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Association between environmental pyrethroid exposure and asthma among U.S. children and adults in National Health and Nutrition Examination Survey (2007–2014)

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Abstract

Objectives: The evidence interpreting the association between environmental pyrethroid exposure and asthma is limited. The objective of this study was to examine the association between pyrethroid exposure and asthma among U.S. children and adults.

Methods: Participants were collected from the National Health and Nutrition Examination Survey (NHANES, 2007-2014), including children and adults. 3-phenoxybenzoic acid (3-PBA) was used as a biomarker for pyrethroid metabolites. Multiple logistic regression models were constructed to estimate the association of urinary 3-PBA with asthma among children and adults and to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Additionally, a restricted cubic spline plot with three knots was applied to assess the potential nonlinear relationship between pyrethroid exposure and asthma.

Results: Collectively, 7,776 participants were enrolled, including 2,236 children and 5,540 adults. The weighted prevalence of asthma in children and adults was 12.23% and 8.66% respectively. After adjusting for age, sex, race/ethnicity, poverty income ratio (PIR), body mass index (BMI), serum cotinine, urinary creatinine and family history of asthma, our results indicated that higher levels of 3-PBA was positively related to the risk of asthma among children (OR: 1.395; 95%CI: 0.880, 2.210) and adults (OR: 1.177; 95%CI: 0.778, 1.781). This positive association seemed to be more pronounced among 12-19-years old children and girls. Furthermore, the restricted cubic spline plot showed a linear relationship between levels of 3-PBA and asthma among children and adults (*p* for nonlinearity was 0.693 and 0.691 respectively).

Conclusions: Our study observed a positive association between 3-PBA and asthma among children and adults while this positive association was more pronounced among children. However, we can not role out the possibility that the possible role of other co-occurring pesticides and other chemicals in the observed trends in asthma incidence. Therefore, further studies are needed to evaluate the possible pathogenic role of pyrethroid insecticides in asthma.

1. Introduction

Asthma is a respiratory disease characterized by chronic inflammation of the airways and airway remodeling, with symptoms such as wheezing, shortness of breath, chest tightness, and coughing (Papi et al. 2018). The chronic inflammatory process in the airways involves a variety of cells, such as mast cells, eosinophils (EOS), and T lymphocytes, as well as different cytokines, including interleukin-4 (IL-4), interleukin-5 (IL-5) (Wasserman 1994). Airway remodeling is a pathological change in the normal structure of the airway, the process and extent of which varies from patient to patient depending on the severity of Asthma (Holgate et al. 2015). It can lead to varying degrees of irreversible airflow restriction, making asthma patients less responsive or even resistant to conventional treatments. The complexity and diversity of the onset and clinical presentation of asthma is a major challenge in diagnosis and treatment. It was estimated that asthma affected 262 million people and caused 461,000 deaths in 2019 (Theo Vos et al. 2020). Asthma not only affects the patient's quality of life, but also leads to serious complications, such as pneumothorax, respiratory failure, and chronic pulmonary heart disease (Kimura et al. 2009, Manden &Siddiqui 2009). Consequently, asthma is still a serious public health issue worldwide.Although the underlying causes of

asthma have not been fully elucidated, genetic susceptibility, environmental factors, and gene-environment interactions have been identified as important risk factors for the development and progression of asthma (Rigoli et al. 2011, Sordillo et al. 2015). Currently, no treatment modalities can provide definitive cure for asthma. Therefore, avoiding the triggers of asthma is of great public health importance to prevent the disease and reduce its incidence.

Pyrethroid pesticides belong to a class of broad-spectrum insecticides and are synthesized by bionic modification of the structure of natural pyrethroids (Burns &Pastoor 2018). Pyrethroids have an obvious advantage over organochlorine pesticides with a half-life of only 33 to 425 days (Tang &Zeng 2019). Additionally, pyrethroids have several characteristics including selective toxicity, rapid metabolism, excretion in mammals, as well as low environmental residues (Saillenfait et al. 2015). Pyrethroids are not only widely used in agriculture, such as controlling leaf-and fruit-eating pests of cotton, vegetables, and fruit trees, but also employed as household insecticides to control flies, cockroaches, and livestock parasites (Hołyńska-Iwan &Szewczyk-Golec 2020). With a gradually increasing proportion of pyrethroids in insecticides and widespread use of that in the environment, pyrethroids residues are commonly detected in surface water, soil, and other environmental media (Agarwal et al. 2015, Liu et al. 2016b). It has been ascertained that pyrethroid exposure can lead to impaired immune system, nervous system, and reproductive system, hence pyrethroid-induced damage to the human body remains a pressing environmental health issue (Lehmler et al. 2020).

Many epidemiology studies have been conducted to explore the associations between environmental chemicals exposure and asthma, including phthalates, organophosphate insecticides, polyaromatic hydrocarbons (PAHs), paraben, and per- and polyfluoroalkyl substances (PFASs) (Humblet et al. 2014, Navaranjan et al. 2021, Quirós-Alcalá et al. 2019). However, scientific evidence on pyrethroid exposure and the prevalence of asthma is relatively scarce (Mattila et al. 2021). Moreover, asthma is one of the most common chronic diseases in the United States, currently affecting an estimated 6.1 million children and approximately 28 million adults (Han et al. 2016, NHC 2021). Accordingly, we used data obtained from the National Health and Nutrition Examination Study (NHANES) to improve our understanding of the effects of pyrethroid exposure on asthma among U.S. children and adults.

2. Methods

2.1. Study design and population

NHANES is a project managed by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC). As a cross-sectional study, NHANES utilized a complex, multistage, probability sampling design to select representative participants of the population in the United States. It aimed to assess the nutritional and health status of children and adults in the U.S. by collecting relevant data. The NHANES survey consisted of both interviews and physical examinations. The interview component included demographic characteristics, socioeconomic, dietary information, lifestyle characteristics, disease history, and other health-related questions, all of which were completed in the respondent's home. The physical examination component was conducted at a mobile medical examination center (MEC) and includes basic medical information, oral health, physiological information, and laboratory tests performed by

trained medical personnel. The survey was conducted every two years with the first survey dating back to 1971 and each survey round was compiled into multiple data files by category to facilitate data use and management. A more detailed description of NHANES can be obtained from the NCHS website (NCHS 2021). The NHANES survey had been approved by the National Health Organization Institutional Review Board, and all participants in the investigation were required to sign an informed consent form. Because NHANES is a publicly available database, data can be accessible to data users and researchers worldwide via the Web. Data were pooled from four independent cross-sectional cycles (2007–2008, 2009–2010, 2011–2012, and 2013–2014), providing a measured value of pyrethroids. Individuals who had completed respiratory health questionnaires and measurements for pyrethroid metabolites were included in our analysis. Participants were excluded if there were missing data or uncertain information in analytical covariates. In addition, pregnant women were excluded from our analysis as well. Ultimately, 7,776 participants were enrolled, including 2,236 children and 5,540 adults. The flow chart of participants' selection is shown in Fig. 1.

2.2 Measurement of pyrethroid

Pyrethroids and their conjugates are excreted in the form of water-soluble metabolites by the action of hepatic microsomal mixed-function oxidase (MFO) and pyrethroid enzymes (Bhatt et al. 2020). Therefore, the measured value of concentrations of pyrethroid metabolites in urine is usually regarded as the basis for monitoring population exposure levels of pyrethroids from all sources and routes. The researchers detected the concentrations of pyrethroid metabolites from urine samples provided by participants at age 6 years and older. Urine samples were collected by the investigators every two years and transported to the National Center for Environmental Health of the CDC, where they were placed and stored at -20℃ until analysis was performed. The determinateness of metabolite concentrations were quantified by high-performance liquid chromatography system with tandem mass spectrometry. More specifically, four kinds of pyrethroid metabolites were measured, including 4-fluoro-3-phenoxybenzoic acid (4F-3-PBA), 3-phenoxybenzoic acid (3-PBA), trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (trans-DCCA), and cis-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (cis-DBCA). On the one hand, the detection rate of other pyrethroid metabolites except 3-PBA is low. On the other hand, 3-PBA is also the most frequently detected biomarker as it covers a large number of pyrethroids pesticides while other measured metabolites are specific for certain pyrethroids (Lin et al. 2021). 3-PBA is a common metabolite of permethrin, cypermethrin, fenvalerate, deltamethrin, cyhalothrin, fenpropathrin, and other commonly used pyrethroid insecticides (Fluegge et al. 2016). Notably, 3-PBA has been extensively used as a biomarker reflecting human pyrethroid exposure levels. Therefore, we only can utilize concentration of 3-PBA to assess levels of pyrethroid exposure. The lower limit of detection (LLOD) 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 (Hornung &Reed 1990). More detailed information about laboratory methods, laboratory quality assurances and monitoring are presented on the website (NHANES 2021).

2.3. Asthma assessment

Asthma assessment was conducted based on the medical conditions file of questionnaire data. In order to assess asthma, participants were asked two questions. Question1: "has a doctor or other health professional ever told you (participants) that study participant has asthma?" Question2: "Do you (participants) still have

asthma?". Taking into account that pyrethroid insecticides could not persist in the environment because they are rapidly degraded within days to months as well as the relatively short half-life of pyrethroids in the body, cases of asthma were determined when individuals responded "yes" to both questionnaire items mentioned above.

2.4. Covariates

All covariates included in the statistical analysis were selected a priori according to previous empirical evidence associated with pyrethroid exposure and asthma (Liu et al. 2016a, Odebeatu et al. 2019). All selected covariates were originated from standardized self-reported questionnaires, examination data, and laboratory measurements in NHANES. Several potential confounders were controlled for in the statistical model: age (years), sex (male or female), body mass index (BMI), race/ethnicity (Mexican American, Other Hispanic, non-Hispanic White, non-Hispanic Black, and Other race), poverty income ratio (PIR), family history of asthma (yes or no), serum cotinine (a biomarker of exposure to environmental tobacco smoke), and urinary creatinine. PIR was divided into three groups: ≤ 1.3, 1.3 to 3.5, ≥ 3.5, which representing low, medium, and high levels respectively (He et al. 2022). For children in the same sex and age group, underweight/normal weight, overweight and obesity were defined as BMI percentile < 85, 85 $\leq$ BMI percentile $\leq$ 95, BMI percentile > 95, respectively (Krebs et al. 2007). While for adults, normal weight, overweight and obesity were defined as BMI percentile < 25.0 kg/m^2, 25.0-29.9 kg/m^2, and $\geq$ 30.0 kg/m^2, respectively. The BMI was classified as normal weight (adults: BMI < 25 kg/m^2; children: BMI < 85th percentile), overweight (adults: 25 kg/m^2 < BMI $\leq$ 29.9 kg/m^2. Serum cotinine was classified as < 0.015 ng/mL, 0.015 to 10 ng/mL, and $\geq$ 10 ng/mL (Hoppin et al. 2013). The family history of asthma was determined by a response to the question in medical conditions questionnaire. The question is that "were close relatives ever told by a health professional that they had asthma?" To account for the effect of urinary dilution on 3-PBA concentrations, a novel creatinine-adjustment method was applied. The specific method is shown in the formula (O'Brien et al. 2016):

$$Ratio = U_{predictd} / U_{observed}$$

$$Creatinine\text{-}adjusted\ 3\text{-}PBA = (urinary\ 3\text{-}PBA) / Ratio$$

First, we transformed urinary creatinine to the natural logarithm and constructed a linear regression equation with sex (categorical variables), BMI (continuous variables), race/ethnicity (categorical variables), and age (continuous variables), which were known to affect urinary creatinine, as the independent variables. Ratio denoted predicted value of creatinine divides by observed value of that (Barr et al. 2005). The value of creatinine-adjusted 3-PBA concentration was calculated by measured urinary 3-PBA concentration divided by the Ratio.

2.5. Statistical methods

We created analytic data files by combing four survey cycles data in order to produce estimates with greater precision and smaller sampling error. Because this analysis combined four survey cycles, we calculated the appropriate multi-year weight according to the formula provided by NHANES. The sampling weight provided by NHANES was used throughout the statistical analysis to make estimates more representative. The result of continuous variables which were normally distributed was presented in terms of mean (standard

deviation) and that of categorical variables were in terms of frequency (weighted percentage). Data from skewed distributions were presented as medians and interquartile range (IQR). Chi-square test (for categorical variables), the t-test (for normally distributed continuous variables) and Mann-Whitney U tests (for skewed distribution variables) were applied to compare differences among two groups. Multivariate logistic regression models were constructed to assess the relationship between urinary 3-PBA and asthma and calculate the odds ratios (ORs) and 95% confidence intervals (CIs) among children and adults (Sanders et al. 2019). 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 as independent variables, respectively. Three primary models were constructed: Model 1 was only adjusted for creatinine; Model 2 was further adjusted for age, sex, race/ethnicity, PIR and BMI, and Model 3 was further adjusted for serum cotinine and history of asthma (completely adjusted model). In addition, a restricted cubic spline function of three knots (the 10th, 50th, and 90th percentiles of the exposure distributions) was applied to examine the potential nonlinear relationship between urinary 3-PBA concentrations and the odds risk of asthma. Subgroup analyses were conducted by sex and age. We used R software (version 4.1.1) for all statistical analyses.

3. Results

3.1. Baseline characteristics of study participants

Table 1 presents weighted characteristics of overall study participants. A total of 7,776 participants were included in the analysis, including 2,236 children (aged 6–19 years) and 5,540 adults (≥ 20 years). The weighted prevalence of asthma was 12.23% for children and 8.66% for adults, respectively. Weighted mean age ± standard error (SE) was 12.53 ± 3.90 years and 47.5 ± 16.73 years, respectively. For children, participants with asthma were likely to be non-Hispanic white, to have a family history of asthma, to have higher levels of creatinine-adjusted 3-PBA as compared to those without asthma. For adults, participants with asthma were likely to be female, as well as to have family history of asthma. Most notably, participants with asthma tend to have relatively higher levels of 3-PBA and creatinine-adjusted 3-PBA as compared to those without asthma.

Table 1
Basic characteristics of study participants by asthma in American children and adults, NHANES 2007–2014.

Characteristics (N = 7,776)	**Children aged 6–19 years (N = 2,236)**				**Adults aged 20 years and older (N = 5,540)**			
Participants	Overall	Without asthma	asthma	*p*-Value[a]	Overall	Without asthma	Asthma	*p*-Value[a]
n (%)	2236	1952 (87.77)	284 (12.23)		5540	5068 (91.34)	472 (8.66)	
Age (SD)	12.53 (3.90)	12.48 (3.88)	12.88 (4.02)	0.234	47.52 (16.73)	47.59 (16.74)	46.77 (16.55)	0.403
Sex, n (%)								
Male (%)	1183 (50.82)	1015 (50.38)	168 (54.01)		2686 (48.53)	2508 (49.72)	178 (36.05)	
Female (%)	1053 (49.18)	937 (49.62)	116 (45.99)	0.396	2854 (51.47)	2560 (50.28)	294 (63.95)	< 0.001
Race/ethnicity, n (%)								
Mexican American	561 (15.40)	515 (16.12)	46 (10.24)		821 (8.30)	788 (8.65)	33 (4.62)	
Other Hispanic	253 (6.91)	211 (6.66)	42 (8.72)		533 (5.28)	488 (5.32)	45 (4.81)	
Non-Hispanic White	622 (55.14)	545 (55.43)	77 (53.03)		2544 (68.90)	2302 (68.63)	242 (71.80)	
Non-Hispanic Black	570 (14.47)	473 (13.63)	97 (20.47)		1073 (10.14)	958 (9.85)	115 (13.15)	
Other Race	230 (8.08)	208 (8.16)	22 (7.53)	0.010	569 (7.38)	532 (7.55)	37 (5.62)	0.001
PIR, n (%)								
≤ 1.3	1025 (34.25)	888 (34.13)	137 (35.08)		1773 (21.91)	1573 (21.13)	200 (30.13)	
1.3–3.5	765 (36.14)	665 (35.16)	100 (43.18)		2047 (35.25)	1904 (35.82)	143 (29.25)	

NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; n, numbers of subjects; %, weighted proportion; BMI, body mass index;

PIR, family poverty income ratio; 3-PBA, 3-phenoxybenzoic acid.

[a]Difference in characteristics between asthma and no asthma.

[b]values were presented as medain [interquartile range].

Characteristics (N = 7,776)	Children aged 6–19 years (N = 2,236)				Adults aged 20 years and older (N = 5,540)			
≥ 3.5	446 (29.60)	399 (30.70)	47 (21.74)	0.059	1720 (42.84)	1591 (43.05)	129 (40.62)	0.006
BMI (kg/m^2), n (%)								
Normal	1891 (85.33)	1667 (85.75)	224 (82.34)		1620 (29.91)	1518 (30.48)	102 (23.94)	
Overweight	222 (9.56)	184 (9.18)	38 (12.28)		1845 (34.03)	1710 (34.37)	135 (30.49)	
Obesity	123 (5.11)	101 (5.07)	22 (5.38)	0.363	2075 (36.06)	1840 (35.15)	235 (45.57)	< 0.001
Cotinine								
< 0.015 (%)	605 (28.60)	547 (29.03)	58 (25.56)		1389 (28.45)	1295 (28.88)	94 (23.93)	
0.015–10 (%)	1517 (64.73)	1306 (64.36)	211 (67.42)		2787 (47.64)	2565 (47.84)	222 (45.54)	
≥ 10 (%)	114 (6.67)	99 (6.62)	15 (7.03)	0.707	1364 (23.91)	1208 (23.28)	156 (30.53)	0.036
Family history of asthma, n (%)								
No	1523 (69.35)	1437 (74.44)	86 (32.87)		4506 (81.29)	4245 (83.43)	261 (58.67)	
Yes	713 (30.65)	515 (25.56)	198 (67.13)	< 0.001	1034 (18.71)	823 (16.57)	211 (41.33)	< 0.001
Urinary creatinine (mg/dL)[b]	105.00 [62.00, 158.25]	103.00 [61.00, 157.00]	115.00 [74.00,172.00]	0.003	107.00 [62.00, 164.00]	106.50 [62.00, 164.00]	111.50 [62.00, 165.00]	0.608
3-PBA (μg/L)[b]	0.52 [0.19, 1.32]	0.51 [0.19, 1.29]	0.67 [0.23, 1.45]	0.057	0.52 [0.19, 1.30]	0.52 [0.18, 1.29]	0.58 [0.23, 1.52]	0.059

NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; n, numbers of subjects; %, weighted proportion; BMI, body mass index;

PIR, family poverty income ratio; 3-PBA, 3-phenoxybenzoic acid.

[a]Difference in characteristics between asthma and no asthma.

[b]values were presented as medain [interquartile range].

Characteristics (N = 7,776)	Children aged 6–19 years (N = 2,236)				Adults aged 20 years and older (N = 5,540)			
Creatinine adjustment	0.52	0.52	0.65	0.044	0.58	0.53	0.60	0.108
3-PBA medain (μg/L)[b]	[0.18, 1.39]	[0.18, 1.39]	[0.22, 1.49]		[0.23, 1.52]	[0.16, 1.36]	[0.21, 1.60]	
NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; n, numbers of subjects; %, weighted proportion; BMI, body mass index;								
PIR, family poverty income ratio; 3-PBA, 3-phenoxybenzoic acid.								
[a]Difference in characteristics between asthma and no asthma.								
[b]values were presented as medain [interquartile range].								

3.2. Association between creatinine-adjusted 3-PBA concentrations and asthma

Regression results for 3-PBA levels and asthma are presented in Table 2. In all three statistical models, the levels of urinary 3-PBA, whether modeled as a continuous variable (natural logarithms transformed) or a categorical variable (modeled as quartiles and took the 25th percentile as a reference), both show a positive association with asthma among children. After adjusting for sex, age, race/ethnicity, PIR, BMI, cotinine, creatinine, and history of asthma, OR between ln-transformed 3-PBA and asthma was 1.067 (95%CI: 0.962, 1.184). Compared to those in the lowest quartile, the adjusted ORs for asthma across increasing quartile were 1.297 (95%CI: 0.773, 2.177), 1.282 (95%CI: 0.765, 2.148), and 1.395 (95%CI: 0.880, 2.210), respectively. Among adults, this positive association became relatively weak. In the fully adjusted model (model 3), the ORs for asthma in the second, third, and fourth quantile was 1.080 (95%CI: 0.782, 1.491), 0.905 (95%CI: 0.635, 1.290), and 1.177 (95%CI: 0.778, 1.781), respectively, compared to those in the lowest quartile. Furthermore, we tested whether there was a non-linear association between ln-transformed 3-PBA and asthma. The restricted cubic spline plot curves in Fig. 2 suggested potential linear associations between 3-PBA concentrations and asthma among children and adolescents (*p* for nonlinearity = 0.693, 0.691 respectively). The restricted spline curve plot (Fig. 2B) shows a slightly increasing trend between levels of 3-PBA and odds risk of asthma among adults. We also explored the potential modification effects of sex and age (Table 3**)**. The positive association appeared to be more pronounced among girls and adolescents (aged 12–19 years). Compared with the lowest quartile, the ORs of asthma at the highest quartile were 3.305 (95%CI: 1.580, 6.912) and 1.989 (95%CI: 1.085, 3.648), respectively. The results also suggested that an increase in 3-PBA was significantly associated with asthma prevalence among girls and adolescents, with a significant dose-response association (*p* for trend = 0.032 and 0.044, respectively). The results of other subgroups were generally consistent with primary analysis although some results were not statistically significant.

Table 2
Association of urinary level of 3-PBA and self-reported asthma in American chindren and adults, NHANES 2007–2014.

	Children		**Adults**	
Model 1	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
ln-transformed 3-PBA	1.107 (0.995,1.232)	0.062	1.049 (0.946, 1.164)	0.360
Quartile 1	Reference		Reference	
Quartile 2	1.492 (0.874, 2.550)	0.140	1.102 (0.799, 1.519)	0.550
Quartile 3	1.629 (0.971, 2.735)	0.064	0.963 (0.671, 1.383)	0.840
Quartile 4	1.627 (0.988, 2.680)	0.056	1.222 (0.825, 1.811)	0.310
P for trend*	0.390		0.270	
Model 2				
ln-transformed 3-PBA	1.106 (0.993,1.231)	0.067	1.037 (0.930, 1.156)	0.507
Quartile 1	Reference		Reference	
Quartile 2	1.539 (0.903, 2.623)	0.111	1.088 (0.785, 1.508)	0.606
Quartile 3	1.590 (0.954, 2.651)	0.074	0.944 (0.649, 1.371)	0.756
Quartile 4	1.613 (0.995, 2.616)	0.052	1.152 (0.769, 1.727)	0.485
P for trend*	0.426		0.432	
Model 3				
ln-transformed 3-PBA	1.067 (0.962, 1.184)	0.214	1. 040 (0.929, 1.164)	0.492
Quartile 1	Reference		Reference	
Quartile 2	1.297 (0.773, 2.177)	0.318	1.080 (0.782, 1.491)	0.635
Quartile 3	1.282 (0.765, 2.148)	0.339	0.905 (0.635, 1.290)	0.574
Quartile 4	1.395 (0.880, 2.210)	0.153	1.177 (0.778, 1.781)	0.434

NHANES, National Health and Nutrition Examination Survey; 3-PBA, 3-phenoxybenzoic acid; OR, Odd ratio; CI,

confidence interval.

Model 1, only adjusted for urinary creatinine;

Model 2, further adjusted for age, sex, race/ethnicity, PIR and BMI;

Model 3, (completely adjusted model), further adjusted for cotinine and family history of asthma.

*Statistical tests for linear trends were conducted by modeling medlan values of quartiles as an continous variable.

	Children	Adults
P for trend*	0.433	0.356
NHANES, National Health and Nutrition Examination Survey; 3-PBA, 3-phenoxybenzoic acid; OR, Odd ratio; CI,		
confidence interval.		
Model 1, only adjusted for urinary creatinine;		
Model 2, further adjusted for age, sex, race/ethnicity, PIR and BMI;		
Model 3, (completely adjusted model), further adjusted for cotinine and family history of asthma.		
*Statistical tests for linear trends were conducted by modeling medIan values of quartiles as an continous variable.		

Table 3
Association between quartiles of 3-PBA with asthma, stratified by age and sex.

Participants		Subgroups	Quartile 1	Quartile 2 OR (95%CI) *p*-Value	Quartile 3 OR (95%CI) *p*-Value	Quartile 4 OR (95%CI) *p*-Value	*P* for trend*
Children	Sex	Male	Reference	0.875 (0.474, 1.613) 0.662	0.695 (0.352, 1.373) 0.288	0.882 (0.460, 1.689) 0.699	0.566
		Female	Reference	2.308 (1.024, 5.203) 0.044	2.358 (1.110, 5.005) 0.027	3.305 (1.580, 6.912) 0.002	0.032
	Age group	6–11 years	Reference	0.834 (0.359, 1.934) 0.666	0.996 (0.479, 2.071) 0.992	0.735 (0.318, 1.700) 0.464	0.560
		12–19 years	Reference	1.697 (0.930, 3.099) 0.084	1.622 (0.877, 3.001) 0.121	1.989 (1.085, 3.648) 0.027	0.044
Adults	Sex	Male	Reference	1.129 (0.579, 2.198) 0.717	1.050 (0.548, 2.013) 0.881	1.214 (0.605, 2.436) 0.578	0.619
		Female	Reference	1.006 (0.608, 1.664) 0.982	0.883 (0.502, 1.556) 0.662	1.154 (0.685, 1.945) 0.583	0.694
	Age group	20–39 years	Reference	1.756 (1.016, 3.034) 0.044	1.060 (0.637, 1.766) 0.818	1.280 (0.615, 2.667) 0.502	0.717
		40–59 years	Reference	0.678 (0.350, 1.313) 0.243	0.917 (0.537, 1.566) 0.746	1.057 (0.494, 2.265) 0.884	0.823

OR, Odd ratio; CI, confidence interval; 3-PBA, 3-phenoxybenzoic acid.

*Statistical tests for linear trends were conducted by modeling medlan values of quartiles as an continous variable.

Participants	Subgroups	Quartile 1	Quartile 2 OR (95%CI) *p*-Value	Quartile 3 OR (95%CI) *p*-Value	Quartile 4 OR (95%CI) *p*-Value	*P* for trend*
	≥ 60 years	Reference	0.861 (0.452, 1.642) 0.644	0.648 (0.320, 1.309) 0.221	1.134 (0.569, 2.260) 0.716	0.864
OR, Odd ratio; CI, confidence interval; 3-PBA, 3-phenoxybenzoic acid.						
*Statistical tests for linear trends were conducted by modeling medlan values of quartiles as an continous variable.						

4. Discussion

4.1. major findings

To the best of our knowledge, this is the first cross-sectional study exploring the potential association of pyrethroid exposure with asthma. Our primary analysis demonstrated a positive correlation between urinary 3-PBA concentrations and asthma among children and adults, although this association does not reach statistical significance. The positive correlation was stronger in children than in adults. When stratified by age and sex, we found a significant association between urinary 3-PBA and asthma in girls and adolescents (aged 12–19 years old). Pyrethroid insecticides are widely used in the US, hence the measurement of urinary pyrethroid metabolites is crucial in assessing human exposure and potential health effects among U.S population. Analysis originated from 2007–2012 NHANES data showed that the median urinary levels of 3-PBA in U.S. children and adults were 0.49 μg/L (interquartile range, 0.17–1.29 μg/L) and 0.47 μg/L (interquartile range, 0.14–1.22 μg/L), respectively (Lehmler et al. 2020). Notably, when we pooled data originated from 2007–2014 NHANES cycle, the median urinary level of 3-PBA was slightly higher than previous results. This finding may suggest that the general population may be at increased risk of pyrethroid exposure over time. Thus, more attention should be paid to the potential health hazards caused by pyrethroid exposure. Prior to our study, only a few epidemiology studies were focusing on potential relationships between pyrethroid metabolites and health conditions, such as hearing loss, diabetes, cardiovascular diseases, cognitive dysfunction, and mortality (Bao et al. 2020, Han et al. 2017, Kim et al. 2021, Park et al. 2019, Xu et al. 2020). Therefore, our research fills in the gap in exploring the potential impact of pyrethroid pesticides on asthma.

The major routes of pyrethroid exposure include oral and nasal inhalation, dietary intake and dermal contact (Darney et al. 2018). More specifically, children are exposed to pyrethroid pesticides through a number of pathways, including: living or studying near areas where pyrethroids are used, parents working in agriculture, eating and drinking contaminated food and water, and household pythroid useage (Buralli et al. 2020). One the one hand, children tend to eat, drink and breathe more in proportion to personal weight than adults (Hyland et al. 2017). One the other hand, children may be at high risk of pyrethroid exposure because of frequent interactions with their surroundings (Werthmann et al. 2021). Moreover, their ability to metabolize

environmental chemicals is weak due to immature bodily functions, rendering more serious health damage. Nevertheless, current evidence about how environmental chemicals exposure affects childhood asthma remains inconsistent. Several studies demonstrated that environmental chemicals had positive associations with asthma in children (Al-Daghri et al. 2013, Meng et al. 2016, Zhang et al. 2021). It was found that the internal exposure concentrations of Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs) were positively associated with childhood asthma (Meng et al. 2016). A systematic review summarizing results from existing epidelogical studies also demonstraed that most studies found positive associations with pesticide exposure and children's respiratory and allergic effects such as asthma (Buralli et al. 2020). However, Odebeatu et al. reported urinary concentration of phthalate metabolites was not significantly associated with current asthma in children (Odebeatu et al. 2019). Similarly, Jackson-Browne et al. also observed a weak association between serum per- and polyfluoroalkyl substances (PFAS) concentration and increased prevalence of asthma in U.S. young children based on the NHANES survey (Jackson-Browne et al. 2020). The development of asthma in children is complex and varied by age, herein, we should interpret this finding with caution, and subsequent prospective studies are in great need to further illustrate the correlation between pyrethroid exposure and asthma among children. For adults, although higher levels of 3-PBA was positively associated with asthma, this association was relatively weak.

4.2. similar studies

Prior to our analysis, although researchers investigated asthma triggered by pyrethroid exposure, no population-based studies exploring potential effects of pyrethroid exposure on asthma were conducted, as relevant studies mainly focused on animal experiments and case reports. Animal studies showed that synthetic pyrethroid insecticides injected in mice can cause asthma symptoms such as runny nose and severe coughing (Mohi El-Din et al. 2014). It was reported that higher levels of cis-permethrin was associated with the development of respiratory symptoms (Reardon et al. 2009). Additionally, a couple of case reports found that inhaling pyrethroid pesticides can trigger symptoms of respiratory irritation, such as sneezing, coughing, chest tightness, and shortness of breath (Lessenger 1992, Moretto 1991, Salome et al. 2000, Spencer &O'Malley 2006). Further, piperonyl butoxide (a synergist for residential pyrethroid insecticides) was shown to be implicated in asthma and/or airway inflammation (Perzanowski et al. 2010). Xu et al. found mosquito-repellent incense was one of the triggers of asthma while the active ingredient of most mosquito-repellent incense was pyrethroid insecticides, which indirectly supported our findings as well (Xu et al. 2016). Moreover, it was reported that urinary 3-PBA concentration was negatively associated with pulmonary function in children, indicating an adverse impact on the respiratory system (Hu et al. 2021). However, there were still inconsistent findings. It was found that higher prenatal levels of cis-permethrin were associated with childhood cough, whereas age 5–6 residential measures of permethrins were not associated with wheeze or asthma among children (Liu et al. 2012, Reardon et al. 2009). Osimitz et al. suggested that pyrethrins and piperonyl butoxide were not likely to cause asthma-related reactions (Osimitz et al. 2009). A recently published scoping review demonstrated that PAHs and organophosphate insecticides were associated with asthma, while pyrethroids may be only potential risk factors for asthma. Admittedly, it is difficult to distinguish the independent role of pyrethroid exposure on prevalence of asthma symptoms in our

analysis. Therefore, a more comprehensive study design exploring associations between exposure to multiple pyrethroids and risk of asthma is needed.

4.3. Underlying mechanisms

Although the potential biological mechanisms underlying the increased risk of asthma attributed to pyrethroid exposure remains to be elucidated, there are still some potential explanations for this association. It is generally accepted that immune abnormalities play an important role in the pathogenesis of asthma. Studies show that pyrethroid insecticides have an adverse effect on the immune system and cause numerous immune disorders and contributing to the impairment of immunity in humans and animals (Chrustek et al. 2018, Skolarczyk et al. 2017). On the one hand, pyrethroid metabolites affect the immune function of the body by damaging cellular components such as lipids, proteins, and DNA (Huang et al. 2016, Ravula &Yenugu 2021). On the other hand, since the immune system is tightly regulated by different hormones, pyrethroids with endocrine-disrupting effects can also interfere with immune function by affecting the synthesis and expression of hormones (Brander et al. 2016). Another important toxicological mechanism is allergenicity (Macan et al. 2006). Immunoglobulin E (IgE) is the primary antibody causing type I hypersensitivity. Abou El-Magd et al. found that chronic exposure to pyrethroid pesticides resulted in elevated serum IgE, suggesting such pesticides may increase the risk of allergic reactions (Abou El-Magd et al. 2011). For mammals, pyrethroids also can exert neurotoxicity through voltage-gated channels, leading to hyperexcitement (Soderlund 2012, Soderlund et al. 2002). Repetitive firing of sensory nerve endings often results in sensory abnormalities and respiratory irritation (Vijverberg &van den Bercken 1990). Furthermore, airway narrowing is well known to be the hallmark and ultimate endpoint of an asthma attack (Brown 2014). Previous studies suggested that pyrethroids, as a neurotoxic agent, may act on airway smooth muscle neurons via voltage-gated ion channels, resulting in prolonged contraction of smooth muscle and airway narrowing, which may play an exacerbating effect on the occurrence and development of asthma (Ray &Fry 2006).

4.4. Strengthens and limitations

Several strengths should be acknowledged in our study. As the first nationally representative study examining the association between pyrethroid exposure and asthma, our principal findings not only filled the gap on this topic but also are inspiring to explore pyrethroid exposure and asthma. For example, children appeared to be more sensitive to asthma events that may be triggered by pyrethroid exposure. In addition, both ln-transformed 3-PBA and quantiles of 3-PBA concentrations were modeled in statistical analysis, strengthening the reliability of results. Nevertheless, it is noteworthy of some limitations. First, due to the heterogeneity of the clinical presentation of asthma, cases of asthma may not be adequately identified by healthcare providers. Similarly, the evaluation of the outcome was not defined by International Classification of Diseases (ICD), thus misclassification bias and recall bias inevitably existed in the questionnaire process. Second, a single measure of urinary 3-PBA may not be sufficient to characterize average exposure (Morgan et al. 2016). Because a single sampling only represents related 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. Third, given the nature of the cross-sectional study, this study design has weak explanatory power for causal relationships. Last, this study cannot rule out the

possibility of other co-exposed chemical pollutants exerting an effect on asthma, such as other pesticides, bisphenol A and phthalates. We can not role out the possibility that the other co-occurring pesticides or other chemicals that could be responsible for the observed increase in asthma occurrence.

5. Conclusion

In summary, we observed a positive association between pyrethroid exposure and asthma, especially for children. This study demonstrated a strong link between pyrethroid exposure and asthma among girls and adolescents. As pyrethroid exposure has become a widespread environmental health issue, there is a great need to conduct longitudinal studies and experimental studies to verify our findings and further elucidate potential mechanisms. Certainly, further studies are needed to evaluate the possible pathogenic role of pyrethroid insecticides in children with asthma.

Declarations

Authorship contributions

Xianwei Guo: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing original draft, Writing review &editing.

Ning Li: Methodology, Validation, Formal analysis, Investigation, Data curation, Writing original draft, Visualization.

Hao Wang: Methodology, Formal analysis, Investigation, Data curation, Visualization.

Qiwei Liang: Writing original draft

Qiuxia Song and **Mingming Liang** : Formal analysis, Data curing

Wanying Su and **Xiuxiu Ding**: Software, Visualization

Chenyu Sun, **Scott Lowe** and **Rachel Bentley**: Writing review &editing

Yehuan Sun: Conceptualization, Resources, Supervision, Writing review &editing.

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

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Conflict of Interest Statement

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

Data availability

Not applicable

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Figures

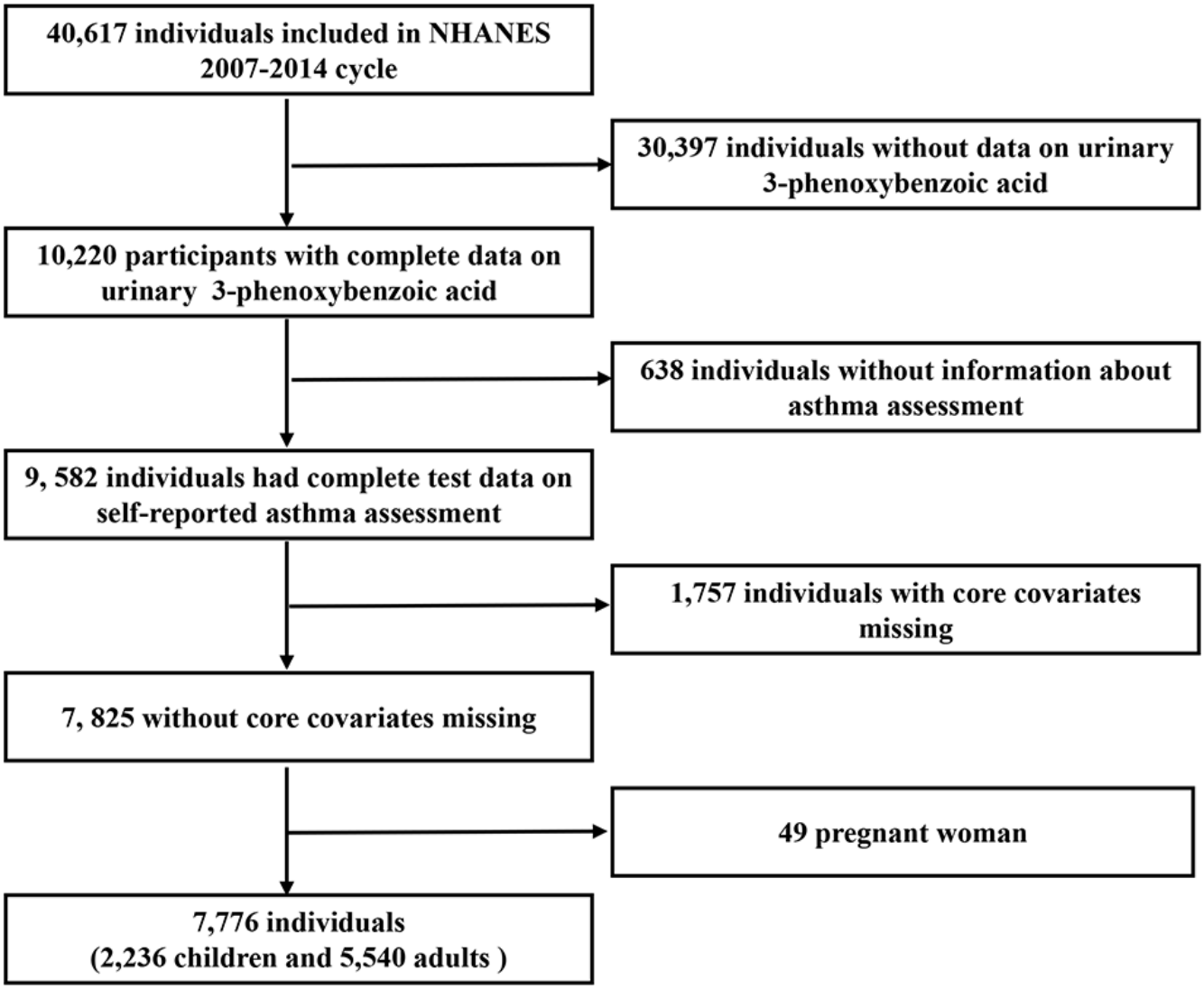

Figure 1

Flow chart of population included in our final analysis (N=7,776), NHANES 2007-2014.

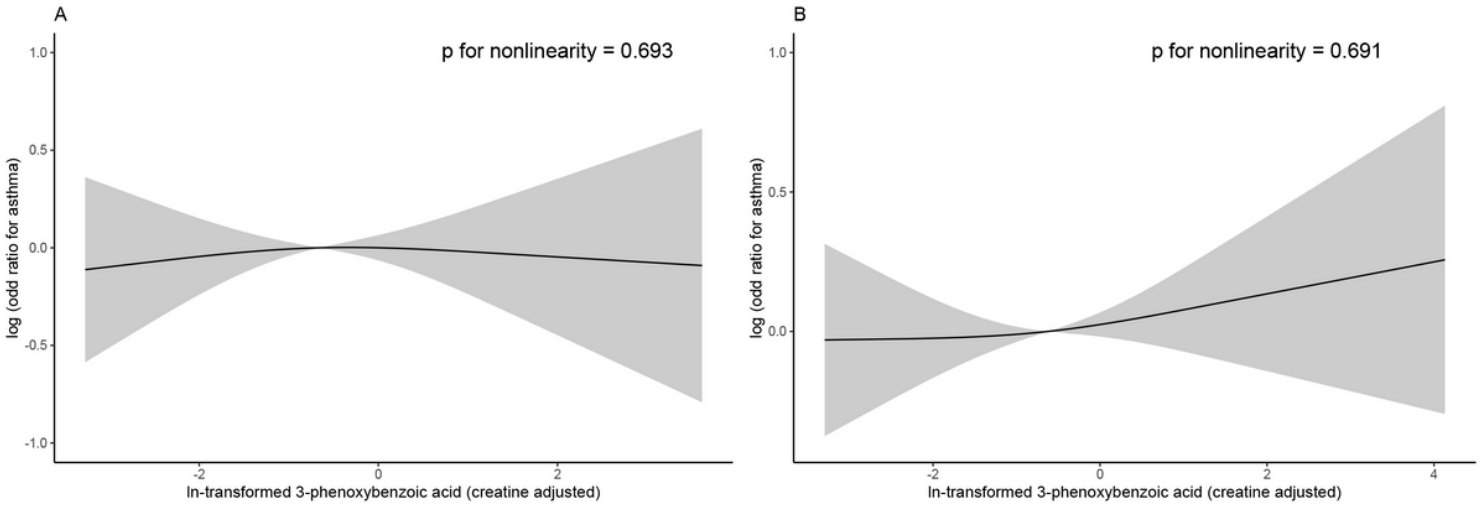

Figure 2

The restricted cubic spline plot of the association between ln-transformed 3-PBA and asthma among children and adults. The associations were adjusted for age, sex, race/ethnicity, PIR, BMI, serum cotinine, urinary creatinine, and family history of asthma. A is for children and B is for adults.