANES 2013–2018

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Background: Glyphosate has raised health concerns due to its widespread detection in environment and human tissues. Limited evidence exists found in the association between urinary glyphosate concentrations and chronic obstructive pulmonary disease.

Methods: Analyzing data from 2588 participants, we applied survey-weighted logistic regression models and cubic spline techniques to quantify link between urinary glyphosate concentrations and prevalence of COPD. Further subgroup and sensitivity analyses were also conducted.

Results: Study revealed a significant association between higher urinary glyphosate concentrations that increased risk of COPD. In fully adjusted models, a one-unit increase in natural logarithm of urinary glyphosate was associated with a 35% increased risk of COPD (OR, 1.35, 95% CI, 1.01–1.82, P=0.043). Subgroup analyses showed consistent associations across different demographic groups with a pronounced association in current smokers and females. Sensitivity analyses and exclusion of participants with chronic kidney disease reinforced the robustness of the findings.

Conclusion: Findings provide evidence of a positive association between urinary glyphosate concentrations and prevalence of COPD in a representative sample of the adult population at the United States of America. Further studies are needed to investigate the influence of factors and other environmental pollutants on COPD.

Keywords: chronic obstructive pulmonary disease, glyphosate, herbicide, national health and nutrition examination survey, urinary concentrations

Introduction

Impacts and Causes of COPD on Public Health

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide, characterized by persistent respiratory symptoms and airflow limitation.[1,2] COPD is mainly caused by exposure to inhaled noxious particles, notably tobacco smoke and pollutants.[3] Effective smoking cessation strategies are crucial for the prevention and treatment of COPD.[4] Despite the well-established relationship between tobacco smoking and COPD, the rapid increase in the prevalence of the disease, even among non-smokers, suggests that other factors may be contributing to its development. Susceptibility to and heterogeneity of COPD are incompletely explained by cigarette smoking, a substantial proportion of COPD risk is related to genetic variation.[5] Environmental influences like particulate matter, carbon monoxide, and VOCs are gaining recognition as factors in the development of COPD.[6–8] Hence, the critical need to explore and minimize exposure to these environmental chemicals as a strategy for COPD prevention is apparent.

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Glyphosate Exposure and Adverse Health Effects

Recent studies have also highlighted the role of environmental toxins, such as glyphosate, in the pathogenesis of COPD.[9] Glyphosate is a herbicide that belongs to the family of organophosphorus compounds,[10] and have several chemical and physical specificities, such as high adsorption, high water solubility and compatibility with other chemical substances.[11] Now, it was the world's most widely used herbicide, has been detected in various environmental media and human tissues, raising concerns about its potential health effects. Numerous epidemiological studies have linked glyphosate exposure to various human health conditions, including metabolic syndrome,[12] adverse reproductive outcomes,[13,14] liver disease,[15] mammalian nervous system,[16] endocrine and reproductive effects,[17] and cognitive impairment.[18]

The Link and Aims Between Glyphosate Exposure and COPD

A recent study has suggested a link between glyphosate exposure and COPD was not statistic significant.[19] However, the evidence remains limited and inconclusive, necessitating further investigation to clarify the relationship. This study aims to leverage the National Health and Nutrition Examination Survey (NHANES) data from 2013 to 2018 to explore the potential association between glyphosate levels, as indicated by urinary concentrations, and the prevalence of COPD. We hypothesize that higher levels of glyphosate in urine will be associated with an increased risk of COPD. By utilizing a large, representative sample of the US adult population and employing robust statistical methods, this study aims to fill the gap in the literature by providing a more comprehensive understanding of the relationship between glyphosate exposure and COPD. Additionally, this study will contribute to the broader understanding of environmental determinants of COPD and inform preventive strategies by identifying potential modifiable risk factors.

Method

Study Population and Design

The National Health and Nutrition Examination Survey (NHANES), managed by the Centers for Disease Control and Prevention (CDC), is a cross-sectional survey designed to gauge the health and nutritional status of the civilian, non-institutionalized population residing in the United States. Notably, the survey employs a stratified, multistage probability sampling method to ensure a representative sample of the population. The NHANES data are accessible to the public through the official NHANES website (http://www.cdc.gov/nchs/nhanes/index.htm). All procedures associated with the NHANES are reviewed and approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. Participants provide their written informed consent, demonstrating their voluntary agreement to partake in the study. In light of the Ethical Review Methods for Life Science and Medical Research Involving Human Beings. We have found that Article 32 of this regulation specifically exempts research from requiring ethical approval under certain conditions. Our study aligns with these exemption conditions as we utilized legally obtained public data and ensured that our research did not interfere with public behavior. Additionally, we conducted our research using anonymized informational data. The Ethics Committee of Affiliated Hospital of Shandong University of Traditional Chinese Medicine has granted an exemption from review for this particular study, ethics number was 2024–0022. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

In the current study, we selected our participant cohort from the NHANES data spanning the years 2013 to 2018. Our initial pool consisted of 11,463 individuals aged 40 years and older, all of whom had complete information regarding Chronic Obstructive Pulmonary Disease (COPD). We then narrowed down our sample to the 3084 participants with accessible urine glyphosate data. Additionally, we excluded 496 participants due to missing covariate information: marital status (n=1), education level (n=5), income-poverty ratio (n=313), alcohol intake (n=149), BMI (n=21), stroke history (n=4), and diabetes mellitus status (n=3). Following these exclusions, the final analysis included 2588 participants, 1969 without COPD and 619 with COPD (Figure 1).

Definition of COPD

Referring to previous studies,[20–22] COPD was identified based on meeting at least one of the following criteria: (1) a ratio of post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) that was less than

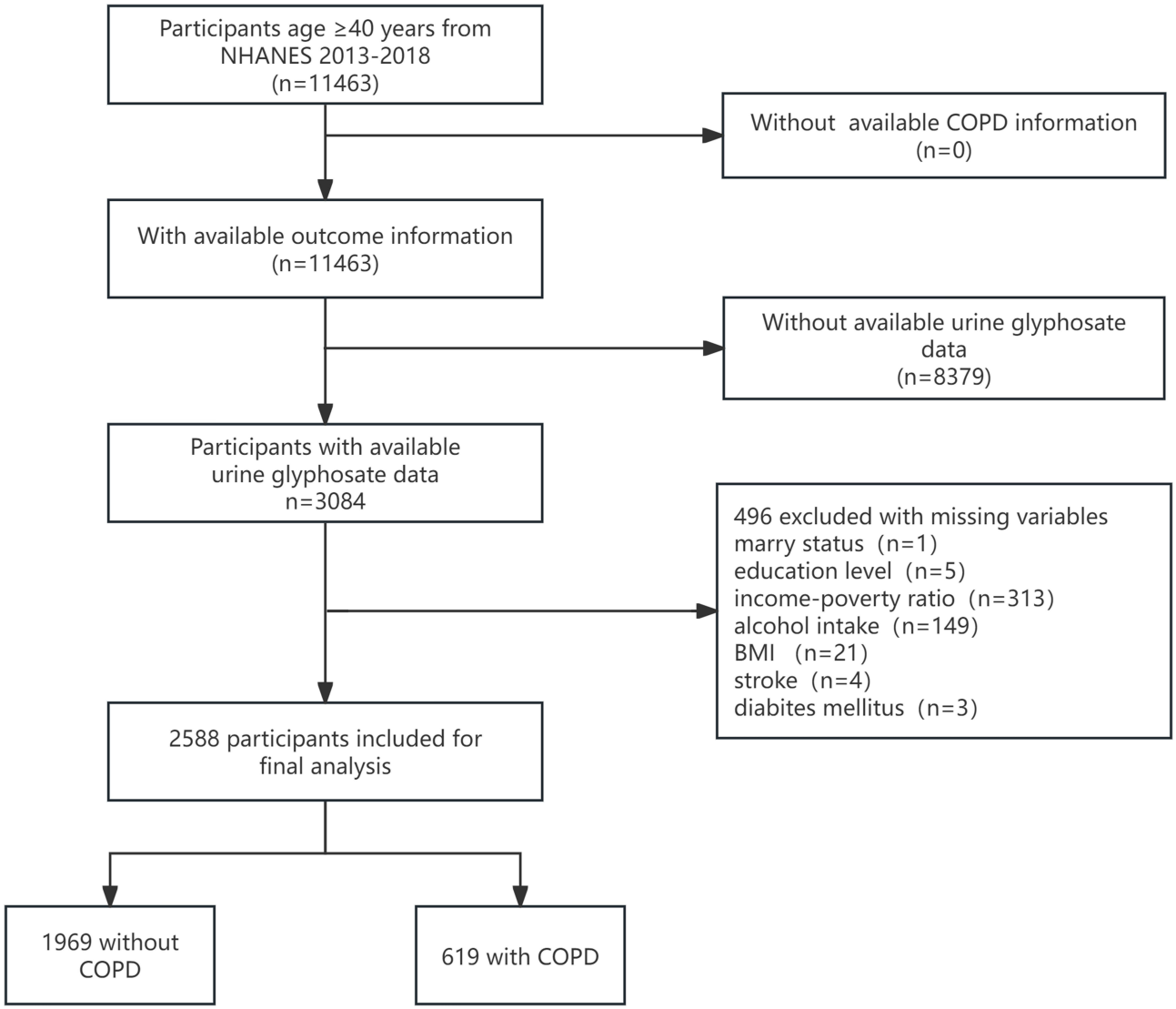

Figure 1 Flow diagram of the screening and enrollment of study participants.

0.7; (2) subjective reports of COPD, emphysema, or chronic bronchitis from the participants. (3) participants were over the age of 40, had a history of smoking or bronchial inflammation, and were on a regimen including any of the following pharmaceuticals: mast cell stabilizers, inhaled corticosteroids, leukotriene modifiers, or selective phosphodiesterase-4 inhibitors.

Quantification of Concentrations and the Sources of Urinary Glyphosate

The primary sources of human exposure to glyphosate include dietary intake through consumption of treated crops, occupational exposure among agricultural workers, and environmental exposure through contaminated water or air. In the NHANES dataset, urinary glyphosate levels are measured as a biomarker of recent exposure to glyphosate-based herbicides. The NHANES does not provide detailed information on the specific routes of exposure for each individual; however, the urinary glyphosate levels reflect the cumulative exposure from all possible sources. Glyphosate levels were measured utilizing 200 μL of urine based on 2D-on-line ion chromatography coupled with tandem mass spectrometry (IC-MS/MS).[23] The detailed expatiation of laboratory procedures for measuring glyphosate levels have been documented in prior publications.[24] For glyphosate concentrations that were beneath the measurable threshold, NHANES substituted

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an estimated figure, which was the result of the lower limit of detection (LLOD) divided by two times the square root of two.

Covariates Measurement

Covariates in this study were chosen by referencing and synthesizing insights from a body of related existing literature:[19,25–27] age, gender, race/ethnicity (Non-Hispanic Black, Non-Hispanic White, Mexican American, Other Hispanic, and Other), marital status (married, never married, living with a partner, and others including widowed, divorced, or separated individuals), educational level (less than high school, high school or equivalent, and above high school), poverty income ratio (PIR), body mass index (BMI), smoking status (former, now, never),[28] physical activity time,[28,29] drinking status (former, current, never),[30] urinary creatinine (mg/ dl), self-reported stroke (yes and no), hypertension (yes and no), hyperlipidemia (yes and no), chronic kidney disease (CKD), and diabetes mellitus (yes, and no).

To be specific, BMI was categorized into underweight or normal weight (<25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2) groups[18]. Hyperlipidemia is diagnosed when at least one of the following conditions is met: the use of lipid-lowering medications; elevated triglyceride levels of 150 mg/dL or higher; high cholesterol levels (total cholesterol of 200 mg/dL or higher, LDL cholesterol of 130 mg/dL or higher, or HDL cholesterol below 40 mg/dL).[31] CKD was defined as estimated glomerular filtration rates (eGFR) < 60, or urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g.[32] eGFR was determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[33] The determinations of hypertension and diabetes mellitus were in accordance with previous study.[28]

Statistical Analysis

To account for the complex survey design, the subsample weight of the urinary glyphosate was applied according to NCHS guidance in this study.[25] To address the skewed distribution of urinary glyphosate levels, a natural logarithmic transformation was implemented to facilitate parametric statistical analysis.[34] Continuous variables are expressed as weighted means with standard deviation (SD), while categorical data are expressed unweighted absolute values (n) and weighted percentages (%). Basic characteristics across the tertiles of glyphosate were compared using *chi-square* test for categorical data, or analysis of variance (ANOVA) for continuous variables, respectively.

The concentrations of urinary glyphosate were either ln-transformed or categorized into tertiles, with the first tertile serving as the reference. Survey weighted logistic regression was adopted to detect the associations between urinary glyphosate and COPD, the estimated risk was presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Four logistic models were constructed in this study: Model 1 did not adjust for covariates; Model 2 adjusted for covariates including age, sex, race; Model 3 further adjusted for education level, marital status, body mass index, physical activity, poverty income ratio, smoking status, and drinking status; Model 4 further adjusted for history of hypertension, chronic kidney disease, stroke, hyperlipidemia and diabetes mellitus. Tests for trend were conducted with multivariate regression models to examine the possibility of nonlinearity. Restricted cubic splines (RCS) were further employed to visualize the potential exposure–response relationships between ln-transformed urinary glyphosate levels and COPD. Potential multi-collinearity was tested using the variance inflation factor (VIF), with VIF > =5 indicating the presence of multi-collinearity.

To detect potential interactions, subgroup was conducted by age (<65 years, and ≥65 years), sex (male and female), smoking status (never, former, and current), CVD history (yes and no), hypertension history (yes and no) hyperlipidemia history (yes and no), DM history (yes and no). Interaction among subgroups was inspected by the likelihood ratio test.

We further performed the following sensitivity analysis. First, to address the potential for bias due to missing data, multivariate imputation by chained equations (MICE) was conducted to fill in missing covariate values and logistic regression models were re-estimated to assess the sensitivity of the results to the imputation process given that the urinary system plays a crucial role in the body's elimination of glyphosate,[35] we excluded patients with CKD (n = 619)) to compare the stability of the results.

All analyses were performed using R Statistical Software (Version 4.2.2, http://www.R-project.org, The R Foundation) and Free Statistics analysis platform (Version 1.9.2, Beijing, China).[36] Two-sided $p < 0.05$ was defined as statistical significance.

Results

Demographic and Clinical Characteristics of Participants

Urinary glyphosate concentration was split into three tertiles (Tertile 1: ≤0.225ng/mL; Tertile 2: 0.226 ~ 0.474ng/mL; Tertile 3: ≥ 0.475ng/mL). The baseline characteristics based on the levels of urinary glyphosate concentration are shown in Table 1. The main analysis consisted of 2588 participants, representing approximately 131,01 million US adults aged ≥40 years. Among all participants, 133 participants were diagnosed with COPD, 52.45% females, a weighted mean urinary glyphosate concentration of 0.506 ng/mL, we observed higher urinary glyphosate levels in participants with COPD compared to those without COPD (0.623 ng/mL vs 0.501) ng/mL. the weighted mean age was 58.36 years, The majority of the subjects were

Table 1 Baseline Characteristics of the Participants in the Analyses According to Urine Glyphosate Concentration (N = 2588)

Variables	Total (N=2588)	Tertile 1(N=863) (≤0.225ng/mL)	Tertile 2(N=862) (0.226–0.474ng/mL)	Tertile 3(N=863) (≥0.475ng/mL)	*p*
Age, years, mean (SD)	58.365 (11.479)	57.071 (11.312)	58.347 (11.361)	59.790 (11.625)	0.0043
Age, n (%)					0.0552
40–64	1685(69.33)	615(73.11)	571(69.53)	499(65.00)	
≥65	903(30.67)	248(26.89)	291(30.47)	364 (35.00)	
Sex (%)					0.1114
Female	1316(52.45)	463 (53.30)	452(55.54)	401(48.33)	
Male	1272(47.55)	400(46.70)	410 (44.46)	462 (51.67)	
Race/ethnicity, n (%)					0.0095
Mexican American	349(6.37)	120(7.22)	124(6.34)	105(5.49)	
Non-Hispanic Black	529(10.09)	157(8.73)	172(10.06)	200(11.60)	
Non-Hispanic White	1105(70.91)	331(68.32)	383 (72.08)	391 (72.51)	
Other Hispanic	247 (4.48)	91(5.23)	77(4.15)	79(4.02)	
Other Race	358(8.14)	164(10.50)	106(7.38)	88(6.37)	
Marital status, n (%)					0.0011
Married	1504(64.04)	521(68.14)	488(61.73)	495(62.00)	
Never married	219(6.98)	67(5.33)	93(10.12)	59(5.52)	
Living with a partner	119(4.19)	47(4.32)	28(2.01)	44(6.31)	
Others	746(24.79)	228(22.22)	253(26.14)	265(26.18)	
Education level, n (%)					0.283
Less than high school	539(11.91)	162(10.80)	190(12.94)	187 (12.06)	
High school	586(22.74)	199(25.03)	185(19.86)	202(23.24)	
Above high school	1463(65.35)	502(64.17)	487(67.19)	474(64.70)	
PIR, mean (SD)	3.244(1.633)	3.384(1.603)	3.167(1.638)	3.171(1.651)	0.169
Smoking status, n (%)					0.6797
Never smoking	1354(54.19)	465(55.36)	442(52.70)	447(54.46)	
Former smoking	750(28.65)	241 (27.08)	254(31.26)	255(27.64)	
Current smoking	484(17.16)	157(17.57)	166(16.04)	161(17.90)	
Drinking status, n (%)					0.0139
Never	349(9.85)	116 (9.34)	113(10.03)	120(10.22)	
Former	582(17.96)	157(13.25)	205(19.51)	220(21.46)	
Current	1657(72.19)	590 (77.41)	544(70.46)	523 (68.32)	
PA time, min, mean (SD)	740.390 (1275.905)	844.398 (1358.827)	656.721 (1172.606)	714.203 (1279.534)	0.1462
BMI kg/m2, n (%)					0.4679
Underweight/normal weigh (<25)	619(24.15)	231(27.07)	202(22.25)	186(22.94)	
Overweight (25–29.9)	851(32.90)	294(33.32)	278(33.00)	279(32.35)	
Obesity (≥30)	1118(42.95)	338(39.60)	382(44.75)	398(44.71)	

(*Continued*)

Table 1 (Continued).

Variables	Total (N=2588)	Tertile 1(N=863) (≤0.225ng/mL)	Tertile 2(N=862) (0.226–0.474ng/mL)	Tertile 3(N=863) (≥0.475ng/mL)	*p*
Creatinine, mg/dl, mean (SD)	111.638 (73.992)	76.761 (53.921)	107.771 (65.973)	153.543 (79.657)	<0.0001
CKD, n (%)					
No	1969(78.94)	688(82.83)	650(76.35)	631(77.39)	0.019
Yes	619(21.06)	175(17.17)	212(23.65)	232(22.61)	
Stroke, n (%)					0.1712
No	2449(95.31)	827(96.08)	826(95.76)	796(94.02)	
Yes	139(4.69)	36 (3.92)	36(4.24)	67(5.98)	
Hypertension, n (%)					0.1044
No	1122(49.07)	393(52.65)	364(46.03)	365(48.33)	
Yes	1466(50.93)	470(47.35)	498(53.97)	498(51.67)	
Hyperlipidemia, n (%)					0.2402
No	579(21.61)	194(23.56)	196(22.07)	189(19.01)	
Yes	2009(78.39)	669(76.44)	666(77.93)	674(80.99)	
Diabetes mellitus, n (%)					0.0806
No	1897(79.49)	656(82.43)	641(78.20)	600(77.64)	
Yes	691(20.51)	207 (17.57)	221(21.80)	263(22.36)	
COPD, n (%)					
No	2455(95.42)	830(97.26)	814(94.81)	811(94.06)	0.0609
Yes	133(4.58)	33(2.74)	48(5.19)	52(5.94)	

Notes: All means and SDs for continuous variables and percentages for categorical variables were weighted. Urinary glyphosate concentration was split into three tertiles (Tertile 1: ≤0.225ng/mL; Tertile 2: 0.226 ~ 0.474ng/mL; Tertile 3: ≥ 0.475ng/mL). PA was calculated by the time during a week. Marital status (others including widowed, divorced, or separated individuals), CKD was defined as estimated glomerular filtration rates (eGFR) < 60, or urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g.

Abbreviations: PIR, poverty income ratio; BMI, body mass index; PA physical activity; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

non-Hispanic whites (70.91%), married (64.04%), never smoking (54.19%), obesity (BMI ≥ 30 kg/m2, 42.95%), and above high school (65.35%). A statistically significant divergence was noted among the groups in parameters such as age, ethnicity, marital status, drinking status, BMI, CKD, and urinary creatinine ($p < 0.05$). On the other hand, variables like sex, smoking status, hypertension, stroke, and diabetes showed no significant variation ($p > 0.05$).

Association Between Urinary Glyphosate and COPD

The result of weighted logistic analysis is shown in Table 2. Analyzing the data with a continuous model, a single unit rise in the ln-transformed urinary glyphosate levels elevated the risk of COPD by 35% in the model with full covariate adjustment (OR 1.35, 95% CI 1.01–1.82, P=0.043). In the categorical model, participants in the higher tertile had a significantly higher risk of COPD in Model 1 (OR 2.24, 95% CI 1.22–4.10, p=0.026) and Model4 (OR 2.16, 95% CI 1.11–4.20, p=0.026), respectively (all p for trend <0.05).

Table 2 Weighted Logistic Regression of the Association Between Urine Glyphosate Concentrations and COPD Outcomes

Variable	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Ln-transformed urinary glyphosate (ng/mL)	1.37(1.08–1.73)	0.01	1.34(1.03–1.72)	0.027	1.35(1.01–1.80)	0.044	1.35(1.01–1.82)	0.043
Categories								
Tertile1 (≤0.225ng/mL)	Reference		Reference		Reference		Reference	
Tertile2 (0.226–0.474ng/mL)	1.94(0.98–3.87)	0.058	1.89(0.95–3.78)	0.069	1.63(0.79–3.37)	0.174	1.64(0.84–3.21)	0.137
Tertile3 (≥ 0.475ng/ mL)	2.24(1.22–4.10)	0.01	2.12(1.11–4.06)	0.025	2.04(1.03–4.00)	0.04	2.16(1.11–4.20)	0.026
P for trend		0.01		0.025		0.038		0.027

Notes: Model 1 did not adjust for covariates. Model 2 adjusted for covariates including age, sex, race. Model 3 further adjusted for education level, marital status, body mass index, physical activity, poverty income ratio, smoking status, and drinking status. Model 4 further adjusted for history of hypertension, chronic kidney disease, stroke, hyperlipidemia and diabetes mellitus.

Abbreviations: OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

As shown in Figure 2, a visual representation of the dose-response relationship indicates a linear association between ln-transformed urinary glyphosate and COPD risk. The RCS model supports this linearity with a non-linearity p-value of 0.10.

Subgroup Analysis

Subgroup analyses were carried out to explore whether the observed association between ln-transformed urinary glyphosate and COPD risk was stable among different groups (Figure 3). The associations were still significant in participants aged <65 years (OR 1.72, 95% CI 1.16–2.55, *P*=0.01), female (OR 1.47, 95% CI 1.05–2.04, *P*=0.03), current smoking (OR 1.90, 95% CI 1.02–3.54, *P*=0.04), without history of hypertension, CKD, hyperlipidemia and diabetes mellitus. Additionally, no noteworthy interactions were observed between urinary glyphosate and the variables within the subgroups (all *P* for interaction >0.05).

Sensitivity Analyses

Supplementary Table 1 demonstrates the association between ln-transformed urinary glyphosate level and the prevalence of COPD after multivariate imputation for covariates (n=3084). A one-unit increase in ln-urinary glyphosate, a 31% increased risk of COPD in the fully adjusted model (OR, 1.31; 95% CI, 1.01–1.70; *P*=0.046). Supplementary Table 2 shows the association between the association between ln-transformed urinary glyphosate level and the prevalence of COPD after excluding CKD participants (n=1969), a one-unit increase in ln-urinary glyphosate, a 45% increased risk of

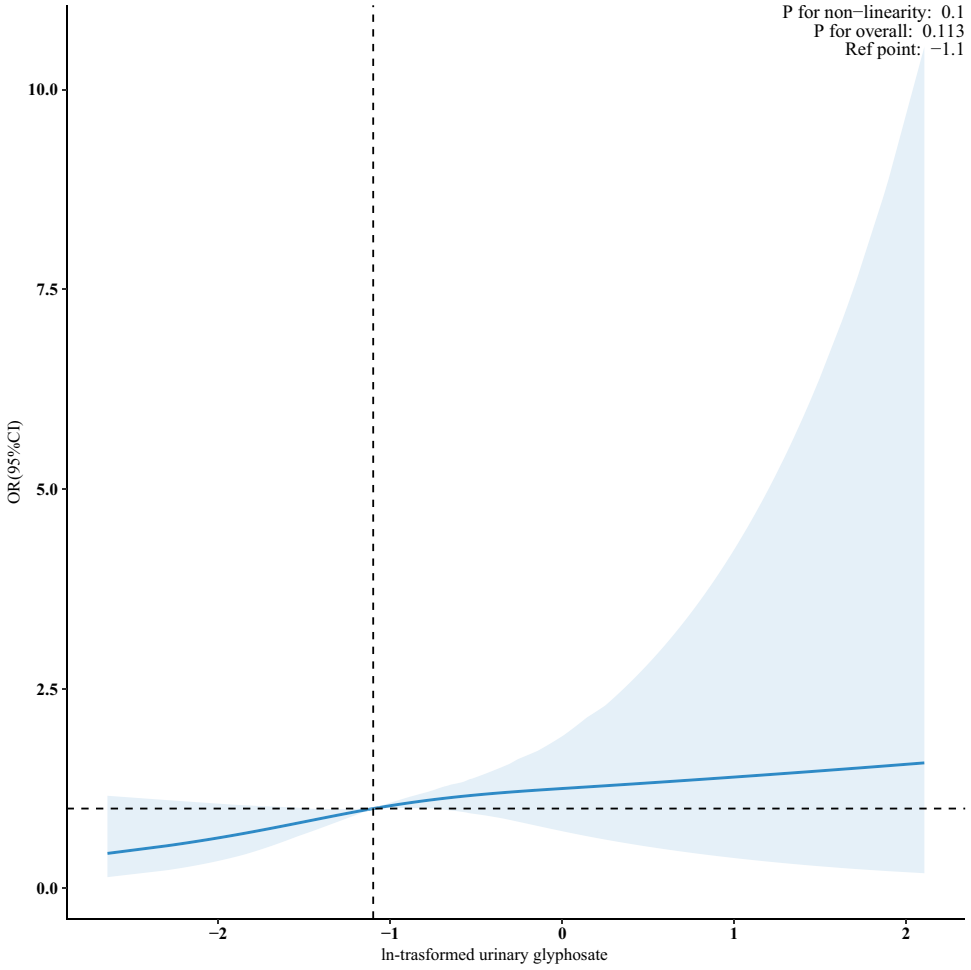

Figure 2 Restricted cubic spline (RCS) plot for ln-transformed urinary glyphosate and COPD. Solid and shaded areas represent the predicted value and 95% confidence intervals. They were adjusted for covariates including age, sex, race, education level, marital status, BMI, physical activity, poverty income ratio, smoking status, drinking status, history of hypertension, CKD, stroke, hyperlipidemia and diabetes mellitus.

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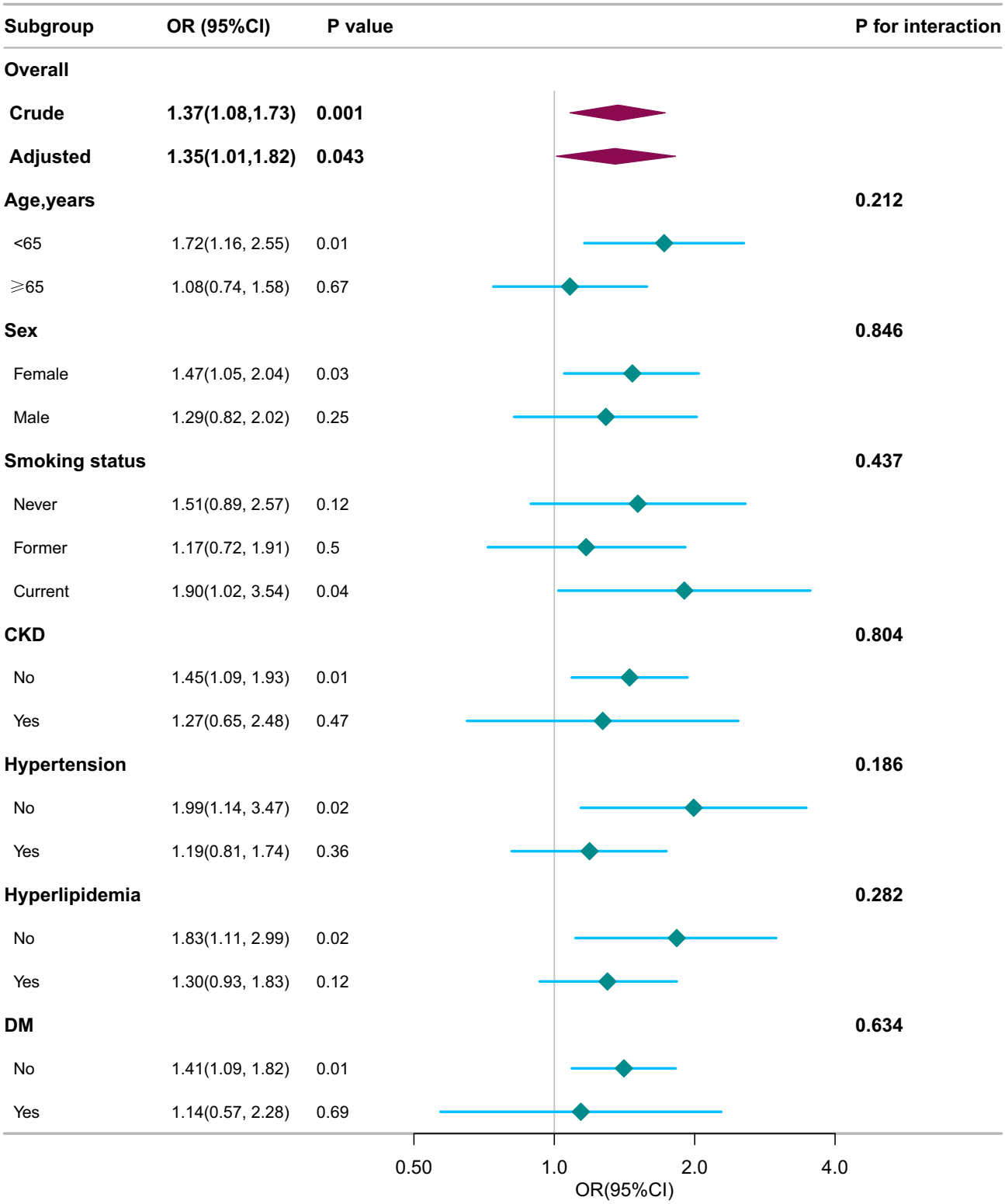

Figure 3 Subgroup analysis for the association between ln-transformed urinary glyphosate and the prevalence of COPD. except for stratification component itself, each stratification factor was adjusted for age, sex, race, education level, marital status, BMI, physical activity, poverty income ratio, smoking status, drinking status, history of hypertension, CKD, stroke, hyperlipidemia and diabetes mellitus.

COPD in the fully adjusted model (OR 1.45, 95% CI 1.09–1.92, *P*=0.012). Furthermore, the results from the classification model were found to be consistent with the primary outcomes, reinforcing the robustness of our findings.

Discussion

The Key Results

The cross-sectional analysis conducted here has demonstrated a linear relationship between urinary glyphosate concentrations and COPD, a link that remains stable upon examination of different subgroups and through sensitivity testing. The findings could contribute to a better understanding of the environmental determinants of COPD and informing preventive strategies.

Compared With Other Literatures

In contrast to our findings, a cross-sectional study of adults age >20 years has indicated that no significant result between urinary glyphosate levels and the prevalence of COPD was observed (OR 0.93, 95% CI 0.75–1.15, P=0.507).[19] This is different from our study, probably because of different participants age, our study looked at people 40 and older. Another cross-sectional survey of adults aged 40 to 65 in Nan province, there is no evidence of association of respiratory symptoms or lung function with the use of specific herbicides like glyphosate.[37] Similar to our findings, a study of male sprayers reported significant relationships between wheezing (no measurement of lung function) and glyphosate.[38] Other findings indicated that exposure to glyphosate had significant negative effects on lung function in maize farmers.[39] Our findings are in line with a growing body of evidence that implicates environmental factors in the development of COPD.[40] While tobacco smoke remains the leading risk factor for COPD, our study emphasizes the potential role of environmental pollutants, such as glyphosate, in contributing to the disease's pathogenesis.

Main Results Analysis

In our analysis, the association between urinary glyphosate concentrations and COPD risk was not consistent across all tertiles. Specifically, while Tertile 3 (≥ 0.475 ng/mL) showed a significant association with COPD risk across all models, the results for Tertile 2 (0.226–0.474 ng/mL) were less consistent. In Model 3, the OR for Tertile 2 was 1.63 (95% CI: 0.79–3.37, p = 0.174), and in Model 4, it was 1.64 (95% CI: 0.84–3.21, p = 0.137), both of which were not statistically significant. The wide confidence intervals in these models suggest considerable uncertainty in the estimate of the OR for Tertile 2. This inconsistency could be attributed to several factors, including the sample size, statistical power, or the possibility of a non-linear dose-response relationship between glyphosate exposure and COPD risk.

The lack of a significant association in Tertile 2, contrasted with the significant association in Tertile 3, may indicate a threshold effect, where only higher levels of glyphosate exposure are associated with an increased risk of COPD. Alternatively, it could reflect variability in exposure levels within Tertile 2, leading to a less clear association. Further research with larger sample sizes and more detailed exposure assessments is needed to clarify these findings.

The subgroup analyses conducted in our study revealed consistent associations across different demographic groups, including age, sex, and smoking status. Notably, the association between urinary glyphosate and COPD was particularly pronounced in current smokers. This finding warrants further investigation, as it suggests a potential synergistic effect between smoking and glyphosate exposure on the risk of COPD. The positive association between urinary glyphosate and COPD was more significant in female participants compared to males. This was an interesting finding, as in a clinical observational study, the investigators found significantly higher GLY residues in the urine of women than men.[41] In addition, we found another valid subgroup group to be participants aged 40–65 years. Further research is required to comprehend the potential mechanisms behind such differences. The sensitivity analyses performed in our study, including multivariate imputation for missing data and exclusion of participants with CKD, further reinforced the robustness of our findings. The consistency of the results across different analytical approaches increases our confidence in the observed association between glyphosate exposure and COPD.

Possible Mechanisms

The biological mechanisms underlying the association between glyphosate exposure and COPD are not yet fully understood. However, it is hypothesized that glyphosate may induce inflammation and oxidative stress,[42,43] which are known to play a critical role in the development of COPD. Repetitive exposure to glyphosate increased IL-33 and Th2 cytokines IL-5 and IL-13.[44,45] Furthermore, glyphosate has been shown to have negative effects on gut microbiota,[46,47] which could indirectly impact respiratory health. Further research is required to comprehend the potential mechanisms behind such differences. It is important to consider the complexity of glyphosate-based herbicides (GBH) when interpreting the results of this study. GBH formulations contain various components, including polyoxyethylene amine (POEA) surfactants, heavy metals, and adjuvants, all of which have their own toxicological profiles. These components, particularly POEA and heavy metals, are known to have significant pulmonary toxicity.[48,49] Therefore, the observed association between urinary glyphosate and COPD may reflect the combined effects of glyphosate and other toxic components in GBH formulations. Future studies should aim to disentangle the individual and combined effects of these components on respiratory health.

Strengths and Limitations

Our research has several advantages, it provides a large, representative sample of the US adult population. This ensures that our findings are generalizable to a broader population; We adjusted for a wide range of potential confounders, it helps to minimize bias and provides more robust estimates of the association between glyphosate exposure and COPD; Our study addresses a significant gap in the literature by examining the association between glyphosate exposure and COPD in a large, population-based sample; We conducted extensive subgroup analyses and sensitivity tests to validate the robustness of our findings. These analyses provide additional confidence in the observed associations and highlight potential differences across demographic groups.

However, our study has some limitations. First, the cross-sectional design of the study precludes any causal inferences about the relationship between glyphosate exposure and COPD. Future research should include follow-up periods of 10 years or more to capture the long-term effects of glyphosate exposure on respiratory health. Second, although we adjusted for a range of potential confounders, residual confounding by unmeasured factors cannot be entirely ruled out. Thirdly, more details on the source of glyphosate and the potential routes of exposure were limited, future studies should include more detailed exposure assessments, such as occupational history and dietary surveys. Lastly, the study only included participants age ≥40 years from the United States, which may limit the generalizability of the results to other populations.

Conclusion

In conclusion, we found a significant positive association between urinary glyphosate concentrations and the prevalence of chronic obstructive pulmonary disease (COPD) among US adults aged 40 years and older. Specifically, a one-unit increase in the natural logarithm of urinary glyphosate was associated with a 35% increased risk of COPD in fully adjusted models (OR, 1.35; 95% CI, 1.01–1.82; P=0.043). Our findings highlight the importance of considering environmental exposures, such as glyphosate, in the prevention and management of COPD. Public health strategies aimed at reducing glyphosate exposure, particularly among high-risk groups, may help mitigate the burden of COPD. Further research is warranted to better understand the long-term effects of glyphosate exposure on respiratory health and to inform evidence-based policies for environmental and public health protection.

Abbreviations

BMI, Body Mass Index; CDC, Centers for Disease Control and Prevention; CI, Confidence Interval; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; eGFR, Estimated Glomerular Filtration Rate; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; IC-MS/MS, Ion Chromatography-Tandem Mass Spectrometry; LLOD, Lower Limit of Detection; NHANES, National Health and Nutrition Examination Survey; NCHS, National Center for Health Statistics; OR, Odds Ratio; PIR, Poverty Income Ratio; RCS, Restricted Cubic Spline; SD, Standard Deviation; UACR, Urine Albumin-to-Creatinine Ratio.

Data Sharing Statement

Data will be made available on request from the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known conflicts of interest in this work.

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