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RESEARCH ARTICLE

Exploratory analysis of the association between pyrethroid exposure and rheumatoid arthritis among US adults: 2007–2014 data analysis from the National Health and Nutrition Examination Survey (NHANES)

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Abstract

Previous studies indicate that pesticide use may play an important role in the occurrence and development of rheumatoid arthritis (RA); however, little is known about the effect of specific pesticides on RA. The objective of this study was to evaluate whether pyrethroid exposure was linked to RA in adults. Data were originated from the 2007–2014 National Health and Nutrition Examination Survey (NHANES). The levels of pyrethroid exposure were assessed by 3-phenoxybenzoic acid (3-PBA) concentrations in urine samples. We built multivariate logistic regression models to assess associations between pyrethroid exposure and RA among US adults. A restricted cubic spline plot (three knots) was applied to test whether there was a nonlinear relationship between exposure to pyrethroid pesticides and the prevalence of RA. Finally, 4384 subjects were included in our analysis with 278 RA patients. In crude model, higher level of 3-PBA (creatinine-adjusted) was positively associated with RA (OR: 1.51, 95% CI: 1.07, 2.15). After adjustment for sex, race/ethnicity, education, body mass index, family poverty income, level of education, marital status, smoking status, alcohol usage, physical activity, hypertension, and urinary creatinine, the highest (vs lowest) quartile of 3-PBA was associated with an increased prevalence of RA (OR: 1.23, 95% CI: 0.86, 1.79). Significantly positive associations between 3-PBA concentration and RA were observed in the population aged between 40 and 59 years and with lower level of education. The restricted cubic spline plot presented an increase in trend and indicated that pyrethroid exposure was linearly associated with occurrence of RA (p for nonlinearity = 0.728). In conclusion, our study indicated that pyrethroid pesticide exposure was associated with an increased risk of RA. Higher levels of pyrethroid exposure were linearly associated with increased prevalence of RA in adults. Certainly, our findings are in great need of further corroboration by prospective studies with strict design.

Keywords Pyrethroid · Rheumatoid arthritis · NHANES

Introduction

Rheumatoid arthritis (RA) is a common systemic autoimmune disease characterized by systemic inflammation, persistent synovitis, and progressive joint destruction (Sparks 2019). Globally, approximately 1% of the population are affected by RA (Cross et al. 2014). RA can cause joint inflammation and synovial hyperplasia, destroying joint cartilage and bone tissue, eventually resulting in severe joint deformity and permanent disability. Long-term systemic inflammation in RA patients may promote the development of complications. It is reported that RA links with multiple systemic diseases, including cardiovascular disease, respiratory diseases, and psychological diseases as well (Jeong et al. 2017). RA seriously influences the quality

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of life of patients and places a heavy financial burden on society and patients' families (McInnes and Schett 2017). At the same time, it also extends a challenge for global public health. Although the pathogenesis of rheumatoid arthritis is not fully understood, it is generally acknowledged that the occurrence and development of RA is influenced by interactions between genetic and environmental factors (Arleevskaya et al. 2022; Deane et al. 2017; Salliot et al. 2020; Venetsanopoulou et al. 2022). Endocrine-disrupting chemicals (EDC) have been reported to influence the development and functions of human immune cells and thus may result in various immune disease, such as RA (Nowak et al. 2019). Published papers indicated that there were positive associations of several EDCs with RA, including polychlorinated biphenyls (PCBs), organochlorine pesticides, and polycyclic aromatic hydrocarbons (PAHs) (Lee et al. 2007; Sun et al. 2020).

Pyrethroids are a type of insecticide derived from the chemical structure of natural pyrethrins. Pyrethroids have a strong toxic effect on insects, and their main mechanism of action is to disrupt the normal physiology of insect nerves, causing them to die from excitement and spasm (Mohammadi et al. 2019). Pyrethroid insecticides have been increasingly applied in agriculture and related sectors due to their advantages, including broad spectrum, effectiveness, and low mammalian toxicity (Ravula and Yenugu 2021). It is expected that the global pyrethroid market will witness a compound annual growth rate (CAGR) of 4% from 2021 to 2026 (IMARC 2021). Pyrethroid pesticide residues can be extensively detected in a range of environments, including soils, surface water, sediments, and indoors (Tang et al. 2018). Additionally, recent studies have documented that urinary pyrethroid metabolites can be commonly detected among the general population in many countries, raising extensive concerns about potential health risks caused by nonoccupational pyrethroid exposure (Li and Kannan 2018, Rodzaj et al. 2021). Although pyrethroids are generally regarded as insecticides with relatively low mammalian toxicity, there is still a great need to conduct epidemiological studies to investigate related health risks associated with chronic low levels of pyrethroid exposure.

A published systematic review reported that environmental and occupational exposure to a variety of pesticides can induce temporary or permanent changes in the immune system, leading to serious chronic diseases, such as inflammatory bowel disease, and rheumatoid arthritis (Mostafalou and Abdollahi 2013). It was documented that several agricultural tasks and pesticide exposure may contribute to the development of RA among farmers (Parks et al. 2019a, 2019b). Although pesticide use is associated with systemic immune disease, the role of specific pesticides in the development of RA has not been established (Corsini et al. 2013). With the increasing use of pyrethroids around the world, it is urgent to improve the understanding of whether pyrethroids affect the development of RA (Mostafalou and Abdollahi 2013). Hence, the primary objective of this study was to investigate the association between pyrethroid exposure, as measured by urine pyrethroid metabolite concentrations, and the prevalence of RA in US adults.

Materials and methods

Study design and population

The National Health and Nutrition Examination Survey (NHANES) was a cross-sectional survey conducted by the National Centre for Health Statistics (NCHS), which was designed to assess the nutritional and health status of non-institutionalized US civilian population. A complex, stratified multistage sampling design was applied to make the sample more representative. The survey was conducted every 2 years, and information covering demographic data, dietary data, examination data, laboratory data, and questionnaire data was collected (Ahluwalia et al. 2016; Guo et al. 2022). All of them can be publicly available at https://www.cdc.gov/nchs/nhanes/. In addition, the official website of NHANES provided relevant guidelines and regulations in terms of data processing and statistical analysis. In our study, urinary pyrethroid metabolites originated from four survey cycles (2007–2008, 2009–2010, 2011–2012, 2013–2014). In our analysis, participants aged ≥ 20 years with complete data about pyrethroid metabolites and core covariates were enrolled. Participants were excluded if there were missing data or uncertain information in analytical covariates. In addition, pregnant women were also excluded from our present analysis. Finally, 4384 participants were included (Fig. 1). The NCHS Research Ethics Review Board reviewed and approved the protocol of the NHANES study, and all participants signed informed consent forms.

Measurements of 3-PBA

The metabolites of pyrethroids are excreted mainly through urine; thus, pyrethroid exposure is usually assessed by the concentration of metabolites in urine samples (Lehmler et al. 2020). Specifically, the main metabolite of pyrethroid insecticides detected in urine is 3-phenoxybenzoic acid (3-PBA), which has been extensively used as a biomarker reflecting human pyrethroid exposure levels. In NHANES, urine samples were stored under frozen conditions (− 30 °C) until they were shipped to the scientific laboratory department for testing. Pyrethroid metabolites were measured in a one-third subsample of participants aged 6 years and older. The measured values of urinary pyrethroid metabolites were originated from laboratory data, including 3-phenoxybenzoic

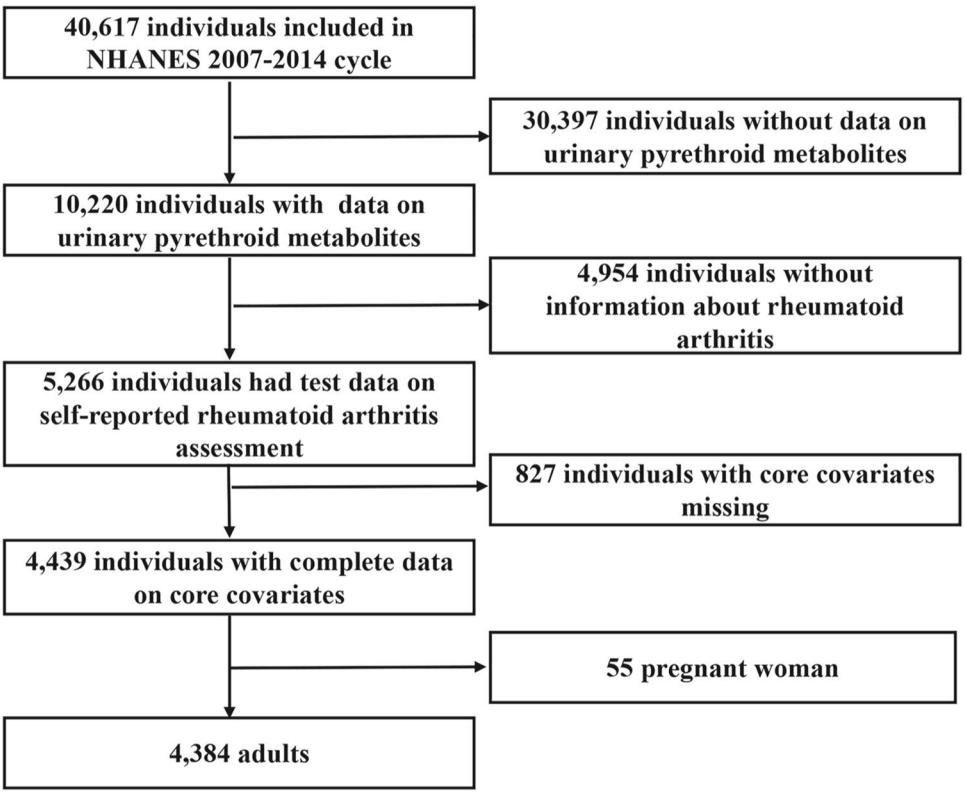

Fig. 1 Flow chart of population included in our final analysis, NHANES 2007–2014

acid (3-PBA), 4-fluoro-3-phenoxybenzoic acid (4F-PBA), and cis-dibromovinyl-dimethylcyclopropane carboxylic acid (DBCA). However, 4-FPBA and DBCA were both excluded from our analyses due to low detection rates (Lee and Choi 2020). The limit of detection (LOD) of 3-PBA was 0.10 ng/mL, and a value less than 0.10 was substituted by the LOD divided by the square root of 2. Detailed procedures and methods can be found in laboratory procedure manual.

Assessment of rheumatoid arthritis

The assessment of rheumatoid arthritis cases was determined by self-report questionnaire questions. The questions consisted of "Has a doctor or other health professional ever told you that you had arthritis" and "Which type of arthritis was it?". Individuals who answered "rheumatoid arthritis" to the latter question were classified into the RA group. In addition, we excluded other types of arthritis in the non-RA group, such as psoriatic arthritis, osteoarthritis, and degenerative arthritis.

Covariates

In accordance with other published studies, we controlled for confounding factors that may affect the association between pyrethroid exposure and rheumatoid arthritis (Li et al. 2021; Sun et al. 2020). Specifically, the covariates included age (continuous variable), sex (male/female), race/ethnicity (Mexican American, non-Hispanic black, non-Hispanic white, and others), BMI level (< 25.0 kg/m^2 (normal weight), 25.0–29.9 kg/m^2 (overweight), and ≥ 30.0 kg/m2(obesity)), family poverty income (≤ 1.35 (lower income), 1.35 to 3.5 (moderate income), ≥ 3.5 (higher income)), level of education (lower than high school, high school or equivalent, and college or above), marital status (married/cohabiting, widowed/divorced/separated, and never married), smoking status, alcohol user (at least 12 alcoholic drinks per year or not), physical activity, hypertension, and urinary creatinine. Smoking status was classified into three categories: never (< 100 cigarettes in the entire life), former smoker (≥ 100 cigarettes and no smoking currently), and current smoker (≥ 100 cigarettes and smoking currently). Physical activity was divided into three levels (no, moderate, and vigorous) according to self-reported questionnaire items (Guo et al. 2022). Hypertension was assessed by blood pressure measurement (an average systolic blood pressure above 140 mmHg/an average diastolic blood pressure above 90 mmHg), self-reported history of hypertension, or taking antihypertensive drugs. Average blood pressure was recorded by the following protocol: (1) If only one blood pressure reading was obtained, that reading is the average; (2) If there is more than one blood pressure reading, the first reading is always excluded from the average. In

addition, the creatinine-corrected 3-PBA concentrations (ug/g creatinine) were applied to reduce the effect of urine dilution on the 3-PBA concentration.

Statistical analysis

The distribution characteristics of continuous variables were described by means with standard deviations (SD), and categorical variables were expressed as the number of cases (n) and percentages (%). Differences in categorical variables were assessed using chi-square tests, while differences in continuous variables were assessed using t tests (normal distribution) or Mann–Whitney tests (skewed distribution). For creatinine-adjusted urinary 3-PBA, continuous variable (natural logarithms transformed) and categorical variable (modeled as quartiles and took the 25th percentile as a reference) were used to model, respectively. Three multivariate logistic regression models were constructed to estimate odds of ratios (ORs) for the risk of RA associated with pyrethroid exposure and corresponding confidence intervals. Model 1 was only adjusted for urinary creatinine. Model 2 was further adjusted for age, sex, race/ethnicity, BMI level, PIR, education level, and marital status. Model 3 was additionally adjusted for alcohol usage, smoking status, physical activity, and hypertension. Moreover, subgroup analyses were conducted by sex (male or female), age (20–39, 40–59, ≥ 60), race, marital status, education, PIR, BMI, alcohol usage, physical activity, smoking status, and hypertension. Finally, a restricted cubic spline plot with three knots was used to examine the possible nonlinear relationship between the risk of RA and 3-PBA levels. All statistical analyses were performed using R software (version 4.1.1), and *P* value less than 0.05 was regarded as statistically significant.

Results

Baseline characteristics of study participants

Ultimately, 4384 participants were included in our analysis. There were 278 RA patients and 4106 subjects without RA. Table 1 summarizes the weighted baseline characteristics of the RA and non-RA participants in the NHANES database. Mean age of all included individuals was 47.56 years. Non-Hispanic white individuals accounted for the largest proportion. The vast majority of individuals had a higher level of education than high school and were in good marital status. Notably, the levels of 3-PBA in RA group were significantly higher than those in non-RA groups. Significant differences between the RA group and the no-RA group were observed in all parameters except alcohol usage.

Association between pyrethroid exposure and rheumatoid arthritis

Table 2 describes the results of multivariate logistic analyses. The ORs of RA were positively associated with ln-transformed 3-PBA in three models. Of note, the result of model 1 (only adjusted for urinary creatinine) suggested that ln-transformed 3-PBA concentrations were significantly associated with the occurrence of RA (OR: 1.13, 95% CI: 1.04, 1.24). When taking the lowest quartile as a reference, the level of 3-PBA in the highest quartile was related to increased prevalence of RA as well. In model 1, participants in the higher quartile of 3-PBA had a significantly higher OR for RA compared with those in the lowest quartile of 3-PBA with an increasing trend (OR for Q2, 1.13 (95% CI: 0.78, 1.64); for Q3, 1.30 (95% CI: 0.91, 1.86); for Q4, 1.51 (95% CI: 1.07, 2.15)). In the completely adjusted model (model 3), the odds ratios and corresponding 95% CI for participants in the second, third, and fourth quartiles were 1.13 (95% CI: 0.77, 1.66), 1.16 (95% CI: 0.80, 1.68), and 1.23 (95% CI: 0.86, 1.79), respectively. In addition, we performed subgroup analyses to estimate the effect estimate of the different groups (Table 3). In most subgroups, there were positive non-significant correlations between higher concentrations of 3-PBA and the prevalence of RA. There were statistically positive correlations between the levels of 3-PBA and the prevalence of RA in participants aged 40–59 years or unmarried or who had a lower level of education. The odds ratios of these groups both had an obvious increasing trend (*P* for trend < 0.05). Furthermore, we utilized a restricted cubic spline model to simulate the potential nonlinear association between pyrethroid exposure and the risk of rheumatoid arthritis. Figure 2 presents a positive dose–response relationship between urinary levels of 3-PBA and the occurrence of RA (*p* for nonlinearity = 0.728), indicating that the risk of RA increased with the concentration of 3-PBA.

Discussion

In general, our results illustrated that levels of 3-PBA were associated with increased prevalence of RA among adults. Notably, this association was more pronounced participants aged 40 to 59 years or had a lower level of education. Prior to our study, there were no epidemiological investigations examining the potential effect of specific pesticide exposure on the prevalence of RA based on a nationally representative sample. Additionally, our study may extend important implications for better understanding associations between pyrethroids and autoimmune diseases.

Pyrethroids have gradually replaced applications of organophosphate and carbamate insecticides and extend a vital role in the agricultural industry and other fields. It

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

Characteristics	Participants ($n=4384$)	Without RA ($n=4106$)	RA ($n=278$)	P-value
N (%)	3591 (100)	3375 (93.7)	216 (6.3)	
Age years, mean (SD)	47.56 (15.62)	46.88 (15.51)	57.54 (13.72)	**< 0.001**
Sex, *n* (%)				
Male	2258 (51.5)	2147 (52.3)	111 (39.9)	**< 0.001**
Female	2126 (48.5)	1959 (47.7)	167 (60.1)	
Race/ethnicity, *n* (%)				
Mexican American	685 (15.6)	648 (15.8)	37 (13.3)	**< 0.001**
Non-Hispanic black	908 (20.7)	824 (20.1)	84 (30.2)	
Non-Hispanic white	1875 (42.8)	1757 (42.8)	118 (42.4)	
Other race	916 (20.9)	877 (21.4)	39 (14.0)	
Education, *n* (%)				
Lower than high school	1030 (23.5)	938 (22.8)	92 (33.1)	**< 0.001**
High school or equivalent	940 (21.4)	872 (21.2)	68 (24.5)	
College or above	2414 (55.1)	2296 (55.9)	118 (42.4)	
Marital status, *n* (%)				
Married/cohabiting	2626 (59.9)	2479 (60.4)	147 (52.9)	**< 0.001**
Never married	943 (21.5)	913 (22.2)	30 (10.8)	
Widowed/divorced/separated	815 (18.6)	714 (17.4)	101 (36.3)	
BMI, *n* (%)				
Normal	1388 (31.7)	1326 (32.3)	62 (22.3)	**< 0.001**
Overweight	1472 (33.6)	1402 (34.1)	70 (25.2)	
Obesity	1524 (34.8)	1378 (33.6)	146 (52.5)	
PIR, *n* (%)				
≤ 1.3	1436 (32.8)	1307 (31.8)	129 (46.4)	**< 0.001**
1 < to < 3.5	1545 (35.2)	1457 (35.5)	88 (31.7)	
≥ 3.5	1403 (32.0)	1342 (32.7)	61 (21.9)	
Smoking status, *n* (%)				
Current	974 (22.2)	896 (21.8)	78 (28.1)	**< 0.001**
Formal	922 (21.0)	846 (20.6)	76 (27.3)	
Never	2488 (56.8)	2364 (57.6)	124 (44.6)	
Alcohol user, *n* (%)				
No	1156 (26.4)	1070 (26.1)	86 (30.9)	**0.086**
Yes	3228 (73.6)	3036 (73.9)	192 (69.1)	
Vigorous or moderate activity, *n* (%)				
No	1310 (29.9)	1174 (28.6)	136 (48.9)	**< 0.001**
Moderate	1383 (31.5)	1292 (31.5)	91 (32.7)	
Vigorous	1691 (38.6)	1640 (39.9)	51 (18.3)	
Hypertension, *n* (%)				
No	2848 (65.0)	2761 (67.2)	87 (31.3)	**< 0.001**
Yes	1536 (35.0)	1345 (32.8)	191 (68.7)	
Urinary 3-PBA (μg/g creatinine)*	0.48 [0.23, 1.10]	0.47 [0.23, 1.08]	0.65 [0.27, 1.34]	**0.004**

The bold values means statistical significance

RA, rheumatoid arthritis; *NHANES*, the National Health and Nutrition Examination Survey; *BMI*, body mass index; *SD*, standard deviation; *N*, numbers of subjects; *PIR*, family poverty-income ratio; *3-PBA*, 3-phenoxybenzoic acid

*Values were presented as median (interquartile range). This value was adjusted for urinary creatinine

is reported that pyrethroids have become the second most widely used insecticide in the world, accounting for more than 30% of the global pesticide market share (Lehmler et al. 2020). The widespread use of pyrethroids results in ubiquitous exposure to pyrethroid pesticides for the general population in recent years (Saillenfait et al. 2015). It was

Table 2 Association between urinary levels of 3-PBA and rheumatoid arthritis in US adults

	Model 1	Model 2	Model 3
Ln	**1.13 (1.04, 1.24)**	1.07 (0.98, 1.18)	1.07 (0.97, 1.17)
Q1	1.00	1.00	1.00
Q2	1.13 (0.78, 1.64)	1.12 (0.77, 1.64)	1.13 (0.77, 1.66)
Q3	1.30 (0.91, 1.86)	1.15 (0.80, 1.67)	1.16 (0.80, 1.68)
Q4	**1.51 (1.07, 2.15)**	1.24 (0.86, 1.79)	1.23 (0.86, 1.79)
P for trend	**0.013**	0.245	0.269

Model 1 was only adjusted for urinary creatinine. Model 2: Further adjustment for sex, age, race/ethnicity, BMI level, PIR, level of education, marital status. Model 3: Further adjustment for smoking status, alcohol usage, physical activity, and hypertension

The bold values means statistical significance

indicated that indoor pyrethroid residue concentrations tend to be higher than those detected in soil, water, and sediment because pyrethroid insecticides can cling to house dust and the absence of primary degrading factors: UV radiation, hydrolysis, and microbial degradation (Tang et al. 2018; Werthmann et al. 2021). Therefore, not only occupationally exposed people are vulnerable to related health hazards attributable to pyrethroid exposure but also the harmful effect of pyrethroid exposure in the general population should not be underestimated. In many countries, the detection rate of pyrethroid metabolites in urine samples from nonoccupationally exposed population is more than 75%. For example, 3-PBA had a detection rate of 80% in the sample of an urban population of Northern Poland (Wielgomas et al. 2013). Almost all Canadian Health Measures Survey participants (99.8%) had pyrethroid metabolites detectable in urine (Ye et al. 2016). According to the latest published paper based on NHANES, the detection rate of 3-PBA was 78.1% in adults and 79.3% in children (Lehmler et al. 2020). It has been well documented that pyrethroids have neurotoxicology, reproductive and developmental toxicity, and immunotoxicology and cause oxidative stress and DNA damage (Mohammadi et al. 2019, Skolarczyk et al. 2017; Zepeda-Arce et al. 2017). In epidemiological studies, there is modest evidence that pyrethroid exposure is correlated with an increased risk of human health, including cardiovascular diseases, diabetes, reproductive health, and cognitive dysfunction (Kim et al. 2021; Koureas et al. 2012; Park et al. 2019; Xue et al. 2021). However, as a kind of recognized endocrine disruptors, little is known about the effect of pyrethroid exposure on autoimmune disease.

Antinuclear antibodies (ANAs), which recognize various nuclear components in cells, often appear in many autoimmune diseases, especially rheumatoid diseases (Abella et al. 2016). Rosenberg and his colleague identified a positive association between ANA positivity and lifetime exposure to pyrethroid insecticides after adjusting for sex, age, and other insecticide exposure, indirectly suggesting that pyrethroid may affect human immune function (Rosenberg et al. 1999). It can be speculated that pyrethroid exposure may be linked with RA as well. Koureas et al. identified that increased frequency of RA was associated with pesticide use among pesticide sprayers (Koureas et al. 2017). Parks et al. provided evidence that multiple types of agricultural tasks and exposures other than pesticides contribute to the risk of RA in farmers (Parks et al. 2019a). They also provided initial support for a potential association between childhood pesticide exposure and the risk of RA (Parks et al. 2018). Moreover, results resulted from occupational exposures showed a statistically significant association of RA mortality with pesticide exposure (Gold et al. 2007). Findings from a Swedish study suggested that RA events in men and women were inconsistently associated with occupational pesticide exposure, which is aetiologically more important for men (Olsson et al. 2004). Previous epidemiological evidence suggested that this association seemed to be more pronounced in men (De Roos et al. 2005; Lundberg et al. 1994). Similarly, the sex difference in the association between pyrethroid exposure and RA may be biologically plausible because sex hormones may play an important role (Cutolo et al. 2002). However, no significant difference between male and female was observed in our study. These inconsistent findings may be explained that prior studies are based on population with occupational exposure, while male are engaged in more agricultural activities. Consequently, more investigations are warranted to explore who is more sensitive to pyrethroid exposure between men and women in general population. Interestingly, we found that participants with lower education (lower than high school) seem to be more susceptible to the effect of pyrethroid exposure. This phenomenon may result from their weak awareness of the immunotoxicity of pyrethroids together with lack of corresponding protective measures. Although our primary findings support the role of environmental pesticide exposure in the development of rheumatoid arthritis, there is a great need to replicate our main findings in other areas.

Although the mechanism of the occurrence and development of RA induced by pyrethroids is still unclear, limited evidence may provide some plausible explanations for the underlying mechanism. It is well documented that each stage of the development of rheumatoid arthritis (RA) is associated with immune cell dysfunction, and immune dysregulation is also the most important mechanism in the pathogenesis of rheumatoid arthritis (Sparks 2019). Previous toxicological study suggested that early pyrethroid exposure may lead to multiple immunological responses (Singh et al. 2013). Specifically, pyrethroid exposure does not only influence the differentiation and regulation of the innate immune response (Parks et al. 2011), but it also interferes with the specific immune function by inducing cell apoptosis or cell cycle arrest (Lee et al. 2007; Wang et al. 2017). A great

Table 3 The results of subgroup analyses

	Q1	Q2	Q3	Q4	*P* for trend
Model 3					
Sex					
Male	1.00	0.88 (0.48,1.63)	0.98 (0.54, 1.78)	1.22 (0.70, 2.15)	0.392
Female	1.00	1.20 (0.49, 1.85)	1.29 (0.79, 2.12)	1.26 (0.78, 2.05)	0.347
Race/ethnicity					
Mexican American	1.00	1.73 (0.56,5.99)	1.53 (0.50, 5.31)	1.49 (0.48, 5.18)	0.610
Non-Hispanic black	1.00	0.80 (0.37,1.71)	1.17 (0.57, 2.40)	1.40 (0.72, 2.77)	0.210
Non-Hispanic white	1.00	0.82 (0.46,1.47)	0.89 (0.50, 1.57)	1.03 (0.60, 1.81)	0.772
Other race	1.00	2.03 (0.65,6.78)	**3.23 (1.14, 10.28)**	2.59 (0.85, 8.67)	0.083
Age group					
20–39	1.00	0.35 (0.09, 1.17)	0.53 (0.17, 1.53)	0.84 (0.31, 2.28)	0.898
40–59	1.00	1.27 (0.67, 2.41)	1.57 (0.86, 2.91)	**1.82 (1.02, 3.23)**	**0.035**
> = 60	1.00	1.04 (0.60, 1.78)	1.12 (0.66, 1.90)	0.88 (0.51, 1.52)	0.695
Marital status					
Married/cohabiting	1.00	0.89 (0.52, 1.50)	1.20 (0.73, 1.98)	1.14 (0.70, 1.88)	0.437
Widowed/divorced/separated	1.00	1.10 (0.59, 2.04)	0.92 (0.48, 1.75)	1.01 (0.54, 1.88)	0.916
Never married	1.00	2.12 (0.51, 11.88)	1.39 (0.32, 7.47)	**4.36 (1.18, 21.93)**	**0.033**
Education					
Lower than high school	1.00	**2.57 (1.12, 5.76)**	**2.61 (1.26, 5.72)**	**2.25 (1.08, 4.93)**	**0.048**
High school or equivalent	1.00	0.87 (0.40, 1.91)	1.42 (0.70, 2.93)	0.73 (0.34, 1.57)	0.585
College or above	1.00	0.74 (0.41, 1.32)	0.73 (0.40, 1.28)	1.18 (0.70, 2.01)	0.402
PIR					
≤ 1.3	1.00	1.11 (0.62, 1.99)	0.93 (0.52 1.66)	1.25 (0.73, 2.18)	0.414
1 < to < 3.5	1.00	0.73 (0.35, 1.45)	1.31 (0.68, 2.53)	1.34 (0.72, 2.54)	0.191
≥ 3.5	1.00	1.18 (0.53, 2.62)	1.19 (0.56, 2.56)	0.95 (0.42, 2.10)	0.890
BMI					
Normal	1.00	0.20 (0.05, 0.58)	0.85 (0.40, 1.85)	1.25 (0.60, 2.53)	0.154
Overweight	1.00	2.03 (0.97, 4.46)	1.14 (0.50, 2.64)	1.41 (0.66, 3.12)	0.728
Obesity	1.00	1.18 (0.68, 2.04)	1.32 (0.79, 2.24)	1.06 (0.63, 1.81)	0.812
Alcohol user					
Yes	1.00	1.05 (0.67, 1.65)	0.89 (0.57, 1.41)	1.12 (0.73, 1.72)	0.704
No	1.00	1.42 (0.67, 3.09)	**2.05 (1.03, 4.31)**	1.60 (0.78, 3.42)	0.179
Physical activity					
No	1.00	1.59 (0.90, 2.86)	1.59 (0.91, 2.81)	1.28 (0.73, 2.26)	0.471
Moderate	1.00	0.96 (0.46, 1.99)	1.56 (0.81, 3.08)	1.56 (0.82, 3.05)	0.096
Vigorous	1.00	0.92 (0.40, 2.09)	0.54 (0.22, 1.30)	0.82 (0.36, 1.84)	0.510
Smoking status					
Never	1.00	0.87 (0.48,1.58)	1.00 (0.58, 1.75)	1.08 (0.62, 1.87)	0.665
Formal	1.00	1.00 (0.50, 2.02)	0.93 (0.46, 1.90)	0.98 (0.48, 2.01)	0.938
Current	1.00	2.13 (0.96, 4.89)	1.42 (0.64, 3.29)	1.67 (0.77, 3.79)	0.372
Hypertension					
Yes	1.00	1.19 (0.74, 1.90)	1.22 (0.77, 1.94)	1.18 (0, 75, 1.87)	0.501
No	1.00	0.85 (0.42, 1.72)	1.08 (0.57, 2.01)	1.43 (0.77, 2.71)	0.169

Model 3 was adjusted for urinary creatinine, sex, age, race/ethnicity, BMI level, PIR, level of education, marital status, smoking status, alcohol usage, physical activity, and hypertension

The bold values means statistical significance

body of experiments and literature have confirmed that the occurrence of RA disease is regulated by the interdependent cytokine network, while pyrethroid pesticide exposure may be associated with changes in the cytokine profile and

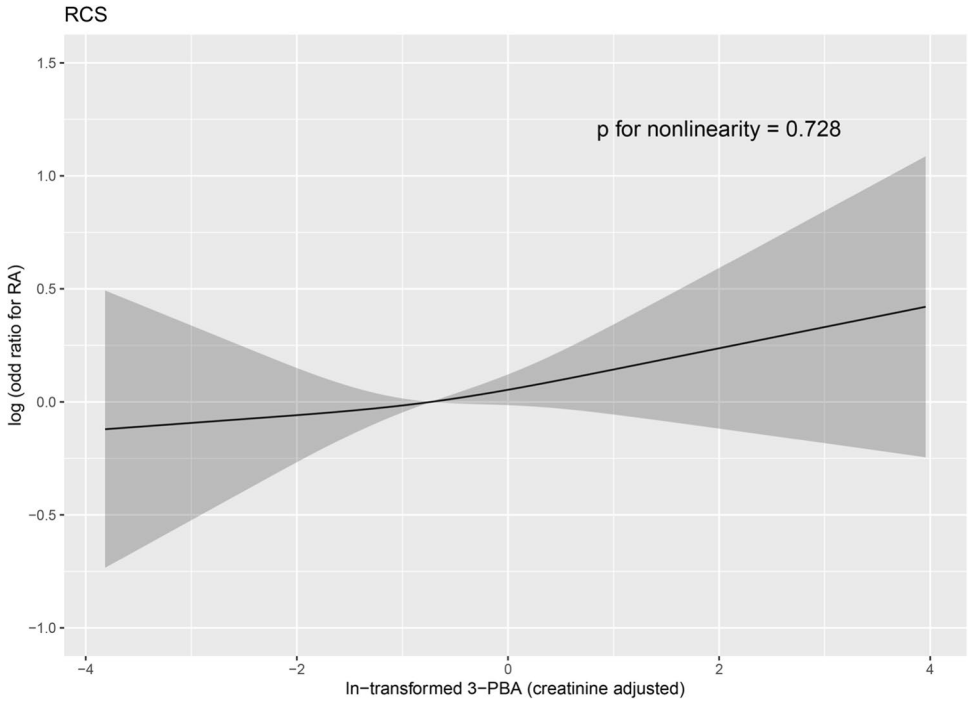

Fig. 2 The restricted cubic spline plot of the association between ln-transformed concentrations of 3-phenoxybenzoic acid (3-PBA) and rheumatoid arthritis (RA). The association was adjusted for age, sex, race/ethnicity, education level, body mass index level, poverty-income ratio, marital status, smoking status, alcohol use, hypertension, physical activity, and urinary creatinine

increased levels of proinflammatory cytokines (Corsini et al. 2013; Holsapple 2002). Furthermore, animal experiments indicate that exposure to pyrethroids, like other endocrine disruptors, could affect the composition of the intestinal microbiota (Rosenfeld 2017), while the altered composition of the human intestinal microbiota can trigger the development of RA (Maeda et al. 2016; Zhou et al. 2021). Several papers report that there is a correlation between the level of 3-PBA and reproductive hormones, such as luteinizing hormone and follicle-stimulating hormone (Han et al. 2008; Meeker et al. 2009). The small fluctuations in these hormones could be associated with similar fluctuations in cytokines and disease activity in RA (Kåss et al. 2010). Therefore, it is hypothesized that pyrethroids can affect the occurrence and development of RA by disturbing reproductive hormones. Notably, there is currently no experimental study on the pathogenesis of rheumatoid arthritis caused by pyrethroid exposure. We only proposed several plausible hypotheses that explain the potentially detrimental role of pyrethroid on RA, and subsequent studies are urgently needed to fill this gap.

The most obvious advantage of this study is that it is the first representative population-based study investigating the association between pyrethroid exposure and RA. Nevertheless, several limitations should be acknowledged in this study. First, we cannot infer any causal correlations between pyrethroid exposure and the occurrence of RA because of the cross-sectional design. Second, people are usually exposed to multiple pesticides at the same time; thus, it is difficult for us to exclude the effects of other types of pesticides on rheumatoid arthritis. Using the concentration of 3-PBA in urine samples to assess pyrethroid exposure is another limitation. On the one hand, 3-PBA is a common nonspecific metabolite, and its pathogenic effect on rheumatoid arthritis may vary among specific types of pesticides. On the other hand, a single sampling only represents pyrethroid pesticide exposure at a certain time but does not present individual changes in urinary 3-PBA in a relatively long period, probably resulting in a misinterpretation of the magnitude of exposure. Last, given that our subjects are drawn from a representative sample of the US population, it is necessary to replicate our results among other races.

Conclusions

Taken together, our study suggested that pyrethroid pesticide exposure was positively associated with RA. In addition, higher levels of pyrethroid exposure were linearly associated with increased prevalence of RA in adults. Our study provided new insights into the relationship between pyrethroid exposure and RA. Certainly, our finding is in great need of further corroboration by prospective study with strict design.

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Author contribution Xianwei Guo: conceptualization, methodology, software, data curation, formal analysis, visualization, writing—original draft, writing—review and editing.

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Wanying Su: validation and visualization.

Qiuxia Song: methodology, writing—original draft, software.

Qiwei Liang: methodology, formal analysis, writing—review and editing.

Chenyu Sun: conceptualization, writing—review and editing.

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Xiuxiu Ding: writing—review and editing.

Scott Lowe: writing—review and editing.

Yehuan Sun: conceptualization, supervision, writing—review and editing.

Data availability All data are mentioned in the body of the manuscript, tables, and figure.

Declarations

Ethics approval and consent to participate The NCHS Research Ethics Review Board reviewed and approved the protocol of the NHANES study, and all participants signed informed consent forms.

Consent for publication There is no conflict of interest that exists in this manuscript, and it is approved by all authors.

Competing interests The authors declare no competing interests.

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