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Association between combined exposure to organochlorine pesticides and history of uterine fibroids in NHANES: findings from four statistical models

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Abstract

Background Organochlorine pesticides (OCPs) are extensively dispersed throughout the environment, which potentially have harmful impacts on the female reproductive system. Therefore, the purpose of this study was to clarify the association between exposure to OCPs and the history of uterine fibroids in American women.

Methods The present study comprised female individuals who were over 20 years old and were selected from the National Health and Nutrition Examination Survey (NHANES). The logistic regression models were used to investigate the associations between eight primary serum OCP compounds and uterine fibroids. The collective impact of OCP compounds on the overall association with uterine fibroids was assessed using three statistical approaches: weighted quantile sum regression (WQS), quantile g-computation model (Qgcomp), and Bayesian kernel machine regression (BKMR) model.

Results In the end, a total of 931 individuals were included in the analysis. Out of the total, 126 participants were identified as patients with uterine fibroids. Upon accounting for covariables, the logistic regression analysis revealed a positive association between the highest tertiles of OCP compounds and ln-transformed OCP compounds and the history of uterine fibroids. The analysis of WQS and Qgcomp showed that a 25% increase in the mixture of OCPs was associated with a higher likelihood of having a history of uterine fibroids, with odds ratios (ORs) of 1.49 (95% CI: 1.02, 2.19) and 1.64 (95% CI: 1.15, 2.35), respectively. The primary factor behind this association was oxychlordane. In addition, the overall findings of BKMR demonstrated a consistent and increasing pattern, indicating a robust positive association between the amount of serum OCP compounds and the history of uterine fibroid.

Conclusion Our study conclusively established associations between OCPs and history of uterine fibroid. The simultaneous exposure to these chemicals is associated with an increased prevalence of uterine fibroid. Among these chemicals, oxychlordane has the most impact on the overall combined effect.

Keywords Uterine fibroid, Organochlorine pesticides, WQS, BKMR, Joint effect

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Introduction

Uterine fibroids, also called uterine smooth muscle tumors or leiomyomas, are the most prevalent noncancerous tumors in the uterus among women of reproductive age [1]. These tumors mostly comprise uterine smooth muscle cells and their growth is significantly affected by endocrine hormones, particularly estrogen and progesterone [2, 3]. The symptoms of uterine fibroids are clinically diverse, ranging from asymptomatic to causing serious complications such as excessive menstrual bleeding, chronic pelvic pain, enlarged uterus, urinary tract compression symptoms, and infertility [4, 5]. While the majority of uterine fibroids are noncancerous, it is important to acknowledge their significant effects on women's health and overall well-being. The development of uterine fibroids can be attributed to intricate genetic, molecular, and cellular processes. These processes include an excessive expression of estrogen receptors and progesterone receptors in the smooth muscle cells of the uterus, as well as an abnormal buildup of extracellular matrix components [6–8]. In addition, environmental factors, such as prolonged exposure to certain endocrine disruptors, have been implicated in the development of uterine fibroids [9].

Organochlorine insecticides (OCPs) are the earliest synthetic pesticides in human history, and their most typical products are dichlorodiphenyltrichloroethane (DDT) and hexachlorocyclohexane (HCH) [10], which were once widely used to control insect pests in crop forests and livestock because of their wide coverage and low acute toxicity [11]. In addition, OCPs are widely distributed in environmental media and can be transported and deposited over long distances through the atmosphere. Organochlorine pesticides accumulate in living organisms and are difficult to degrade due to their stable structure. Therefore, the disappearance of OCPs molecules accumulated in plants and animals is slow [11]. Through bio-enrichment and the food chain, pesticide residues in the environment can enter the human body and tend to interfere with the function of the human health [12]. These chemicals have been shown to have endocrine disrupting effects, or interfering with hormonal functions in the body [13]. Notably, OCPs have been linked to a variety of other health problems, including neurological disorders, immune system dysfunction, and certain types of cancer. For example, studies have shown that long-term exposure to such chemicals may increase the risk of Parkinson's disease and non-Hodgkin's lymphoma [14, 15]. These findings have prompted further research into the broader health effects of OCPs, in particular their prevalence in the environment and possible effects on hormonal systems. Recently, interest has increased regarding the effect of environmental pollutants on the development of uterine fibroids. Although in vivo/in vitro experimental studies on humans and animals have indicated the toxicity of persistent organic pollutants (POPs) on the female reproductive system, studies investigating the effects of exposure to OCPs on the uterine fibroids are limited [16–19]. A previous study reported that organochlorine pesticides were able to stimulate leiomyoma cell growth and induce an estrogenic response on the molecular level in leiomyoma cells [20]. Results from the Endometriosis: Natural History, Diagnosis and Outcomes (ENDO) Study indicated that higher geometric mean concentrations of several organochlorine pesticides from women with fibroids compared with women without fibroids [21].

In present study, we investigated whether there were associations between environmental exposure to OCPs and history uterine fibroids in the National Health and Nutrition Examination Survey (NHANES) database of American women. We used three multi-pollutant statistical methods: weighted quantile sum (WQS), quantile-based gcount (Qgcomp), and Bayesian kernel machine regression (BKMR). This was done since multicollinearity could limit the results of multivariate logistic regression analyses. In order to better understand the effects of endocrine disruptors on the reproductive health of women, this study's findings are highly relevant.

Materials and methods

Study design and population

This study is based on the NHANES database, a cross-sectional survey aimed at evaluating the health status of the population in the United States. The study was conducted by the Centers for Disease Control and Prevention [22, 23]. The survey was conducted every two years and took a representative sample from 15 cities (county) across the United States [24]. The representation of their samples is ensured through multi-stage complex samples, all surveys are approved by the National Center for Health Statistics Ethical Review Board, [23, 25]with written and informed consent provided by all participants, and all data is collected by trained medical personnel. In this study, publicly available data originating from three survey cycles (1999–2000, 2001–2002, 2003–2004) were downloaded and combined into a complete dataset, in which tests were conducted on the levels of OCP compounds. The independent variables were the levels of OCP compounds measured in the participants' serum. The dependent variable was the history diagnosis of uterine fibroids in the subjects. Subjects with full data on uterine fibroids, core characteristics, and OCP compounds were enrolled. Participants had to be women and at least 20 years old. The study did not include participants whose analytical factors were either absent or had

ambiguous information. Figure 1 presented the detailed selection process.

Measurements of serum organochlorine pesticides compounds

Starting from the 1999–2001 NHANES cycle, the researchers selected one-third of the participants for the measurement of organochlorine pesticides compounds levels. For analysis, serum samples were processed, preserved, and forwarded to the Centers for Disease Control and Prevention's Division of Environmental Health Laboratory Sciences, National Center for Environmental Health. Utilizing high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry (HRGS/ID-HRMS), these analytes in serum were quantified. 13C12-labeled internal standards are introduced into the serum samples during the analysis procedure. Following this, the intended analytes are obtained through the utilization of liquid–liquid extraction or C18 solid-phase extraction, which are both effective methods. Subsequently, a multi-column automated cleansing and enrichment procedure is carried out [26]. Hexachlorobenzene (HCB), p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), mirex, oxychlordane (OCD), trans-nonachlor (TNC), heptachlor epoxide (HCE), p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT), and beta-hexachlorocyclohexane (beta-HCH) were all detected in three survey cycles and were adjusted for lipid blood content. In the case of targeted OCP compounds that exhibited measured values falling below the limit of detection (LOD), the LOD divided by the square root of 2 was utilized to substitute these values. The official website (https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2003/DataFiles/L28OCP_C.htm) provides comprehensive information pertaining to laboratory procedures, quality control, and the analysis of the obtained results.

Ascertainment of uterine fibroids

In order to ascertain the history of uterine fibroids in the past of the participants, we employed self-reported medical information obtained through questionnaires. The participants of the NHANES questionnaire survey responded to the subsequent inquiry: 'Has a doctor or other health professional ever told you that you had uterine fibroids? (Uterine fibroids are noncancerous growths that can occur in different anatomical sites on or within the uterus.)'. A positive response to this question indicated a self-reported history of uterine fibroids.

Definition of covariates

Demographic variables (age, ethnicity, education level, marital status, and family poverty-income ratio (PIR)), anthropometric measurements (body mass index (BMI)), health-related behaviors (smoking status, alcohol usage), and women's reproductive health (ever been pregnant, oophorectomy, ever use of birth control pills, and menarche age) were extracted from the database according to the previously published articles [27, 28].

Two age groups of participants were identified: 20–39 years old and 40–59 years old. Four groups were created based on our stratification of ethnicity: Mexican American, non-Hispanic White, non-Hispanic Black, and other race. Three categories based on educational attainment were established: college or above, high school or equivalent, and lower than high school. Marital status fell into three categories (never married, widowed/divorced/separated, and married/cohabiting). The PIR, a continuous variable, serves as an indicator of socioeconomic status and is determined by the ratio of family income

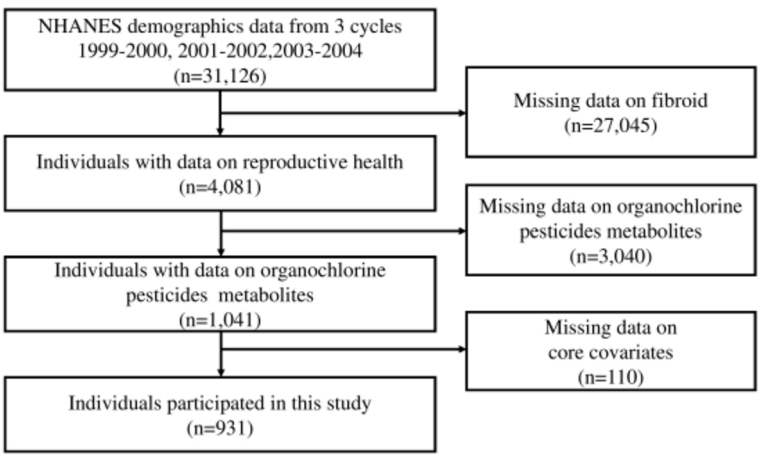

Fig. 1 Flowchart of the study participants' selection ($n = 931$)

to the poverty threshold. Individuals were classified according to their PIR level as high income (> 3.5), moderate income (> 1.3 to 3.5), or poor income (≤ 1.3). BMI was coded into obesity, overweight, and underweight or normal weight. People were considered non-smokers if they had smoked less than 100 cigarettes in the past. A person's drinking status was classified as either "alcohol users" or "non-alcohol users" according to their annual alcohol consumption. In terms of pregnancy history, ovarian surgery, and birth control pill usage, participants were categorized according to their responses to the questionnaire. Menarche age was also coded as categorical variable, including over 13 years,12–13 years, and less than 12 years.

Statistical analysis

Continuous data were shown with means and standard deviations (SD) for demographic descriptive information, whereas categorical variables were shown with frequencies and percentages. Notably, serum OCP compounds, due to their skewed distribution, were represented by median and interquartile ranges (IQR). When comparing categorical data, the Chi-square test was used; when comparing continuous variables, the T-test or Mann–Whitney U test was used, depending on the normality of the distribution. Additionally, we applied the Spearman correlation coefficient to evaluate correlations among different OCP compounds.

Logistic regression model

In our analysis, we used appropriate sampling weight during the data processing to account for complex survey design considering stratification, clustering, and oversampling [24]. Specifically, when combining data from the 1999–2000 and 2001–2002 cycles, we applied the 4-year weights (wtmec4yr) using the formula: weight = 2/n* wtmec4yr, where n is the number of cycles included. For cycles after 2001–2002, we used the 2-year weights (wtmec2yr) and applied the formula: weight = 2/n* wtmec2yr. After calculating the combined weights, we used the "svy_design" function to apply these weights, enabling weighted logistic regression analysis to ensure population-representative estimates and accurate variance estimation. Three logistic regression models were developed to compute the odds of uterine fibroids associated with individual OCP compounds, along with the corresponding confidence intervals (CIs). The OCP compounds were analyzed both as ln-transformed continuous variables and as categorical variables (the reference being the lowest quartile) for the calculation. Model 1 was not controlled for any covariates. Model 2 was adjusted for age and ethnicity. Model 3 was further adjusted for education level, marital status, BMI level, PIR, smoking status, alcohol usage, menarche age, pregnancy history, ovarian surgery, and birth control pill usage. In addition, to evaluate the validity of the results, we carried out sensitivity analyses. In the fully adjusted model, age and BMI were included as continuous variables (sensitivity i). We conducted additional unweighted logistic regression analysis to assess the relationship between each chemical and history of uterine fibroids (sensitivity ii).

Weighted quantile sum regression model

Weighted Quantile Sum (WQS) and regression modeling is a mixed-effects strategy commonly used to explore the relationship between multiple chemical exposures and outcomes [29]. Given that logistic regression cannot simultaneously consider the overall health effects of multiple chemicals, this study used WQS regression to assess the overall effects of eight OCP compounds on history of uterine fibroids. The model assesses the relationship between multiple exposures and outcomes by calculating a weighted index and calculating the relative contribution of each exposure [30]. The weight values for each exposure range from 0 to 1, and the sum of the weights is 1 [31]. In this study, the original data were randomly divided into 40% of the training set and the remaining 60% of the validation set, and a significance level ($p < 0.05$) was set to test for the significance of each bootstrap weight. The WQS model was also adjusted for the above variables.

Quantile g-computation model

In addition to the WQS model, there is a new model available for hybrid exposures called Quantile g-computation (Qgcomp) [32]. Qgcomp can be utilized to quantitatively analyze the alteration in the prevalence of uterine fibroids when there is a simultaneous increase of one quantile in the levels of the eight serum OCP compounds. The impact of OCP compounds on the history of uterine fibroids can be examined through the associated weights, which also facilitate the identification of significant elements within the mixture. The distinction between WQS and Qgcomp lies in the fact that the latter does not impose a restriction on the association between all OCP compounds and the history of uterine fibroids to be in the same direction [32]. The variables adjusted in the Qgcomp model was the same as the WQS model.

Bayesian kernel machine regression model

The Bayesian Kernel Machine Regression (BKMR) model is a sophisticated statistical method specifically designed to analyze the health effects of mixtures of environmental exposures. It was developed to tackle the inherent complexities of studying multiple pollutant exposures. BKMR enables researchers to explore the potential

impact of a combination of different exposures, such as chemical substances, on health outcomes [33]. An important characteristic of this system is its capacity to handle non-linear associations and interactions between many exposures [33]. BKMR, unlike conventional regression models, employs a kernel machine framework to address the issue of multicollinearity in environmental data. This methodology considers the combined impacts of exposures, enabling a more adaptable modeling of the exposure–response association. Crucially, BKMR has the ability to evaluate the impacts of individual and combined exposures, providing valuable information on which elements of the mixture are the most detrimental or advantageous. Consequently, our analysis incorporated the following components: (1) In the univariate model, we individually examined the connection between each type of OCP compounds and history of uterine fibroids, assuming the other OCP compounds remained constant at their median values; (2) To evaluate the combined influence, we compared the predicted impact of all exposure factors at a specific percentile to their effects when each is at its 50th percentile. Moreover, posterior inclusion probability (PIP) was calculated for the identification of the relatively important components in the mixture. Notably, a priori parameters (50,000 iterations) are considered to ensure convergence, and the adjusted cofounders were consistent with that in WQS regression.

All statistical analyses above were performed based on R software, and $P<0.05$ was considered statistically significant. For the WQS regression model, Qgcomp regression model and BKMR model, the "gWQS", "qgcomp"and "bkmr" packages were used respectively.

Results

Study participants' characteristics

Ultimately, a comprehensive examination encompassed a total of 931 participants, consisting of 126 persons diagnosed with uterine fibroids and 805 individuals did not. Table 1 details the characteristics of both groups from the NHANES database. Predominantly, participants were 20–39 years old (62.73%) and Non-Hispanic White (47.91%). Educational attainment was high, with 55.42% having a college education or higher, and 37.92% possessing a high school diploma or equivalent. A significant majority of the individuals (64.55%) were married or in a partnership. Overweight or obesity was prevalent in 71.00% of the participants. Income levels varied, with 29.32% from low-income, 36.09% from middle-income, and 34.59% from high-income families. When comparing the uterine fibroid group with the control group, several notable differences were observed. The uterine fibroid group was older on average, with a higher proportion of individuals in the 40–59 age range compared to controls. Ethnically, the uterine fibroid group had a significantly higher percentage of non-Hispanic Black participants ($p<0.05$), whereas the control group had a greater proportion of non-Hispanic White participants. The uterine fibroid group also exhibited higher levels of educational attainment, with a greater proportion having completed college or higher education compared to controls. Furthermore, individuals in the uterine fibroid group were more likely to be married or in a partnership, have higher rates of overweight or obesity, and come from higher-income families. Additionally, a greater proportion of individuals with uterine fibroids had undergone oophorectomy and used birth control pills compared to the control group. Furthermore, Table 2 displays the variance in OCP compounds levels between individuals with uterine fibroids and those in the control group, showing that the majority of these OCP metabolite contaminants surpassed the minimum detection threshold in the serum samples of the participants.

The matrix of the eight OCP compounds is shown in Fig. 2 after Spearman's rank correlation analyses were used to determine the correlation coefficients. The majority of compounds exhibit positive correlations, with values ranging from 0.22 to 0.88. The highest correlation ($r=0.88$, $P<0.05$) was seen between OCD and TNC. p,p'-DDH and beta-HCH, as well as p,p'-DDT and p,p'-DDE, had correlation coefficients of 0.72 and 0.59, respectively. Therefore, it is needed to construct a comprehensive model that examines the impact of a mixture of OCPs on the development of uterine fibroids.

Association between each kind of OCP compounds and history of uterine fibroids

To evaluate the association between each kind of OCP compounds and **history of uterine fibroids** among U.S. women, the survey-weighted logistic regression was employed. Table 3 provided a summary of the findings. The model 1 revealed that history of uterine fibroids were positively associated with ln-transformed HCB, p,p'-DDE, OCD, TNC, and beta-HCH. Only Ln-transformed OCD was positively associated with history of uterine fibroids after controlling for age and ethnicity. After controlling for all variables, the ORs of ln-transformed HCB and OCD with the prevalence of uterine fibroids were (OR: 1.53; 95% CI: 1.05, 2.23) and (OR: 1.56; 95% CI: 1.05, 2.32) respectively. When further dividing the corresponding OCP compounds into quantile groups and taking the lowest quantile as the reference, the fully-adjusted model showed that the highest quantile of HCB (OR: 1.97; 95% CI: 1.14, 3.40, p for trend=0.025) and OCD (OR: 6.00; 95% CI: 2.47, 14.59, p for trend=0.001) were positively associated with the history of uterine fibroids. The p for trend of HCB and OCD was less than 0.05, indicating that a linear trend may exist.

Table 1 Characteristics of the fibroid and non-fibroid participants in the NHANES database

Characteristics	Participants (*n* = 931)	Without fibroid (*n* = 805)	Fibroid (*n* = 126)	*P*-value
Year, n (%)				
1999–2000	178 (19.2)	152 (18.9)	26 (20.6)	0.14
2001–2002	400 (42.7)	356 (44.2)	44 (34.9)	
2003–2004	353 (38.0)	297 (36.9)	56 (44.5)	
Age, n (%)				**< 0.001**
20–39	584 (62.73)	547 (67.95)	37 (29.37)	
40–59	347 (37.27)	258 (32.05)	89 (70.63)	
Ethnicity, n (%)				**< 0.001**
Mexican American	219 (23.52)	203 (25.22)	16 (12.70)	
Non-Hispanic Black	177 (19.01)	132 (16.40)	45 (35.71)	
Non-Hispanic White	446 (47.91)	392 (48.70)	54 (42.86)	
Other race	89 (9.56)	78 (9.69)	11 (8.73)	
Education, n (%)				**0.044**
Lower than high school	62 (6.66)	60 (7.45)	2 (1.59)	
High school or equivalent	353 (37.92)	305 (37.89)	48 (38.10)	
College or above	516 (55.42)	440 (54.66)	76 (60.32)	
Marital status, n (%)				**0.043**
Married/cohabiting	601 (64.55)	515 (63.98)	86 (68.25)	
Widowed/divorced/separated	139 (14.93)	115 (14.29)	24 (19.05)	
Never married	191 (20.52)	175 (21.74)	16 (12.70)	
BMI, n (%)				0.066
Underweight or normal	270 (29.00)	244 (30.31)	26 (20.63)	
Overweight	231 (24.81)	199 (24.72)	32 (25.40)	
Obesity	430 (46.19)	362 (44.97)	68 (53.97)	
PIR, n (%)				**< 0.001**
< 1.3	273 (29.32)	252 (31.30)	21 (16.67)	
1 −3.5	336 (36.09)	295 (36.65)	41 (32.54)	
> 3.5	322 (34.59)	258 (32.05)	64 (50.79)	
Smoking status, n (%)				0.610
No	533 (57.25)	464 (57.64)	69 (54.76)	
Yes	398 (42.75)	341 (42.36)	57 (45.24)	
Alcohol usage, n (%)				0.876
No	141 (15.15)	123 (15.28)	18 (14.29)	
Yes	790 (84.85)	682 (84.72)	108 (85.71)	
Ever been pregnant, n (%)				0.079
No	141 (15.15)	129 (16.02)	12 (9.52)	
Yes	790 (84.85)	676 (83.98)	114 (90.48)	
Oophorectomy, n (%)				**< 0.001**
No	858 (92.16)	766 (95.16)	92 (73.02)	
Yes	73 (7.84)	39 (4.84)	34 (26.98)	
Ever use of birth control pills, n (%)				**0.011**
No	228 (24.49)	209 (25.96)	19 (15.08)	
Yes	703 (75.51)	596 (74.04)	107 (84.92)	
Menarche age, n (%)				0.148
< = 11	232 (24.92)	192 (23.85)	40 (31.75)	
12–13	481 (51.66)	420 (52.17)	61 (48.41)	
> = 14	218 (23.42)	193 (23.98)	25 (19.84)	

The bold values means statistical significance

NHANES the National Health and Nutrition Examination Survey, *BMI* body mass index, *PIR* family poverty-income ratio

Table 2 Concentration of serum OCPs in study population with and without fibroid in NHANES database

OCP (ng/g)	≥LOD (%)	Total		Non-fibroid		Fibroid	
		Median	IQR	Median	IQR	Median	IQR
Hexachlorobenzene	100	0.066	0.063–0.129	0.064	0.063–0.121	0.084	0.063–0.176
Dichlorodiphenyldichloroethylene	99.9	1.319	0.677–3.191	1.264	0.640–2.964	2.100	1.049–4.343
Mirex	100	0.021	0.012–0.027	0.021	0.012–0.026	0.023	0.021–0.032
Oxychlordane	100	0.051	0.025–0.091	0.048	0.023–0.084	0.082	0.055–0.134
Trans-nonachlor	100	0.078	0.041–0.141	0.073	0.038–0.130	0.116	0.072–0.182
Heptachlor epoxide	100	0.024	0.021–0.042	0.023	0.021–0.040	0.031	0.021–0.054
Dichlorodiphenyltrichloroethane	100	0.035	0.031–0.050	0.035	0.031–0.049	0.035	0.034–0.053
Beta-hexachlorocyclohexane	100	0.036	0.021–0.082	0.034	0.021–0.079	0.057	0.031–0.099

OCPs Organochlorine pesticides, *NHANES* National Health and Nutrition Examination Survey, *LOD* Limits of detection, *IQR* Interquartile range

OCP concentrations have been adjusted for lipid blood content

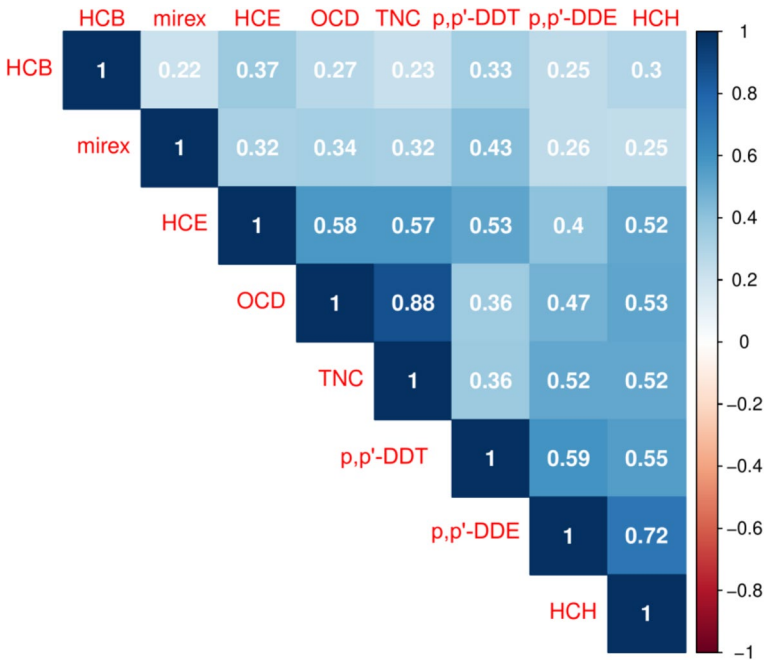

Fig. 2 Spearman association matrix of eight organochlorine pesticides compounds in NHANES. Abbreviation: HCB: hexachlorobenzene. p,p'-DDE: dichlorodiphenyldichloroethylene. OCD: oxychlordane. TNC: trans-nonachlor. HCE: heptachlor epoxide. p,p'-DDT: dichlorodiphenyltrichloroethane. HCH: Beta-hexachlorocyclohexane

While this indicates the presence of a trend, it does not necessarily imply that the association is strictly linear, and other forms of association (e.g., non-linear) may also be possible. The results of the sensitivity analyses showed our results were stable and were presented in Table 4.

Associations between co-exposure to OCP compounds and history of uterine fibroids

Using WQS regression, one unit increase in cumulative OCP metabolite exposure was marginally associated with history of uterine fibroids after controlling for the confounding factors (OR = 1.49; 95%CI: 1.02, 2.19). The result of weights distribution revealed that OCD (51.0%) made the largest contributor to the WQS index, followed by beta-HCH (32.5%) and mirex (9.9%), showing that OCD may dominate in the serum OCP compounds (Fig. 3). In the Qgcomp, the results showed that a quartile increase in OCP mixture was significantly associated with increased likelihood of history of uterine fibroids (OR: 1.64, 95% CI:1.15, 2.35). Four serum OCP

Table 3 Odds ratios for the association between organochlorine pesticides exposure and fibroid in three models

	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
HCB			
Ln	**1.50(1.07,2.12)**	1.37(0.95, 2.00)	**1.53(1.05,2.23)**
Q1	Reference	Reference	Reference
Q2	0.62(0.22,1.74)	0.54(0.21, 1.44)	0.60(0.21, 1.74)
Q3	1.29(0.67,2.49)	1.07(0.57, 1.99)	1.11(0.55, 2.23)
Q4	**1.89(1.11,3.20)**	1.68(0.98, 2.88)	**1.97(1.14, 3.40)**
P for trend	**0.018**	0.062	**0.025**
p,p'-DDE			
Ln	**1.43(1.16,1.76)**	1.18(0.86, 1.62)	1.21(0.85, 1.73)
Q1	Reference	Reference	Reference
Q2	1.57(0.79,3.09)	1.12(0.56, 2.25)	1.03(0.49, 2.14)
Q3	1.82(0.78,4.25)	1.11(0.41, 2.96)	0.92(0.34, 2.51)
Q4	**3.49(1.71,7.13)**	1.67(0.73, 3.79)	1.60(0.63, 4.09)
P for trend	**0.003**	0.313	0.461
Mirex			
Ln	1.11(0.85,1.46)	1.00(0.74,1.37)	1.01(0.74,1.37)
Q1	Reference	Reference	Reference
Q2	0.90(0.41,1.97)	0.79(0.36,1.74)	0.76(0.32,1.81)
Q3	1.94(0.91,4.13)	1.55(0.74,3.24)	1.76(0.77,4.03)
Q4	1.83(0.90,3.70)	1.34(0.64,2.81)	1.50(0.61,3.71)
P for trend	**0.037**	0.225	0.179
OCD			
Ln	**2.34(1.65,3.31)**	**1.70(1.16,2.48)**	**1.56(1.05,2.32)**
Q1	Reference	Reference	Reference
Q2	**3.19(1.15, 8.87)**	**2.69(0.97, 7.46)**	2.41(0.88, 6.58)
Q3	**6.37(3.63,11.16)**	4.16(2.24, 7.72)	3.53(2.00, 6.23)
Q4	**12.54(5.58,28.17)**	6.86(2.80,16.82)	**6.00(2.47,14.59)**
P for trend	**< 0.001**	**< 0.001**	**0.001**
TNC			
Ln	**1.78(1.27,2.49)**	1.29(0.89,1.87)	1.18(0.78,1.76)
Q1	Reference	Reference	Reference
Q2	**3.63(1.71, 7.71)**	2.53(1.14,5.57)	1.95(0.84,4.51)
Q3	**4.42(2.03, 9.61)**	2.41(1.02,5.74)	2.08(0.84,5.13)
Q4	**6.38(2.48,16.39)**	3.15(1.15,8.61)	2.43(0.83,7.06)
P for trend	**0.001**	0.100	0.19
HCE			
Ln	1.20(0.83,1.74)	0.96(0.66,1.40)	0.88(0.58,1.33)
Q1	Reference	Reference	Reference
Q2	**0.09(0.01,0.73)**	0.08(0.01,0.66)	0.09(0.01,0.83)
Q3	1.62(0.86,3.05)	1.37(0.75,2.51)	1.55(0.81,2.97)
Q4	1.58(0.81,3.08)	1.10(0.54,2.25)	0.96(0.44,2.09)
P for trend	0.100	0.537	0.665
p,p'-DDT			
Ln	1.17(0.91,1.50)	1.04(0.72, 1.51)	1.13(0.77,1.66)
Q1	Reference	Reference	Reference
Q2	1.16(0.54,2.48)	1.05(0.48, 2.28)	1.06(0.47,2.39)
Q3	1.45(0.67,3.11)	1.26(0.58, 2.73)	1.54(0.67,3.51)
Q4	1.83(0.85,3.98)	1.40(0.59, 3.32)	1.60(0.67,3.79)
P for trend	0.101	0.394	0.196
HCH			
Ln	**1.38(1.16,1.64)**	1.15(0.86, 1.54)	1.14(0.84, 1.56)
Q1	Reference	Reference	Reference
Q2	0.89(0.36,2.22)	0.76(0.29, 1.99)	0.82(0.32, 2.14)
Q3	**3.15(1.58,6.29)**	1.99(0.82, 4.80)	1.55(0.67, 3.59)
Q4	**3.21(1.65,6.24)**	1.95(0.75, 5.07)	1.61(0.63, 4.11)
P for trend	**< 0.001**	0.094	0.221

The sample size for the logistic regression model was 931(Without fibroid ($n = 805$), With fibroid ($n = 126$))

Ln means ln-transformed organochlorine pesticide

Model 1 was not adjusted

Model 2 was adjusted for age, ethnicity

Model 3 was further adjusted for education level, marital status, BMI level, and PIR smoking status, alcohol usage, menarche age, ever been pregnant, oophorectomy, and ever taken birth control pills

The bold values mean statistical significance

Statistical tests for linear trends were conducted by modeling median values of quartiles as continous variable

OR odds ratio, *CI* confidence interval, *HCB* hexachlorobenzene, *p,p'-DDE* dichlorodiphenyldichloroethylene, *OCD* oxychlordane, *TNC* trans-nonachlor, *HCE* heptachlor epoxide, *p,p'-DDT* dichlorodiphenyltrichloroethane, *HCH* Beta-hexachlorocyclohexane

compounds were positively associated with history of uterine fibroids, whereas four serum OCP compounds were adversely associated with history of uterine fibroids (Fig. 4). Among the positive direction, OCD (64.9%) contributed the most to the association with uterine fibroid, followed by mirex (14.3%), HCB (13.4%) and p,p-DDE (7.4%). Among the negative direction, TNC (45.7%) had the largest contribution, followed by beta-HCH (22.8%), HCE (17.8%) and p,p-DDT (13.7%). Moreover, the following results are based on the BKMR analysis. When OCP concentrations were fixed at the median and substantial positive trends were observed for OCD, Fig. 5A presented the univariate exposure–response function data. The joint effect of OCPs mixture on history of uterine fibroids can be seen in Fig. 5B, where the total effect was consistent upward, demonstrating a robust positive connection between serum OCP compounds and history of uterine fibroids. Table 5 shows the posterior inclusion probabilities (PIPs) of all OCP compounds with OCD having the highest PIP (0.922). The summarized ORs in joint-effect models were presented in Table 6.

Discussion

In this U.S. NHANES investigation, increased serum OCP compounds were associated with history of uterine fibroids in women adults. And such association was more pronounced in OCD. There have been no epidemiologic

Table 4 Sensitivity analysis for the association between organochlorine pesticides exposure and fibroid

	Ln-transformed	Q1 OR (95%CI)	Q2 OR (95%CI)	Q3 OR (95%CI)	Q4 OR (95%CI)	*P* for trend
Sensitivity analysis i						
HCB	1.48(1.01,2.18)	Reference	0.61(0.23,1.62)	1.11(0.56,2.21)	**1.90(1.10,3.28)**	0.032
p,p′-DDE	1.03(0.71,1.49)	Reference	0.91(0.43,1.93)	0.74(0.27,2.02)	0.99(0.36,2.68)	0.858
Mirex	0.93(0.67, 1.29)	Reference	0.63(0.26,1.57)	1.45(0.59,3.53)	1.21(0.47,3.08)	0.361
OCD	1.56(1.04,2.33)	Reference	2.22(0.83,5.93)	**2.84(1.51,5.33)**	**4.03(1.65,9.81)**	0.013
TNC	0.92(0.58,1.47)	Reference	1.52(0.63,3.66)	1.39(0.50,3.84)	1.43(0.44,4.60)	0.793
HCE	0.69(0.44,1.08)	Reference	**0.11(0.01,0.97)**	1.26(0.63,2.53)	0.66(0.29,1.49)	0.527
p,p′-DDT	0.96(0.63,1.45)	Reference	0.90(0.41,2.01)	1.26(0.52,3.07)	1.16(0.46,2.91)	0.598
HCH	0.95(0.65,1.38)	Reference	0.73(0.27,1.92)	1.12(0.46,2.75)	1.04(0.37,2.94)	0.811
Sensitivity analysis ii						
HCB	1.42(0.95,2.08)	Reference	0.72(0.25,1.75)	1.15(0.66,1.98)	**1.72(1.01,2.96)**	0.062
p,p′-DDE	1.13(0.89,1.43)	Reference	1.37(0.69,2.80)	1.26(0.62,2.62)	1.57(0.73,3.44)	0.413
Mirex	0.96(0.72,1.25)	Reference	0.84(0.46,1.54)	1.42(0.68,2.93)	1.56(0.86,2.87)	0.170
OCD	**1.47(1.08,2.03)**	Reference	**2.71(1.12, 7.43)**	**4.65(2.02,12.43)**	**4.70(1.98,12.88)**	**< 0.001**
TNC	1.23(0.92,1.66)	Reference	**3.12(1.38,7.90)**	**3.39(1.51,8.56)**	**3.02(1.30,7.82)**	**0.047**
HCE	1.00(0.72,1.36)	Reference	0.21(0.01,1.08)	1.63(0.96,2.76)	1.05(0.59,1.83)	0.073
p,p′-DDT	1.03(0.76,1.37)	Reference	1.03(0.58,1.86)	1.40(0.70,2.77)	1.09(0.58,2.08)	0.252
HCH	1.06(0.82,1.35)	Reference	0.86(0.38,1.83)	1.57(0.86,2.88)	1.09(0.55,2.18)	0.093

Sensitivity analysis i: Age and BMI was treated as a continuous variable

Sensitivity analysis ii: The results of unweighted multivariate logistic regression

Ln means ln-transformed organochlorine pesticide

The model was adjusted for age, ethnicity, education level, marital status, BMI level, and PIR smoking status,

alcohol usage, menarche age, ever been pregnant, oophorectomy, and ever taken birth control pills

The bold values mean statistical significance

Statistical tests for linear trends were conducted by modeling median values of quartiles as continous variable

OR odds ratio, *CI* confidence interval, *HCB* hexachlorobenzene, *p,p′-DDE* dichlorodiphenyldichloroethylene, *OCD* oxychlordane, *TNC* trans-nonachlor, *HCE* heptachlor epoxide, *p,p′-DDT* dichlorodiphenyltrichloroethane, *HCH* Beta-hexachlorocyclohexane

studies to examined OCPs exposure and history of uterine fibroids using NHANES database prior to this study. In addition, our investigation may provide valuable insights into the association between OCP exposures and female reproductive diseases.

OCPs are POPs [34], and their use in crop production has been banned due to their toxicity to both humans and animals [35]. However, these substances are more stable in environmental media, have a half-life of several years, are resistant to degradation, and can persist in the environment, so they can still be detected in large quantities in the environment and the human body [36, 37]. In addition, OCPs can produce many toxic effects on the body, including immunotoxicity, reproductive developmental toxicity and carcinogenicity [38–40].

Overall, the statistical models in our study are all reinforcing the same conclusion, that OCP compounds are associated with an increased likelihood of history of uterine fibroids. However, there are some differences in their approaches. Logistic regression focuses on the effect of individual OCP compounds on history of uterine fibroids. Since there may be interactions between different OCP compounds, using mixed exposure models like WQS, Qgcomp, and BKMR is necessary to capture these complex associations. The WQS model identifies the optimal weights for each OCP metabolite, allowing for a composite measure of exposure to multiple OCPs. This helps assess the overall impact of OCP exposure, accounting for varying contributions of individual compounds. Qgcomp, on the other hand, is used to estimate the joint effect of multiple exposures by combining them into a single index, while also accounting for potential associations among the compounds. Finally, BKMR allows us to explore the non-linear, joint effects of OCP compounds and their interactions, providing a flexible way to model complex relationships in the data.

In order to explore the potential association between OCPs and history of uterine fibroids, the following points should be addressed: The association between OCPs and endometriosis offers significant insights. Research has found that the occurrence of substances such beta-HCH and mirex in samples of serum is linked

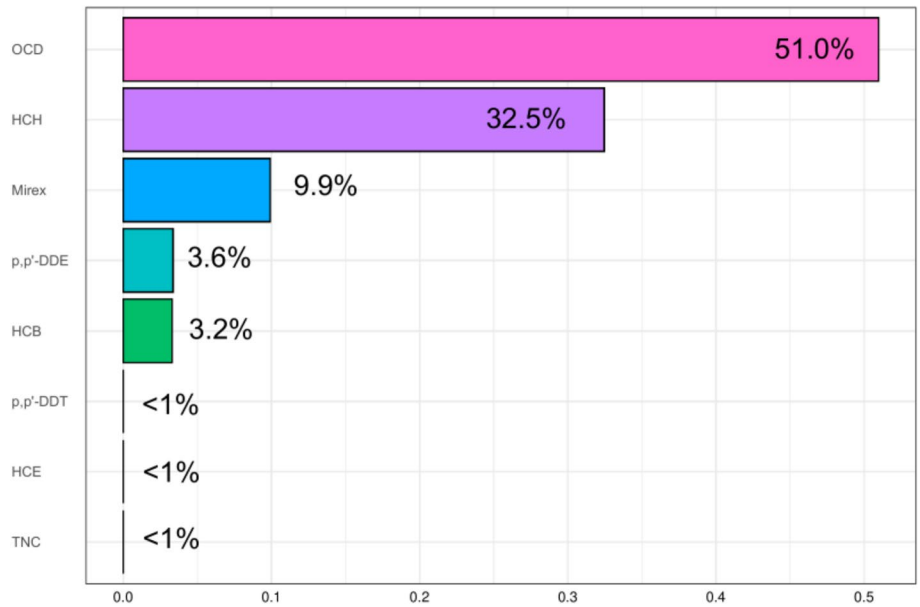

Fig. 3 The weights of each OCP compounds in positive WQS model regression index for fibroid. Models were adjusted for age, ethnicity, education level, marital status, BMI level, and PIR smoking status, alcohol usage, menarche age, ever been pregnant, oophorectomy, and ever taken birth control pills

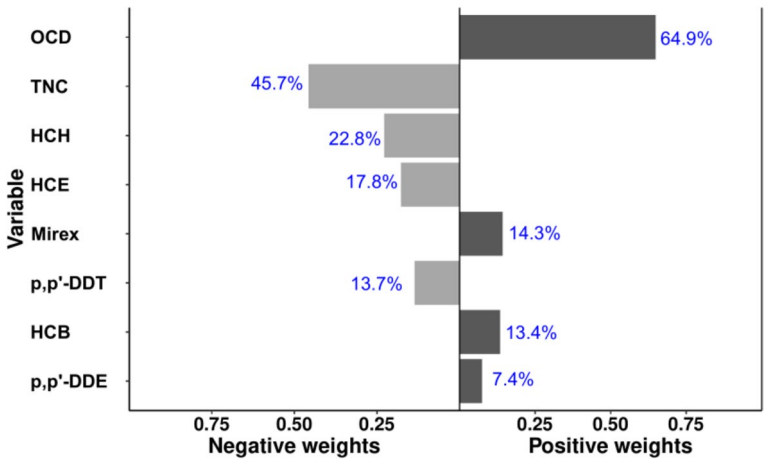

Fig. 4 Weights corresponding to the proportion of the positive or negative partial effect per serum OCP compounds in the quantile g-computation model. The Qgcomp was adjusted for age, ethnicity, education level, marital status, BMI level, and PIR smoking status, alcohol usage, menarche age, ever been pregnant, oophorectomy, and ever taken birth control pills

to an increased risk of endometriosis [41]. The association between these pesticides and hormone balance and uterine health may be attributed to their estrogenic properties [42]. Given the substantial association between endometriosis and hormonal fluctuations, it is reasonable to infer that OCPs could potentially impact hormone-related uterine fibroids [43]. Additionally, Qi et al. conducted a study specifically examining the presence of OCPs residues in the bodies of mothers and the potential impact on newborns. According to this study, exposure to these pollutants may affect reproductive health in women [44]. Researchers discovered in a cellular experiment that the impact of organochlorine pesticides on the growth of leiomyosarcomas is mainly due to their capacity to imitate estrogen. These compounds have the ability to disrupt normal hormone communication by specifically binding to estrogen receptors, which in turn affects the overall balance of hormone levels in

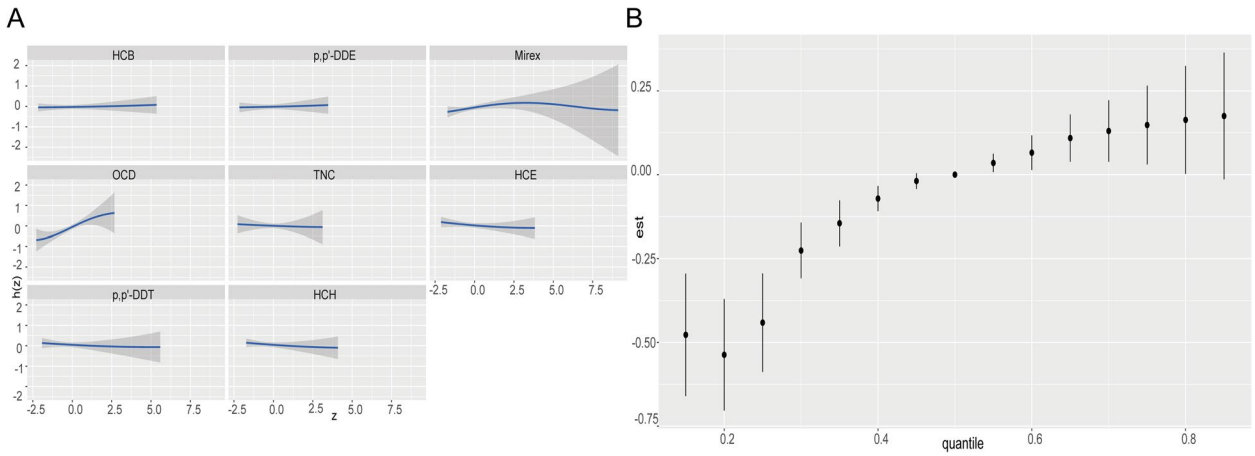

Fig. 5 The effects of the OCP mixtures on fibroid estimated by Bayesian kernel machine regression. The model was adjusted for age, ethnicity, education level, marital status, BMI level, and PIR smoking status, alcohol usage, menarche age, ever been pregnant, oophorectomy, and ever taken birth control pills. **A** Univariate exposure–response relationships; **B** Overall effect of the OCP mixtures

Table 5 Posterior inclusion probability for each of the organochlorine pesticides metabolites

Organochlorine pesticides metabolites	PIP
Hexachlorobenzene	0.028
Dichlorodiphenyldichloroethylene	0.026
Mirex	0.258
Oxychlordane	0.922
Trans-nonachlor	0.338
Heptachlor epoxide	0.129
Dichlorodiphenyltrichloroethane	0.079
Beta-hexachlorocyclohexane	0.128

The sample size was 931(Without fibroid ($n=805$), With fibroid ($n=126$))

PIP Posterior inclusion probability

Table 6 The summarized ORs in joint-effect models

Model	OR	Lower CI	Upper CI
WQS	1.49	1.02	2.19
Qgcomp	1.64	1.15	2.35

OR odds ratio, *CI* confidence interval

the body [20]. This endocrine disruption may lead to estrogen-sensitive tissues, such as abnormal proliferation of the uterine myometrium, which in turn promotes the formation and growth of fibroids. At the same time, the accumulation of chemicals in the body may exacerbate such effects, especially in the case of prolonged exposure [20]. Consequently, OCP residues may thereby promote reproductive diseases such uterine fibroids in addition to reducing fertility in women. Interestingly, although our study is consistent with findings from studies of endocrine-disrupting chemicals, where similar compounds have been shown to influence estrogen-sensitive tissues and increase the prevalence of reproductive health issues, the findings of other studies, such as that of Upson et al., where OCP plasma concentrations were inversely associated with uterine fibroid prevalence, highlight the complexity of this relationship and the need for further research to clarify these discrepancies [45].

Notably, we observed differential associations between specific OCP metabolites and the history of uterine fibroids, with oxychlordane (OCD) showing a positive association, while others, such as mirex, did not. This variation can be attributed to several factors, particularly the distinct metabolic processes and exposure sources associated with different OCPs. A single pesticide is metabolized in the human body into multiple metabolites, each reflecting different aspects of exposure. These metabolites may vary in their biological activity, persistence, and ability to bind to estrogen receptors, which can influence their effect on human health. For example, some metabolites may be quickly metabolized and eliminated from the body, resulting in lower concentrations in tissues, while others are more persistent and accumulate at higher concentrations. Given that OCP has multiple metabolites with distinct characteristics, mixed exposure models are better suited for capturing the combined effects of these compounds. These models provide a clearer understanding of how various OCP metabolites, both individually and collectively, contribute to the history of uterine fibroids.

When comparing OCP exposure levels across different regions, we found notable variations. For instance, in this study, the detected DDE level was 1.319 (0.677–3.191) ng/g, while the DDT level was 0.035 (0.031–0.050) ng/g.

These values are considerably lower compared to those reported in a cross-sectional study from France, where the DDE level reached 30.18 (57.76–126.1) ng/g and the DDT level was 1.57 (< LOQ–2.36) ng/g [46]. Similarly, a population-based study conducted in Tehran found that the median DDE level was 15.48 ng/g, with a median DDT level of 15.62 ng/g [47]. These differences in exposure levels could be attributed to several factors, including regional differences in environmental contamination, dietary habits, agricultural practices, and historical use of OCPs. In addition, differences in study populations could be considered. For example, the NHANES study focuses on US adults, while the French study included both men and women and the Tehran study focused on males. Sampling periods also varied, which could influence the observed exposure levels. Acknowledging these limitations, future studies should aim to harmonize methodological designs, clarify compound definitions, and consider broader and more diverse populations to provide a clearer context for comparison and understanding of the complex associations.

The cross-sectional study we conducted had certain limitations to be mentioned. Firstly, the study relied on self-reported diagnosis of uterine fibroids, which may introduce reporting bias or inaccuracy. However, the NHANES dataset is a well-established and widely used resource in epidemiological research, with rigorous protocols for data collection and quality assurance. Prior studies utilizing NHANES data have demonstrated its reliability for examining associations between exposures and health outcomes, providing confidence in the validity of the findings despite the reliance on self-reported data [27, 48]. Secondly, the fact that NHANES is a cross-sectional survey poses challenges in establishing a causal relationship between organochlorine pesticide exposure and uterine fibroids. Notably, we acknowledge that OCPs have a long half-life, which reflects long-term exposure rather than acute or point exposure. Furthermore, it is well-established that the presence of uterine fibroids does not significantly impact the metabolism or concentration of OCPs, as these pesticides primarily represent accumulated exposure over an extended period of time. While the cross-sectional nature of our study limits our ability to establish a clear temporal relationship between exposure and outcome, it is important to note that the cumulative effects of long-term exposure to OCPs could influence health outcomes over time. Future longitudinal studies would be better suited to address the timing and potential delayed effects of such exposures on the development of uterine fibroids. Thirdly, while we included commonly recognized confounders, there may be other relevant factors, such as dietary intake, occupational exposure, or genetic predisposition, that were unavailable in the NHANES dataset. The exclusion of these factors may introduce residual confounding, which could potentially impact the study's findings. Future research incorporating a broader range of covariates, or longitudinal data, would be better positioned to address these potential confounding factors and provide a more nuanced understanding of the relationship between OCP exposure and uterine fibroids. Fourth, while we used logistic regression models with NHANES sampling weights to assess associations, these weights were not applied in the mixed exposure models (WQS, Qgcomp, and BKMR), as they are not compatible with these methods. Several advantages of this study were also presented as follows. Firstly, we applied multiple statistical models such as WQS, Qgcomp, and BKMR to our analyses, providing insights into nonlinear associations and interactions between multiple exposures in environmental health studies. Secondly, in order to improve the robustness, sensitivity analyses were performed, and the results suggested the statistical stability of this cross-sectional study.

Conclusion

In conclusion, this study observed an association between serum OCPs levels and history of uterine fibroids among US female adults. The primary factor behind this association was OCD. This discovery provides a fresh perspective for clinical research. However, due to the cross-sectional character of our study, we are unable to establish their causality. Therefore, additional cohort studies are necessary in the future to validate the reported results.

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Authors' contributions

Yue Chen: Conceptualization, Methodology, Data curation, Software, Formal analysis, Visualization, Writing – original draft, Writing –review & editing. Xianwei Guo: Conceptualization, Methodology, Data curation, Software, Formal analysis, Visualization, Writing – original draft, Writing –review & editing. Junle Wu: Data curation, Methodology, Writing – review & editing. Ruiwen Weng: Data curation, Methodology, Writing – review & editing. Xiuping Wang: Data curation, Methodology, Writing – review & editing. Yi Liu: Data curation, Methodology, Writing – review & editing. Xiaoli Wang: Formal analysis, Visualization, Writing – revised draft, Writing –revision & editing. Hengwei Liu: Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing, Funding acquisition.

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Data availability
Data will be made available on request.

Declarations

Ethics approval and consent to participate
This study was conducted according to the guideline laid down in the Declaration of Helsinki, and all procedures involving study participants were approved by the Institutional Review Board of the National Center for Health Statistics (NCHS). Ethical review and approval were waived for this study as it solely used publicly available data for research and publication. Informed consent was obtained from all subjects involved in the NHANES.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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