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Urinary 3-phenoxybenzoic acid (3-PBA) concentration and pulmonary function in children: A National Health and Nutrition Examination Survey (NHANES) 2007–2012 analysis☆

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ABSTRACT

Epidemiological studies have reported association of urinary 3-phenoxybenzoic acid (3-PBA), a major metabolite of pyrethroid insecticides (PYRs), with respiratory disease. However, knowledge regarding its effect on pulmonary function in susceptible children is limited. This study aimed to assess the associations between environmental 3-PBA concentrations and pulmonary function in children aged 6–17 years. Using data on 1174 children aged 6–17 years from the U.S. National Health and Nutrition Examination Survey (NHANES) 2007–2012, the exposure to PYRs was assessed by measuring urinary 3-PBA concentrations and pulmonary function was assessed by spirometry. Multivariable linear regression and generalized linear models (GLMs) were used to examine the associations between 3-PBA concentrations and pulmonary function in children, controlling for confounders. We found that 3-PBA concentrations were inversely associated with forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF) in the pediatric population (p-trends < 0.05). When stratified by age (6–10 and 11–17 years) and gender (boys and girls), the adverse effects of PYR exposures on pulmonary function were more pronounced among boys aged 11–17 years. Among this age group, 3-PBA concentrations were negatively associated with FEV_1, FVC, forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$), and PEF. However, among children aged 6–10 years, no associations were found between 3-PBA concentrations and any of the pulmonary function measures, in either boys or girls. Our findings suggest that environmental PYR exposures may adversely affect children's pulmonary function, with the strongest associations among 11–17 years old boys.

Author contributions

GD conceived and supervised the manuscript. PH and WS drafted the manuscript. AV, HG, CC, and ML provided critical comments and substantially revised the manuscript. All authors reviewed and approved this manuscript. E-mail addresses.

1. Introduction

Pyrethroids (PYRs) are a class of synthetic insecticides that have become widely used, primarily due to low mammalian toxicities and persistency (Horton et al., 2011; United States Environment Protection Agency (U.S. EPA). 2013b). PYRs are frequently used for agriculture, residential pest control, and public health, accounting for more than 30% of insecticides on the world market (U.S. EPA, 2017; Liu et al., 2019). Exposure to pesticides among the general population is mainly through diet, with other contributions from inhalation of contaminated air, dermal contact absorption, and unintentional ingestion (Barr et al., 2010; Ye et al., 2019). 3-

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Abbreviations

3-PBA	3-phenoxybenzoic acid
4-F-3PBA	4-fluoro-3-phenoxybenzoic acid
trans-DCCA	trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid
cis-DBCA	cis-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid
PYRs	Pyrethroid insecticides
ATS	American Thoracic Society
ERS	European Respiratory Society
CHMS	Canadian Health Measures Survey
CDC	Centers for Disease Control
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
CPES	Children's Pesticide Exposure Study
95% CI	95% Confidence interval
GLM	Generalized linear model
Cr	Creatinine;
FVC	Forced vital capacity
FEV_1	Forced expiratory volume in 1 s
$FEF_{25-75\%}$	Forced expiratory flow between 25% and 75% of FVC
PEF	Peak expiratory flow
URTI	Upper respiratory tract infection
LOD	Limit of detection
PIR	Poverty income ratio
BMI	Body mass index
IQR	Interquartile range
CTEPP	Children's Total Exposure to Persistent Organic Pollutants
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas
OP	Organophosphate
OCs	Organochlorine compounds
p.p'-DDE	p.p'-dichlorodiphenyldichloroethylene

phenoxybenzoic acid (3-PBA), a non-specific metabolite of several commonly used PYRs, including permethrin, cypermethrin, cyhalothrin, deltamethrin, and fenvalerate, has been measured in urine samples in several nation-wide biomonitoring programs throughout the world (Hwang et al., 2019; Lee et al., 2019). In the U.S. general population, higher 3-PBA concentrations have been reported in children compared with adults, raising concerns about the potential health consequences of PYR exposures in children (Barr et al., 2010; Ferguson et al., 2017; Lee et al., 2019).

Previous studies on the impact of PYR exposures on children's respiratory health have mostly focused on the development of allergic diseases (Kim et al., 2019; Liu et al., 2012; Reardon et al., 2009; Raherison et al., 2019; Salameh et al., 2003, 2006; Salam et al., 2004). Several prospective studies documented that prenatal PYR exposures may increase the risk of early-onset eczema, asthma, and respiratory tract infections among school-aged children (Liu et al., 2012; Reardon et al., 2009). Cross-sectional and case-control studies also suggested that postnatal exposures to PYR have been associated with asthma, wheezing, and allergic effects in early childhood (Raherison et al., 2019; Salameh et al., 2003, 2006; Salam et al., 2004). Evidence from animal models indicated that pesticide exposures exacerbate or trigger asthma attacks through stimulation of inflammatory cells, damaged bronchial epithelium, and induced airway hyper-reactivity and airway remodeling (Ban et al., 2006; Fryer et al., 2004; Nishino et al., 2013). Only a few studies have examined the effects of PYR exposures on pulmonary function, especially in developing children. Most recently, a nationally representative Canadian study, using data from the Canadian Health Measures Survey (CHMS), found associations between total PYR metabolites concentrations (ΣPYR) and lower forced expiratory volume in 1 s (FEV_1) in children aged 6–11 years (n = 1023), and lower forced vital capacity (FVC) in adolescents aged 12–19 years (n = 974) (Ye et al., 2016a). However, despite the existence of objective measures of PYR exposure and pulmonary function, the associations have not been well characterized among other pediatric populations or if there is any gender difference in effects. Considering that PYR metabolite concentrations in urine vary across the geographical regions, countries, and populations, a study on a nationally representative U.S. population is warranted.

Therefore, in the present study, we evaluated the exposure levels to PYRs in 6–17 years old children from the U.S. National Health and Nutrition Examination Survey (NHANES) 2007–2012, and then examined the relationships between the 3-PBA concentrations and children's pulmonary function. Furthermore, we also evaluated age and gender as potential effect modifiers of these associations.

2. Materials and methods

2.1. Study population

In this study, we used publicly available data from the NHANES, a U.S. nationwide cross-sectional survey conducted by the Centers for Disease Control and Prevention (CDC)'s National Center for Health Statistics (NCHS). The survey consisted of a combination of interviews, physical examination, and laboratory tests to assess the health and nutritional status of adults and children. Detailed description and protocols about the NHANES study can be found online at http://www.cdc.gov/nchs/nhanes.htm. All participants provided written informed consent, and the NCHS obtained institutional review board approval to conduct the surveys.

The population-based cross-sectional study screened the data of participants in three consecutive NHANES cycles (NHANES, 2007–2008, 2009–2010, and 2011–2012). Data on pulmonary function parameters and PYR exposure biomarkers were retrieved from the survey dataset. PYR exposure measurements were conducted on a random subsample of participants ≥6 years of age. For the three NHANES cycles, a total of 8030 participants were included as follow: 2694 in the 2007–2008 cycle, 2831 in the 2009–2010 cycle, and 2505 in the 2011–2012 cycle. The study population was restricted to children aged 6–17 years, thus reducing the sample size to 2146 eligible children. Of these, 116 children with missing data on 3-PBA measurements were excluded. We further excluded children with missing data on measures of spirometry (n = 560), serum cotinine (n = 2), family income to poverty ratio (n = 85), and urinary creatinine (n = 209). The final study population consisted of 1174 children with complete data on the covariates and outcomes (Fig. 1).

2.2. Demographic covariates

Information on covariates was collected from the self-reported questionnaire, physical examination, and laboratory measurements. Age, gender, race/ethnicity, and poverty status were ascertained through the questionnaires. We categorized age into 6–10 and 11–17 years, based on the protocol used for spirometry which

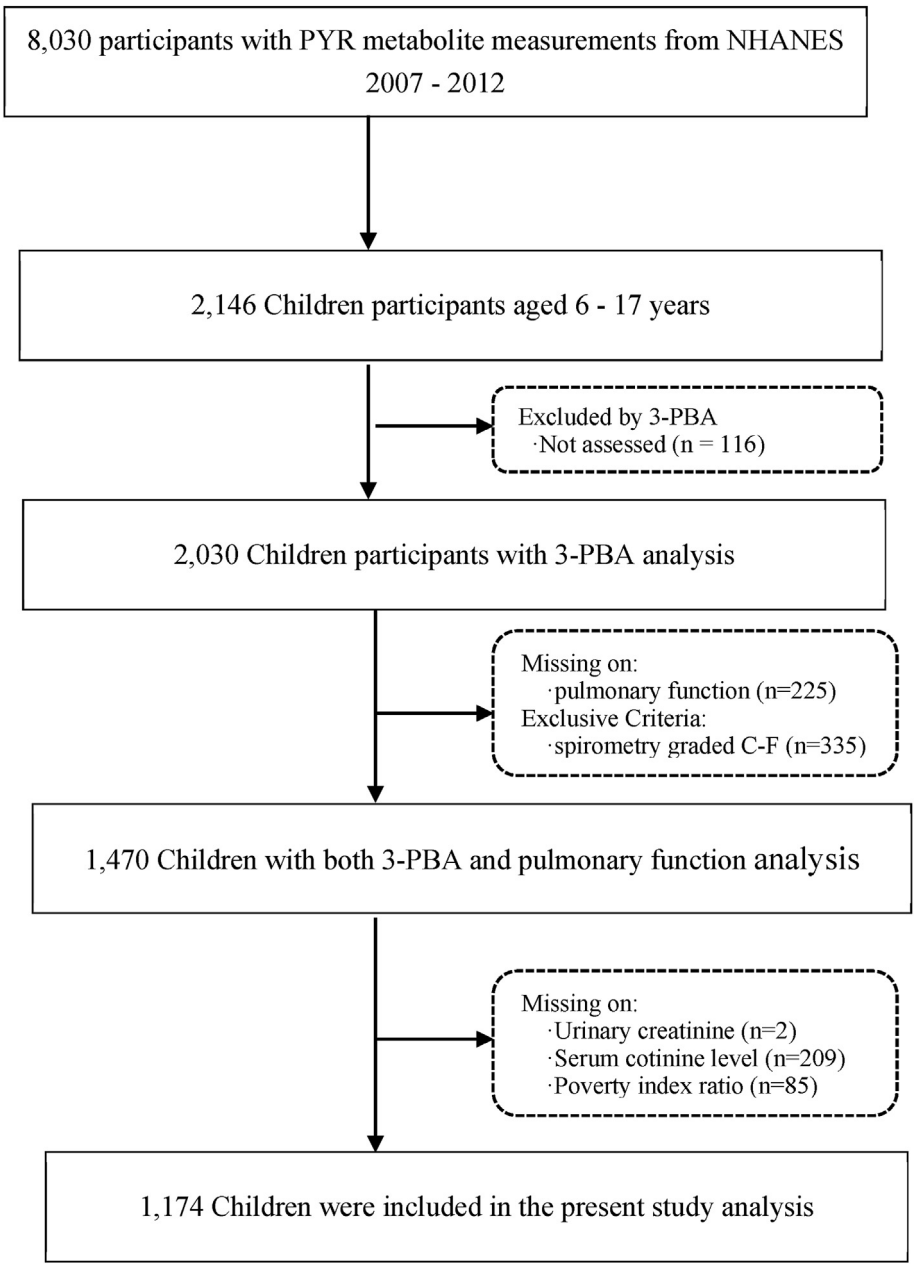

Fig. 1. Flow diagram of the study population.

was different in children 10 and younger compared to those of 11 years and older (NCHS. 2007–2008). Poverty status was determined by the poverty income ratio which was calculated by dividing the family income by the poverty guidelines of a specific survey year. Race/ethnicity was classified as "non-Hispanic white", "non-Hispanic black", "Mexican-American," and "Other". Age and gender-specific growth charts were used to calculate body mass index (BMI) which was then categorized as underweight (BMI < 5th percentile), normal weight (BMI 5th to < 85th percentile), overweight (BMI 85th to < 95th percentile), or obese (BMI ≥ 95th percentile) (Kuczmarski et al., 2000). Serum cotinine concentrations (a biomarker for smoking status) was categorized as < limit of detection (LOD), < 1 ng/mL, and ≥1 ng/mL.

2.3. Exposure information

The most frequently utilized PYR biomarker is 3-PBA, which is a urinary metabolite of several PYRs including permethrin, cypermethrin, and their degradates (Hwang et al., 2019; Lee et al., 2019). In our study, we used urinary metabolite measurements of 3-PBA in spot urine samples provided by participants during the physical examination. The other metabolites [4-fluoro-3-phenoxybenzoic acid (4-F-3PBA), trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (trans-DCCA), and cis-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (cis-DBCA)] were also measured; however, they were not finally included in our analyses because of low detection frequencies (≤15%). Samples were measured using a high-performance liquid

chromatography/tandem mass spectrometry at CDC's National Center for Environmental Health laboratory. The details about detection methods and quality control were described elsewhere (Barr et al., 2010) and can be found at the official site (https://wwwn.cdc.gov/Nchs/Nhanes/2007-2008/UPHOPM_E.htm).

The limit of detections (LODs) for 3-PBA, 4-F-3PBA, trans-DCCA, and cis-DBCA were 0.1 μg/L, 0.1 μg/L, 0.6 μg/L, and 0.5 μg/L, respectively. The concentrations below the LOD were replaced with LOD/$\sqrt{2}$. The metabolite concentrations were adjusted using creatinine levels to correct for variable urine dilutions in the spot urine samples. Urine creatinine levels were assessed by the modified Jaffe colorimetric method using automated Beckman analyzers (Beckman Instruments, Inc., Brea, CA) (Barr et al., 2010).

2.4. Outcome assessment

Participants aged ≥6 years were eligible for the spirometry component of the NHANES. Participants with an acute respiratory condition, with persistent cough, taking medication for tuberculosis, and those who had recent thoracic or abdominal surgery were excluded from pulmonary function testing. The spirometry testing protocol and quality control procedures followed the American Thoracic Society (ATS) guidelines (CDC. 2011). Every subject repeated the test at the most eight times to achieve at least three acceptable and reproducible criteria. The forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were rated by quality grade (A to F), and we further restricted our analysis to participants with FEV_1 and FVC values grade A or B (Miller et al., 2005). We focused our data analysis on five pulmonary function metrics, which included FVC, FEV_1, FEV_1: FVC ratio, forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$), and peak expiratory flow rate (PEF).

2.5. Statistical analysis

Descriptive statistical analyses summarized demographic characteristics, urinary 3-PBA concentrations and pulmonary function of the study population. Demographic characteristics were compared between the pesticide data set (n = 2030) and study population (n = 1174) using Mann-Whitney *U* test for the continuous variables and Chi-square tests for the categorical variables. Because of the high proportion (22.6%) of samples with 3-PBA values < LOD, a three-level ordinal variable was defined: all samples with concentrations < LOD were assigned to the low-exposure group (reference group), detectable concentrations < median, and detectable concentrations ≥ median to form the middle- and high-exposure groups. The distributions of pulmonary function (FEV_1, FVC, FEV_1: FVC, $FEF_{25-75\%}$, PEF) were non-normally distributed; thus, $\log_{10}$-transformed values were modeled as continuous variables in the analysis.

The associations of 3-PBA concentrations as continuous variable with pulmonary function in children were first analyzed by multivariable linear regression model. Considering the skewed distribution of 3-PBA concentrations, we used the $\log_{10}$-transformed values in the linear models. The 3-PBA concentrations were also set as categorical variables and analyzed by generalized linear models (GLMs) using the low-exposure group as the reference group. Tests for trend (*p*-trend) were conducted by treating ordinal categories of 3-PBA as an integer values in the linear model (Meeker et al., 2011).

We applied the same approach to perform several sensitivity analyses to confirm our results. In the sensitivity analyses, we reran all models for the lung function measures by using z-scores according to the Global Lung Function Initiative equations (Quanjer et al., 2012). In order to explore potential effect modification of age (6–10 and 11–17 years) and gender (boys and girls), we also stratified analyses by age and gender. The cut-off points to categorize the population into two age groups, accounted for the changes in the association between age and pulmonary function during the children growth spurt that occurs around the ages of 10–12 years (Wang et al., 1993). Potential confounders, selected from previous studies of PYR exposures on respiratory symptoms, included age, gender, height, race, BMI-for age, NHANES cycles, serum cotinine concentrations, and poverty income ratio (PIR). In our study, there were 127 children who had wheezing or whistling in the past 12 months according to the Respiratory Health questionnaire data. Since pulmonary function parameters may be adversely affected by wheezing, we also adjusted for the binary variable (yes/no) answer to the questionnaire item "Have you had wheezing or whistling in your chest in the past 12 months?" in our regression models.

All statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL); $p < 0.05$ (two-tailed) was considered statistically significant.

3. Results

The socio-demographic characteristics of the participants included in the study were shown in Table 1. The mean (standard deviation, SD) age was 11.58 (3.35) years and 52% of the participants were boys. More than half of the children were normal weight (57.7%), with 2.2% underweight, and 40.1% overweight or obese. Only 10% children in our study reported wheezing or whistling in the past 12 months. FVC and FEV_1 values were lower among girls compared to boys, differed by race/ethnicity, and increased with age. The demographic characteristics were similar between the 2030 children in the PYR data set and children in this study (n = 1174) (Table S1).

The distributions of pulmonary function measures and urinary 3-PBA concentrations were summarized in Table 2. The geometric mean (interquartile range, IQR) for FEV_1, FVC, FEV_1: FVC, $FEF_{25-75\%}$, and PEF were 2380.0 (1780.0–3190.0) mL, 2770.0 (2070.0–3700.0) mL, 0.86 (0.83–0.91) %, 2650.0 (2000.0–3680.0) mL/s, and 5540.0 (4220.0–7350.0) mL/s, respectively. The detection frequency of 3-PBA measured in urine was 77.4%. The median (IQR) of unadjusted and creatinine-adjusted 3-PBA concentrations were 0.46 (0.14–1.20) μg/L and 0.50 (0.21–1.21) μg/g Cr, respectively.

The characteristics of the study population related to the 3-PBA concentrations were presented in Table S2. Children with higher 3-PBA concentrations were more likely to be girls, aged 11–17 years old, non-Hispanic White, and have more vegetables in their diet. In addition, children in the lowest PIR had higher 3-PBA concentrations than children in the higher PIR. The serum cotinine level was positively associated with the 3-PBA concentrations.

The associations of urinary 3-PBA concentrations with pulmonary function were summarized in Table 3. We found that 3-PBA concentrations, when treated as continuous variables, were negatively associated with FEV_1 [β = −0.01, 95% confidence interval (CI): −0.02, −0.002], FVC (β = −0.01, 95% CI: −0.02, −0.004), and PEF (β = −0.01, 95% CI: −0.02, −0.01). No associations were found between urinary 3-PBA concentrations and other pulmonary function measures. When 3-PBA concentrations were treated as categorical variables, the results were similar to those of continuous variables, and all of the negative trends were significant (*p*-trends < 0.05). In addition, we conducted sensitivity analyses for the pulmonary function measurements using z-scores, and the results were similar (Table S3).

In the sensitivity analyses, where we assessed whether age or gender modified the associations between 3-PBA concentrations

Table 1
Demographic characteristics of children 6–17 years of age: NHANES 2007–2012 (n = 1174).

	Study population		FEV_1 (mL)	FVC (mL)	FEV_1: FVC	$FEF_{25-75\%}$ (mL/s)	PEF (mL/s)
Characteristic	N	(%)	Mean ± SD				
Time of life (Years)							
6 - 10	481	41.0	1720.0 ± 415.0	2000.0 ± 495.0	0.86 ± 0.06	1990.0 ± 615.0	4110.0 ± 1070.0
11–17	693	59.0	3150.0 ± 796.0	3670.0 ± 945.0	0.86 ± 0.06	3520.0 ± 1086.0	7190.0 ± 1760.0
Gender							
Boys	613	52.2	2780.0 ± 1100.0	3270.0 ± 1290.0	0.85 ± 0.06	3020.0 ± 1320.0	6310.0 ± 2410.0
Girls	561	47.8	2330.0 ± 743.0	2670.0 ± 849.0	0.87 ± 0.06	2750.0 ± 1010.0	5510.0 ± 1700.0
Race							
White (non-Hispanic)	356·	30.3	2640.0 ± 980.0	3120.0 ± 1190.0	0.85 ± 0.06	2870.0 ± 1110.0	5932.0 ± 2135.0
Mexican American	288	24.5	2630.0 ± 1010.0	3040.0 ± 1180.0	0.87 ± 0.06	3000.0 ± 1230.0	5830.0 ± 2130.0
Black (non-Hispanic)	278	23.7	2390.0 ± 931.0	2770.0 ± 1070.0	0.86 ± 0.06	2750.0 ± 1230.0	5920.0 ± 2230.0
Other	252	21.5	2570.0 ± 928.0	2970.0 ± 1070.0	0.87 ± 0.06	2950.0 ± 1200.0	6034.0 ± 2070.0
Serum cotinine level							
Below LOD	309	26.3	2550.0 ± 870.0	2960.0 ± 1020.0	0.86 ± 0.06	2870.0 ± 1070.0	5830.0 ± 1930.0
<1 ng/ml	726	61.8	2530.0 ± 990.0	2940.0 ± 1149.0	0.86 ± 0.06	2870.0 ± 1230.0	5890.0 ± 2170.0
≥1 ng/mL	139	11.8	2770.0 ± 1080.0	3260.0 ± 1290.0	0.85 ± 0.06	3040.0 ± 1270.0	6360.0 ± 2420.0
Poverty index ratio (PIR)							
Below poverty level (<1.85)	649	55.3	2470.0 ± 930.0	2865.0 ± 1083.0	0.87 ± 0.06	2830.0 ± 1170.0	5740.0 ± 2090.0
Above poverty level (1.85–5)	525	44.7	2670.0 ± 1004.0	3130.0 ± 1190.0	0.86 ± 0.06	2970.0 ± 1210.0	6160.0 ± 2180.0
BMI-for age [a]							
Underweight	26	2.2	2060.0 ± 538.0	2370.0 ± 640.0	0.88 ± 0.05	2332.0 ± 670.0	4840.0 ± 1190.0
Average	677	57.7	2470.0 ± 970.0	2850.0 ± 1120.0	0.87 ± 0.06	2820.0 ± 1190.0	5750.0 ± 2170.0
Overweight	211	18.0	2640.0 ± 1020.0	3070.0 ± 1160.0	0.86 ± 0.06	3006.0 ± 1290.0	6170.0 ± 2190.0
Obese	260	22.1	2780.0 ± 930.0	3320.0 ± 1140.0	0.84 ± 0.06	3040.0 ± 1120.0	6290.0 ± 2020.0
NHANES cycles							
2007–2008	360	30.7	2570.0 ± 1003.0	3010.0 ± 1180.0	0.86 ± 0.06	2890.0 ± 1270.0	5900.0 ± 2190.0
2009–2010	416	35.4	2620.0 ± 981.0	3060.0 ± 1180.0	0.86 ± 0.06	2910.0 ± 1140.0	6010.0 ± 2110.0
2011–2012	398	33.9	2450.0 ± 921.0	2870.0 ± 1050.0	0.87 ± 0.06	2870.0 ± 1160.0	5860.0 ± 2130.0
Urinary creatinine (mg/dL) [b]							
<102.0	584	49.7	2313.0 ± 890.0	2680.0 ± 1050.0	0.87 ± 0.06	2650.0 ± 1080.0	5405.0 ± 2000.0
≥102.0	590	50.3	2800.0 ± 980.0	3280.0 ± 1150.0	0.86 ± 0.06	3130.0 ± 1240.0	6440.0 ± 2160.0
Have you had wheezing or whistling in your chest in the past 12 months?							
Yes	127	10.8	2580.0 ± 1080.0	3055.0 ± 1270.0	0.85 ± 0.06	2800.0 ± 1310.0	5957.0 ± 2370.0
No	1047	89.2	2560.0 ± 960.0	2970.0 ± 1120.0	0.86 ± 0.06	2900.0 ± 1180.0	5920.0 ± 2110.0

[a] NHANES classified participants as underweight (BMI < 5th percentile), normal weight (BMI 5th to < 85th percentile), overweight (BMI 85th to < 95th percentile), or obese (BMI ≥ 95th percentile) according the U.S. CDC gender-specific growth charts based on age in months and years.
[b] Cut-off points: median for urinary creatinine.

Table 2
The distributions of pulmonary function and pyrethroid urinary metabolite concentrations in children aged 6–17 years.

Characteristic	Detection Rate	GM	Percentile			
	N (%)		25th	50th	75th	95th
FEV_1 (mL)	/	2380.0	1780.0	2500.0	3190.0	4420.0
FVC (mL)	/	2770.0	2070.0	2840.0	3700.0	5130.0
FEV_1: FVC (%)	/	0.86	0.83	0.87	0.91	0.95
$FEF_{25-75\%}$ (mL/s)	/	2650.0	2000.0	2680.0	3680.0	5100.0
PEF (mL/s)	/	5540.0	4220.0	5700.0	7350.0	9800.0
3-PBA (μg/L)	909 (77.4)	0.46	0.14	0.45	1.20	5.74
3-PBA (μg/g Cr)	909 (77.4)	0.50	0.21	0.46	1.21	5.51

GM: Geometric Mean; LODs: 3-PBA, 0.1 μg/L.

and pulmonary function measures, we found that the adverse effect of 3-PBA on pulmonary function was stronger among boys aged 11–17 years (Table 4). Among this age group, 3-PBA concentrations, when treated as continuous variables, were negatively associated with FEV_1 (β = −0.02, 95% CI = −0.04, −0.01), FVC (β = −0.02, 95% CI = −0.03, −0.01), $FEF_{25-75\%}$ (β = −0.03, 95% CI = −0.05, −0.002), and PEF (β = −0.03, 95% CI = −0.05, −0.01). The 3-PBA concentrations as categorical variables were negatively associated with PEF (*p*-trend = 0.045). Positive association was only found between 3-PBA and FEV_1: FVC in girls aged 11–17 years. However, among children aged 6–10 years, no associations were found between 3-PBA concentrations and any of the pulmonary function measures

Table 3
Regression Coefficients (95% CI) for pulmonary function by urinary 3-PBA in children aged 6–17 years in the NHANES 2007–2012 survey (n = 1174).

		FEV_1 (mL)	FVC (mL)	FEV_1: FVC (%)	$FEF_{25-75\%}$ (mL/s)	PEF (mL/s)
Exposure (μg/g)	N	Adjusted β (95% CI)[a]				
3-PBA						
Continuous[b]	1174	−0.01 (−0.02, −0.002)*	−0.01 (−0.02, −0.004)*	0.002 (−0.001, 0.01)	−0.01 (−0.02,0.01)	−0.01 (−0.02, −0.01)*
Low (≤0.10)	265	Reference	Reference	Reference	Reference	Reference
Middle (0.22–0.46)	454	0.003 (−0.01, 0.02)	0.01(-0.01, 0.01)	0.003 (−0.001, 0.01)	0.01 (−0.01, 0.03)	0.01 (−0.01, 0.02)
High (0.47–1.21)	455	−0.01 (−0.03, 0.001)	−0.02 (−0.03, −0.002)	0.002 (−0.002, 0.01)	−0.01 (−0.03, 0.01)	−0.01 (−0.03, 0.002)
p for trend		0.025*	0.008*	0.404	0.286	0.042*

*Significant at $p < 0.05$.
[a] Adjusted for age, gender, height, race, BMI-for age, NHANES cycles, serum cotinine concentrations, family income to poverty ratio, and "have you had wheezing or whistling in your chest in the past 12 months?" (yes/no).
[b] Urine 3-PBA concentrations were adjusted for creatinine then $\log_{10}$-transformed.

Table 4
Regression Coefficients (95% CI) for the association between the urinary 3-PBA and pulmonary function stratified by age (6–10 and 11–17) and gender.

	FEV_1 (mL)	FVC (mL)	FEV_1: FVC (%)	$FEF_{25-75\%}$ (mL/s)	PEF (mL/s)
3-PBA	Adjustedβ (95% CI)[b]				
6–10 years old					
Boys					
Continuous [a]	−0.002 (−0.02, 0.02)	0.001 (−0.02, 0.02)	−0.002 (−0.01, 0.01)	−0.01 (−0.04, 0.02)	−0.003 (−0.03, 0.02)
Low	Reference	Reference	Reference	Reference	Reference
Middle	0.001 (−0.03, 0.03)	−0.003 (−0.03, 0.02)	0.003 (−0.01, 0.01)	0.003 (−0.04, 0.05)	0.002 (−0.03, 0.04)
High	−0.02 (−0.04, 0.01)	−0.01 (−0.04, 0.01)	−0.003 (−0.01, 0.01)	−0.03 (−0.07, 0.02)	−0.01 (−0.04, 0.03)
P for trend	0.146	0.274	0.355	0.110	0.559
Girls					
Continuous [a]	−0.002 (−0.02, 0.01)	−0.004 (−0.02, 0.01)	0.003 (−0.004, 0.01)	0.01 (−0.02, 0.04)	−0.01 (−0.03, 0.01)
Low	Reference	Reference	Reference	Reference	Reference
Middle	−0.001 (−0.03, 0.02)	−0.004 (−0.03, 0.02)	0.003 (−0.01, 0.01)	0.01 (−0.03, 0.06)	−0.01 (−0.04, 0.03)
High	0.001 (−0.02, 0.02)	−0.004 (−0.03, 0.02)	0.004 (−0.01, 0.01)	0.02 (−0.02, 0.06)	−0.01 (−0.04, 0.02)
P for trend	0.955	0.772	0.427	0.378	0.469
11–17 years old					
Boys					
Continuous [a]	−0.02 (−0.04, −0.01) *	−0.02 (−0.03, −0.01) *	−0.001 (−0.01, 0.01)	−0.03 (−0.05, −0.002) *	−0.03(-0.05, −0.01) *
Low	Reference	Reference	Reference	Reference	Reference
Middle	0.09 (−0.02, 0.03)	0.002 (−0.02, 0.03)	0.01 (−0.003, 0.01)	0.02 (−0.01, 0.06)	0.003 (−0.02, 0.03)
High	−0.02 (−0.05, 0.01)	−0.02 (−0.05, 0.01)	0.001 (−0.01, 0.01)	−0.02 (−0.06, 0.02)	−0.03 (−0.06, −0.01)
P for trend	0.119	0.111	0.929	0.224	0.045 *
Girls					
Continuous [a]	−0.01 (−0.02, 0.01)	−0.01 (−0.02, 0.002)	0.01 (0.001, 0.02) *	0.003 (−0.02, 0.03)	−0.004 (−0.02, 0.01)
Low	Reference	Reference	Reference	Reference	Reference
Middle	0.003 (−0.02, 0.02)	0.001 (−0.02, 0.02)	0.004 (−0.01, 0.01)	0.01 (−0.02, 0.04)	0.02 (−0.01, 0.04)
High	−0.003 (−0.02, 0.02)	−0.01 (−0.03, 0.01)	0.01 (0.001, 0.02)	0.01 (−0.02, 0.05)	0.004 (−0.02, 0.03)
P for trend	0.711	0.199	0.035 *	0.551	0.970

* Significant at $p < 0.05$.
[a] Urine 3-PBA concentrations were adjusted for creatinine then $\log_{10}$-transformed.
[b] Adjusted for height, race, BMI-for age, NHANES cycles, serum cotinine concentrations, family income to poverty ratio, and "have you had wheezing or whistling in your chest in the past 12 months?" (yes/no).

in either boys or girls. In addition, the results were similar in the sensitivity analyses when using z-scores for the pulmonary function measurements (Table S4).

4. Discussion

In this study, we observed negative associations between urinary 3-PBA, used as a proxy for the environmental exposures to PYR, and pulmonary function measures among children aged 6–17 years in the U.S. Moreover, we found stronger associations between 3-PBA and measures of pulmonary function among boys aged 11–17 years old.

4.1. Urinary 3-PBA concentrations in children

As shown in Table S5, we compared the present results with those observed for children in other surveys conducted in U.S., Germany, Poland, China, and South Korea. Although the concentrations of urinary 3-BPA found by us were higher than those on a previous study done on a similar NHANES population (GM 0.50 vs 0.37 μg/g Cr) (Barr et al., 2010), they were similar with two other studies from U.S., including an observational study from the Children's Total Exposure to Persistent Organic Pollutants (CTEPP) study from 2006 and the Children's Pesticide Exposure Study published in 2007 (CPES) (0.50 vs 0.5 and 0.58 μg/g Cr, respectively) (Lu et al., 2006; Morgan et al., 2007). However, the U.S. children had relative higher 3-PBA concentrations (0.50 μg/g Cr) when compared to the corresponding population from European countries such as Germany (0.24 μg/g Cr) (Becker et al., 2006) and Poland (0.25 μg/g Cr) (Wielgomas et al., 2013a), but substantially lower concentrations comparing with those from Asian countries such as China (0.97 μg/g Cr) (Ye et al., 2017a) and South Korea (1.34 μg/g Cr) (Jo et al., 2015).

The differences in urinary 3-PBA concentrations between our study and other reference values reported in European and Asian data may be caused by a variety of factors. Firstly, the pattern in the use of pesticide, especially the indoor use of pesticides might be the reason for the differences. A study conducted in Northern California reported use of pesticides as high as 35% for indoor and around 45% for outdoor applications in 481 participating households during 2007–2009 surveys (Wu et al., 2013). This level of utilization is higher than the 32% for indoors and 16% for outdoor use in households in Europe (the Pélagie cohort study) (Glorennec et al., 2017). Secondly, PYRs are widely used for agricultural and residential settings in China, with an annual utilization of more than 3000 tons (approximately 6.6 million pounds) (Qi et al., 2012; Ye et al., 2017b). The recently estimated annual use of PYRs in the U.S. ranges from several thousand to two million pounds (Schettgen et al., 2016), about a third compared to the Chinese levels. According to the Korean National Environmental Health Survey data, 3-PBA concentrations in the general population were more than 3 times higher in Korea than in U.S., probably due the wider exposure of the Korean people to various forms of PYRs such as sprays and fumigants (Yoo et al., 2016).

Of note, the detection frequency of 3-PBA in urine was 77.4%, whereas the detection concentrations were much lower, $\leq$ 15%, for other three nonspecific metabolites (4-F-3PBA, trans-DCCA, and cis-DBCA), which may indicate that either they were present, but to concentrations below the LOD or that the time window in which the urine samples were collected the children had lower exposure (Ding et al., 2012).

4.2. Association of pesticide exposure with pulmonary function

There are only a few epidemiologic studies that assessed the association between exposure to environmental pesticide and pulmonary function in children. To our knowledge, two studies have evaluated the effect of organophosphate insecticides (OPs) exposure on children's pulmonary function (Raanan et al., 2016; Ye et al., 2016b). The Health Assessment of Mothers and Children of Salinas (CHAMACOS) study found that prenatal exposures to OPs was associated with lower FEV_1 and FVC among 279 school-age children living in an agricultural community in California (Raanan et al., 2016). Recently, CHMS cross-sectional study in Canada found no associations between childhood OP exposure and pulmonary function in children aged 12–19 years (n = 980). (Ye et al., 2016b). Two other studies have assessed early life stage (both prenatal and postnatal) exposures to organochlorine compounds (OCs) in relation to pulmonary function and found decreased in FVC and FEV_1 with increasing blood concentrations of p, p'- dichlorodiphenyldichloroethylene (p, p'-DDE) in school-aged children (Abellan et al., 2019; Pallavi et al., 2017). In our study, the urinary 3-PBA concentrations were negatively associated with FEV_1, FVC, and PEF in children, consistent with the previous reports (Abellan et al., 2019; Pallavi et al., 2017; Raanan et al., 2016; Ye et al., 2016a, 2016b). In addition, we also observed gender specific response with positive association of 3-PBA with FEV_1: FVC in girls who aged 11–17 years, but not in boys. We have no clear explanation for this finding, which might be incidental.

The study most closely related to ours is the CHMS study, which enrolled 1997 participants aged 6–19 years and reported on the ΣPYR (the sum of 3-PBA, 4-fluoro-3-PBA, cis-DCCA, trans-DCCA, and cis-DBCA) exposure. That study found that ΣPYR concentrations were associated with lower FEV_1 in children aged 6–11 years, and lower FVC in adolescents aged 12–19 years (Ye et al., 2016a). However, we cannot directly compare our results with those from the CHMS study due to differences in assessing the exposure (ΣPYR compared to one metabolite in our study), the limit of detection (LOD = 0.01 μg/L in the Canadian study vs. 0.10 μg/L in the NHANES), and the confounders used in the Canadian study compared to ours (i.e. dwelling type and daily energy expenditure). Nonetheless, taken collectively, the findings from all the aforementioned studies suggest that the potential adverse effects of PYR exposures on respiratory function should be carefully considered in susceptible children.

The underlying biological mechanisms of how PYRs affect pulmonary function remains to be elucidated, but it is possible to involve multiple pathways (De et al., 2012; Diel et al., 2003; Ray et al., 2006). PYRs as a neurotoxicant can directly target the voltage-gated sodium channels of neurons in airway smooth muscles, and result in an increased contraction of smooth muscle and excessive airway narrowing (Ray et al., 2006). In addition, the endocrine-disrupting effect and immunotoxic reaction of PYRs may indirectly affect the physiological function of the lungs (Chang et al., 2018; De et al., 2012; Diel et al., 2003). Additional research is warranted to identify the pathogenic mechanisms.

In our study, the adverse pulmonary effects of PYRs exposure were more pronounced among boys aged 11–17 years. Regarding the age-dependent association between urinary 3-PBA concentrations and pulmonary function, two factors may contribute to explain the differences. A dose effect response may account for the difference in response, with older children having a higher exposure to pyrethroid insecticides via ingestion, proportional to their body weight, which may have resulted in higher 3-PBA concentrations. Furthermore, an age-specific response may be also explained by the differences in metabolism and excretion of PYRs. One previous study has investigated urinary PYR excretion in

children and adults, suggesting that the adult had a significantly higher PYR excretion rate than the children (Fortin et al., 2008). Thus, we could infer that the older children excreted higher amounts of 3-PBA than the younger children. The way by which 3-PBA affects children pulmonary function in a gender-specific manner is not well understood. As limited evidence is available regarding the different vulnerability among boys and girls, further mechanistic interrogation is needed.

Our study used a large sample, representative for the U.S. general population, which rendered our findings generalizable. The detailed information collection from NHANES study allowed a wide range of potential confounders to be included, such as PIR and serum cotinine concentrations. Finally, the large sample available allowed for subgroup analyses by age and gender. However, there are several limitations to this study. Firstly, the NHANES study has cross-sectional design, where the exposures and assessment of pulmonary function was measured at one time point. Thus, it is not possible to determine a causal relationship between PYR exposures and pulmonary function. Therefore, these associations should be replicated using prospective data with serial 3-PBA and spirometry measurements. Secondly, the half-life of 3-PBA is only few hours in the human body, thus, the reliability of obtaining children's 3-PBA metabolites in the spot urine sample as the surrogate of long-term exposure is uncertain, which could lead to exposure measurement error or misclassification (Attfield et al., 2014; Quirós-Alcalá et al., 2014). However, in cases of chronic exposure, a biomarker measured at a single time point may provide a representative dosimeter even if the toxicant has a short half-life. Several previous studies reported that a spot urine sample had moderate sensitivity for predicting an individual's longer-term exposure over several weeks or months (Kolaczinski et al., 2004; Wielgomas, 2013). Considering that children recruited in the NHANES study usually have steady habits and living environment, urinary metabolite concentrations in single-spot urine analysis may reflect a relatively moderate, yet constant exposure to PYR. Thus, analyzing a single urine sample might appropriately assess long-time exposures. Thirdly, we examined only the association between 3-PBA concentration and pulmonary function, but there may be other environmental exposures that are related to outcome that we were not able to investigate with the available data. Lastly, we could assess pulmonary function at a time point, but could not predict long term outcomes on the pulmonary health of the individuals as they aged or any relationship with respiratory disorders such as asthma or upper respiratory tract infection (URTI).

5. Conclusions

In summary, we found that environmental exposures to PYR may adversely affect pulmonary function in children, and the effect was more pronounced among boys aged 11–17 years. Given the widespread use of PYRs worldwide, future studies with prospective designs are necessary to confirm the associations reported in our study and to follow up the trajectory of the respiratory health into adulthood.

Declaration of competing interest

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

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Appendix A. Supplementary data

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