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Characterization of pesticide exposures and their associations with asthma morbidity in a predominantly low-income urban pediatric cohort in Baltimore City

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Abstract

Background: Pesticides may impact respiratory health, yet evidence of their impact on pediatric asthma morbidity is limited, particularly among urban children.

Objective: To characterize pesticide biomarker concentrations and evaluate their associations with pediatric asthma morbidity among predominantly low-income, Black children in Baltimore City, USA.

Methods: We measured urinary concentrations of 10 biomarkers for pyrethroid insecticides (cyfluthrin:4F-3PBA, permethrin:3PBA), organophosphate insecticides (chlorpyrifos:TCPY, malathion:MDA, parathion-PNP, diazinon-IMPY), and herbicides (glyphosate-AMPA, GPS; 2,4-dichlorophenoxyacetic acid-2,4-D; 2,4,5-trichlorophenoxyacetic acid -2,4,5-T) among 148 children (5–17 years) with established asthma. Urine samples and asthma morbidity measures (asthma symptoms, healthcare utilization, lung function and inflammation) were collected every

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Declaration of interests

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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three months for a year. Generalized estimating equations were used to examine associations between pesticide biomarker concentrations and asthma morbidity measures, controlling for age, sex, race, caregiver education, season, and environmental tobacco smoke. In sensitivity analyses, we assessed the robustness of our results after accounting for environmental co-exposures.

Results: Frequently detected ($\geq 90\%$ detection) pesticide biomarker concentrations (IMPY, 3PBA, PNP, TCPY, AMPA, GPS) varied considerably within children over the follow-up period (intraclass correlation coefficients: 0.1–0.2). Consistent positive significant associations were observed between the chlorpyrifos biomarker, TCPY, and asthma symptoms. Urinary concentrations of TCPY were associated with increased odds of coughing, wheezing, or chest tightness (adjusted Odds Ratio, aOR, TCPY:1.60, 95% Confidence Interval, CI:1.17–2.18). Urinary concentrations of TCPY were also associated with maximal symptom days (aOR:1.38, CI:1.02–1.86), exercise-related symptoms (aOR:1.63, CI:1.09–2.44), and hospitalizations for asthma (aOR:2.84, CI:1.08–7.43). We did not observe consistent evidence of associations between the pesticide exposures assessed and lung function or inflammation measures.

Conclusion: Among predominantly Black children with asthma, we found evidence that chlorpyrifos is associated with asthma morbidity. Further research is needed to assess the contribution of pesticide exposure to pediatric respiratory health and characterize exposure sources among vulnerable populations to inform targeted interventions against potentially harmful pesticide exposures.

Keywords

Pesticides; Respiratory Health; Exposure Assessment; Vulnerable Populations

Introduction

Asthma is a chronic obstructive airway disease that disproportionately impacts racial and ethnic minoritized populations and children living in inner cities in areas of high poverty [1,2]. Since asthma has no cure, effective disease management and control partly focuses on identifying and minimizing exposures to environmental triggers [3]. While studies have demonstrated that air pollution is a recognized risk factor for pediatric asthma morbidity in urban settings, less is known about the role of other contaminants, like pesticides. Prior studies have targeted children living near agricultural areas or with parental occupational exposure to pesticides [4,5], with sparse evidence on inner-city children. Dilapidated housing conditions in disadvantaged neighborhoods increase the likelihood of pest infestations [6–10], where pesticide use is high and promoted to control pests recognized to increase asthma morbidity risk [7,9,11]. Pesticides can also persist indoors long after applications have occurred, posing long-term exposure risks for children [12]. Exposure to pesticides among children in urban settings may occur through inhalation from indoor residential use, consumption of treated food commodities, and from track-in of pesticide residues from outdoors [9,13–15].

Pesticides, including organophosphorus and pyrethroid insecticides, are frequently used in agricultural, residential, and gardening applications [16–18]. Exposure to pesticides is ubiquitous among humans with widespread exposures detected among U.S. children

[19–22]. For example, glyphosate, the most commonly used herbicide in the U.S., has been detected in >80% of urine samples from U.S. adults and children [23,24], and among pregnant women in urban locations [25]. Regulatory restrictions have been enacted worldwide to ban select pesticides or applications in efforts to limit human exposure. However, in recent decades, the U.S. has relied heavily on voluntary cancellations from pesticide manufacturers and lagged behind the European Union, Brazil, and China in prohibiting the use of pesticides, including many that are considered hazardous to human health [26]. Exposure to these pesticides has continued in the U.S. population, raising concerns about their potential health risks [27–29], including adverse respiratory health effects [4,5,30].

Limited toxicological studies indicate that pesticides could induce or aggravate asthma through several mechanisms, including modifications of autonomic function and immune response [31–33]. For example, experimental studies in vertebrates have indicated that pyrethroids decrease gene expression related to immune function and induce apoptosis in thymus cells, decreasing immune response. This is hypothesized to result from activation of the glucocorticoid receptor, which can cause immunosuppression [34]. Other mechanisms by which pesticides like pyrethroids and others including organophosphates could impact respiratory health involve oxidative stress [35], a well-accepted mechanism in the pathogenesis of asthma that can initiate and augment inflammatory processes [19,36,37]. Pesticides, including glyphosate, could also induce airway inflammation by increasing neutrophil and eosinophil counts, cytokine production and mast cell degranulation as reported in mice [38].

Despite the potential for increased pesticide exposures among children with asthma in inner cities due to residential uses, track-in of residues from outdoors, and consumption of foods treated with pesticides, studies characterizing pesticide exposure and the role of pesticides on asthma morbidity in this population remain sparse. Here, we aimed to address current knowledge gaps by characterizing exposures to select pesticides and examining their associations with respiratory morbidity in a group of predominantly Black children with established asthma in a low-income urban setting. We hypothesized that exposure to the target pesticides would be positively associated with increased asthma morbidity.

Methods

Study Population

In the present study, we used data and biobanked specimens from the Mouse Allergen and Asthma Cohort Study (MAACS), which sought to assess the contribution of air pollutants and indoor allergens on disease morbidity among children with asthma. We aimed to characterize exposures to select pesticides and examine their association with respiratory morbidity as defined by a suite of standard respiratory symptoms, medication use, and healthcare utilization in children with established asthma. Briefly, the MAACS study sample consisted of 148 children with asthma in Baltimore City, Maryland, who were observed over a 12-month follow-up period. Recruitment procedures for the cohort have been detailed in previously published work [39–41]. Briefly, MAACS participants were recruited and enrolled between April 2007 and June 2009. Children aged 5 to 17 years

were recruited through the Emergency Department (ED) of the Johns Hopkins Hospital, at health fairs, and by word of mouth. Children were eligible to participate in the study if they were diagnosed with asthma by a physician within a year of study enrollment, experienced two or more asthma exacerbation events in the previous 12 months, and were prescribed a controller medication or met criteria for persistent asthma per the National Asthma Education and Prevention Program (NAEPP) [42]. We defined exacerbations as asthma-related symptoms necessitating an unplanned medical visit or administration of an oral corticosteroid. Enrollment was restricted to non-pregnant females and non-smokers, confirmed by urinary cotinine testing. Study protocols received approval from the Johns Hopkins School of Medicine Institutional Review Board and each child's parent or guardian provided informed consent before study enrollment.

Study Procedures and Clinical Assessments of Asthma Morbidity

Each child completed up to five clinic visits that were conducted every three months over a year. At the first clinical visit, demographic information was obtained through parental report. Trained study staff assessed atopy, defined as having at least one positive response to skin prick testing with a wheal >2 mm greater in size compared to the negative control [43,44]. The skin prick test was administered with a MultiTest II device (Lincoln Diagnostics, Decatur, IL) [39].

At each visit, study staff recorded the number of days in the prior two weeks with rescue medication use and asthma-related symptoms including: general symptoms (cough, tightness of chest, wheeze), symptom-related nighttime waking, symptoms related to exercise (cough or tightness of chest when going upstairs or running), cough absent a cold, and slowed activity due to asthma. We generated a "maximal symptom days" variable, defined as the largest value reported among the maximum number of days in the prior two weeks experiencing general symptoms, symptom-related nighttime waking, or slowed activity due to asthma [45,46]. Information on healthcare utilization was also captured by querying participants about emergency department (ED) visits, acute care visits (unscheduled visits for asthma-related symptoms), asthma-related hospitalizations, and any unscheduled physician visits in the prior three months.

Study staff also assessed pulmonary function (FVC: forced vital capacity; and FEV₁: forced expiratory volume in the first second) at each visit using a KoKo spirometer (nSpire Health, Longmont, Colorado). We estimated percent predicted values of lung function parameters based on multi-ethnic, age-specific reference equations from the Global Lung Initiative [47], and defined bronchodilator reversibility as a ≥12% FEV₁ increase 15 minutes after administration of two puffs of short-acting β-agonist. Lastly, we evaluated pulmonary inflammation using a NIOX Mino (Aerocrine, Solana, Sweden) to quantify the fraction of exhaled nitric oxide (FeNO) levels according to American Thoracic Society/European Respiratory Society guidelines [48].

Pesticide Exposure Assessment

At each clinic visit, participants provided spot urine samples (n=650) in polypropylene urine containers, which were aliquoted and frozen at -80°C. Samples were sent to NSF

International (Ann Arbor, Michigan, USA) for laboratory analysis of pesticide biomarkers using liquid or gas chromatography with tandem mass spectrometry. Briefly, for the first set of pesticide biomarkers measured via LC-MS/MS, a Thermo Scientific Transcend TXII Turbulent Flow system interfaced with a Thermo Scientific Quantiva triple quadrupole mass spectrometer was used to evaluate eight different pesticides in MRM positive and negative mode. The method was developed based upon the Centers for Disease Control and Prevention (CDC) “Specific Organophosphorous Pesticides, Synthetic Pyrethroids, and Select Herbicides (Universal Pesticides) Method 6103.03,” [49]. In total, we measured four biomarkers for organophosphorus insecticides (2-isopropyl-4-methyl-pyrimidinol: IMPY; 2[(dimethoxyphosphorothioyl) sulfanyl] succinic acid: MDA; 3, 5, 6-trichloro-2-pyridino: TCPY; 4-nitrophenol: PNP), two biomarkers for pyrethroid insecticides (3-phenoxybenzoic acid: 3PBA; 4-fluoro-3-phenoxybenzoic acid: 4F-3PBA), and two biomarkers for herbicides (2,4-dichlorophenoxyacetic acid: 2,4-D; 2,4,5-trichlorophenoxyacetic acid: 2,4,5-T). The NSF method used for biomarker analysis was evaluated against acceptance criteria comparable to that established by a previously validated CDC method. Correlation coefficient (R^2) ranges for the validated analyte calibration curve were ≥ 0.992 . The precision (%RSD) and method accuracy (% nominal concentration) were confirmed through validation runs across three days ($n=18$), comprised of six replicate analyses of analytes spiked at four concentrations in pooled control human urine, reflecting both the inter- and intra-day assay variability (quality control information of analytical procedures is detailed in the supplemental materials).

For glyphosate (GPS; N-(phosphonomethyl) glycine) and its metabolite AMPA (aminomethylphosphonic acid)), GC-MS/MS was used to develop an in-house method, described previously by Conrad et al. [50] utilizing an Agilent 7890B gas chromatograph coupled to an Agilent 7000C triple quadrupole mass spectrometer [51]. Each batch run included at least five calibration standards and duplicate quality control (QC) samples at three concentrations within the established calibration range, or a minimum of 5% of the total number of samples within the batch run. Calibration curves had an R^2 of ≥ 0.98 , and at all concentrations, the percentage deviation allowed from nominal QC values was $\pm 15\%$ or ± 2 standard deviations of the mean for each QC level from previously collected QC data. If at least 67% of the total number QC samples for a given concentration met the criteria, the batch run was accepted. When more than two QC samples per concentration were analyzed, 50% of the QC samples per concentration must had to meet the validation criteria.

Both NSF methods performed well in the German External Quality Assessment Scheme (G-EQUAS). To account for urinary dilution, we corrected pesticide biomarker levels using specific gravity: $C_{sg} = [(C \times 1.024 - 1) / (SG - 1)]$, where C_{sg} is the pesticide biomarker concentration (ng/mL) corrected for specific gravity, C is the biomarker concentration (ng/mL) observed, 1.024 is the median specific gravity among our study sample, and SG is each participant's urinary specific gravity [52]. We measured specific gravity with a digital refractometer (ATAGOTM3741, Tokyo, Japan). Limits of detection (LOD) for the pesticide biomarkers ranged between 0.1 to 0.3 ng/mL. For concentrations $< LOD$, we retained values read from the instrument when a signal $< LOD$ was detected and substituted values with the $LOD/\sqrt{2}$ in the absence of a signal [53].

Data Analyses

We estimated descriptive statistics across study visits for participant baseline characteristics and pesticide biomarker concentrations. We examined differences in pesticide biomarker concentrations or detection frequencies based on demographic characteristics, including sex, age, annual household income, caregiver's education level, and body mass index (BMI), using Chi-square and Wilcoxon-Mann-Whitney tests. We focused on frequently detected (detection frequency $\geq 90\%$) pesticide biomarkers, using $\log_{10}$ -transformed concentrations to account for their skewed distribution.

To quantify between- and within-child concentration variability for frequently detected biomarkers, we used mixed effects models to calculate intraclass correlation coefficients (ICCs), restricting these analyses to participants that provided two or more urine samples. We then examined associations of pesticide biomarker concentrations with measures of asthma morbidity using generalized estimating equations (GEE) to account for repeated measurements among participants. We used log-transformed pesticide biomarker concentrations in the models based on their distribution and to reduce the influence of outliers. We fit crude and multivariable binomial regression models to assess associations between repeated pesticide exposure measures and binary outcomes (i.e., medication use, symptoms, healthcare utilization), while we used multivariable linear regression for continuous outcomes (i.e., FEV1/FVC%, FeNO). Final covariate model selection included sex, age (years), race/ethnicity (African American/Black vs. Other), caregiver's education level (less than high school, high school graduate, and some college or more), season, and environmental tobacco smoke (presence of smokers in the home). We based covariate selection on a directed acyclic graph and established predictors of pediatric asthma morbidity not on the causal pathway based on the literature [4]. Based on the exploratory nature of our analysis, we did not adjust our results for multiple comparisons. Rather, we assessed the consistency of associations between the pesticide biomarkers and outcome measures examined and considered the overall context of results when interpreting statistical significance using p-values [54,55].

Sensitivity analyses were conducted to assess the robustness of our results, when separately adjusting for additional asthma morbidity risk factors in our models. These included participant age- and sex-standardized body mass index (BMI) percentiles [56] modeled continuously; degree of atopy (i.e., the total number of positive skin prick tests to reflect each child's allergic sensitization); and exposure to fine particulate matter with an aerodynamic diameter < 2.5 microns ($PM_{2.5}$) and nitrogen dioxide (NO_2) in the participants' homes. Household indoor-air measurements of both $PM_{2.5}$ and NO_2 were taken for a week within two weeks of each clinic visit, as described previously [40,41,57]. Briefly, airborne $PM_{2.5}$ was collected over 5–7 days on a 37-mm Teflon filter at a flow rate of 4 L/min using IOM Inhalable Dust Samples (SKC, Inc., Eighty Four, PA), while passive samplers were used to measure NO_2 (Ogawa and Co. Inc., Pompano Beach, FL) [40,41,57]. We additionally adjusted for chemical co-exposures previously associated with morbidity in our cohort, including bisphenol A [46] and phthalates [58] by including urinary biomarker concentrations for these chemicals as additional covariates in the main models, running separate models with each co-exposure.

An additional sensitivity analysis was performed by excluding outliers (exposure values more than 1.5 times above interquartile range) of the model. We carried out all analyses using Stata/IC software (version 14.2, StataCorp, College Station, Texas) and MATLAB (The MathWorks, Inc., Natick, Massachusetts).

Results

Study Population Characteristics

Children enrolled in our study were predominantly Black (91%), approximately 57% were male, and 11.2 (SD: 4.0) years of age on average. Participants were predominantly from a low socio-economic background with most of the caregivers reporting an annual household income <\$35,000 (69%), not having college education (63%), and having government-based healthcare insurance (86%) (Table 1). Most enrolled children had at least two positive skin prick tests (91%), reported having at least one asthma-related acute healthcare visit in the prior three months (93%), and reported an asthma-related ED visit in the 12-months of study follow-up (68%) (Table 2).

Pesticide Biomarker Concentrations

We identified detectable concentrations for most urine samples collected (i.e., biomarker concentrations with a detection frequency $\geq 90\%$ of samples) for biomarkers of five organophosphorus pesticides (IMPY, PNP, TCPY, AMPA, GPS) and for pyrethroid insecticides, 3PBA (Table 3). Other biomarkers were less frequently detected (<7% for pyrethroid insecticide 4F-3PBA and for the organophosphorus pesticide MDA, and 58% and 30% detection for the herbicide biomarkers 2,4-D and 2,4,5-T, respectively). Concentrations for uncorrected pesticide biomarker are summarized in the supplementary materials (Table S1). For pesticide biomarkers frequently detected (detection frequency $\geq 90\%$), within-child concentrations varied considerably during the follow-up period (ICCs: 0.1–0.2).

Associations of Pesticide Exposures with Asthma Morbidity

We present the results from multivariable models for asthma morbidity outcomes in Figure 1. Positive associations were consistent for both TCPY and AMPA with increased odds of select asthma symptoms. Specifically, we observed that 10-fold increases in urinary concentrations of TCPY and AMPA were associated with a 38% and 31% increased odds of maximal symptoms days, respectively (adjusted Odds Ratio, aOR, TCPY: 1.38, 95% Confidence Interval, CI: 1.02–1.86; AMPA: 1.31, CI: 0.90–1.91). Similarly, we observed 10-fold increases in TCPY and AMPA to be positively associated with odds of coughing, chest tightness, or wheeze by 60% and 50%, respectively (aOR TCPY: 1.60, CI: 1.17–2.18; AMPA: 1.50, CI: 1.01–2.25). We also observed consistent positive associations with exercise-related symptoms (aOR TCPY: 1.63, CI: 1.09–2.44; AMPA: 1.65, CI: 0.93–2.92). Albeit not statistically significant, effect estimates for TCPY and AMPA remained consistently positive in their relationship with the additional asthma-related symptoms evaluated (Figure 1) in both crude and adjusted models (Table S2). Our results remained robust when further individually adjusting for environmental co-exposures (PM_{2.5}, NO₂, BPA, and phthalates) and when excluding high-leverage observations (results not shown).

We did not observe consistent evidence linking asthma symptoms and other pesticide biomarker concentrations.

For healthcare utilization (Table S3), we found that TCPY biomarker concentrations were associated with increased odds of hospitalizations (aOR TCPY: 2.84, CI: 1.08–7.43). However, consistent trends of associations were not observed with the additional healthcare utilization variables for this biomarker, or others assessed. Lastly, overall, the pesticide biomarkers evaluated in the present study were not consistently associated with reduced lung function or increased lung inflammation (Table S4), although we observed that the glyphosate biomarker, AMPA, was inversely associated with lung function, albeit this finding was not statistically significant (aOR FEV1: –2.70, CI: –5.59–0.19; FEV1/FVC%: –1.75, CI: –3.52–0.02).

Discussion

The present study identified positive associations between concentrations of select urinary pesticide biomarkers and respiratory morbidity indicators in a sample of participants with asthma, largely composed of Black children from lower socioeconomic backgrounds. Specifically, we observed consistent positive associations between urinary levels of TCPY (biomarker of chlorpyrifos) and asthma symptoms. Our results highlight the ongoing need for pesticide biomonitoring in non-occupational populations, particularly in low-income and racially or ethnically diverse communities who often face higher exposure burdens to contaminants that may adversely impact respiratory health [59]. Exposure disparities in the study population may have been due to multiple sources, including consumption of treated food commodities, indoor residential uses, and track-in from outdoors though further studies are needed to investigate predominant sources in urban settings [9,13–15].

We observed widespread exposure to pesticides and exposure disparities, particularly organophosphorus insecticides. Detection frequencies and median urinary concentrations of parent-specific pesticide biomarkers, including TCPY, PNP and IMPY, were higher in our study population compared to U.S. children aged 6–17 years (NHANES 2007–2010, Table S5) [19]. Our results are consistent with previously reported pesticide exposure disparities [19,21,60], indicating that non-Hispanic Black populations experience pesticide exposures up to five times higher than the general U.S. population [59]. Furthermore, the median TCPY concentration (3.6 ng/mL) in our study was twice as high as those reported in more recent studies of Black children in the U.S. [19,61]. Declining exposure trends have been observed in the U.S. general population following regulatory actions like the ban of chlorpyrifos in 2000 for indoor residential uses due to health concerns, particularly among children [9,19,21,62]. Still, urinary TCPY (chlorpyrifos biomarker) concentrations in our study population measured 7–9 years post-ban (2007–2009) were comparable to pre-ban levels in U.S. children (NHANES 1999–2000) and to the highest quartile of exposure most recently estimated among U.S. children (NHANES 2015–2016). Chlorpyrifos is found to persist in indoor environments [9], which may explain the levels observed in our study population. Despite a complete ban for chlorpyrifos use on food commodities in 2021, its use was reinstated for select crops, including apples, strawberries, and citrus, in 2023 [63]. These findings suggest exposures and disparities may continue despite ban efforts.

We also observed higher exposures to the herbicide 2,4,5-T than those observed among U.S. children, ages 6–19 years (NHANES 2007–2010, Table S5) [19] even though its use in the U.S. was discontinued in 1985 [64]. The CDC stopped biomonitoring 2,4,5-T in 2011. Although this is not a frequently measured chemical in epidemiological studies, a study recently (2017) detected 2,4,5-T in U.S. adults [65]. Our finding highlights the need to consider continued biomonitoring of pesticides, including banned substances, among vulnerable and racially diverse communities and children, to evaluate the long-term impacts of policy changes on reducing pesticide exposure disparities.

In contrast, glyphosate, the most heavily applied pesticide globally, continues to increase in use [66], yet there is still limited evidence on human exposure levels in the U.S. [67,68]. The CDC has only started to quantify urinary glyphosate concentrations in the U.S. (NHANES: 2013–14, 2015–16, and 2017–18) and, to date, has not characterized AMPA, a main breakdown product and the primary metabolite of glyphosate [69]. While samples from the present study were collected earlier (2007–2009), the median urinary concentration of glyphosate (0.5 ng/mL) was comparable to levels more recently observed among U.S. children (NHANES 2013–2016, Table S5) [24,68]. The geometric mean urinary AMPA concentration in this study (0.6 ng/mL) was also similar to that observed among 14-year-olds from an agricultural region in California participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study sampled in 2014–2015 (0.72 ng/mL) [70]. Notably, glyphosate was linked to increased asthma morbidity in the present study and emerging studies also indicate that exposures to this herbicide may also be linked to other adverse health risks [25,70,71]. Exposure to glyphosate among the general population can occur from consumption of treated food commodities and from use in residential and recreational areas [72], but predominant sources remain understudied in urban settings. Our findings justify ongoing biomonitoring efforts that are comprehensive and inclusive of all racial and ethnic groups.

While previous studies report positive associations between pesticide exposures with asthma prevalence and incidence and allergic effects in children [4,5,30], few have focused on respiratory morbidity in children with established asthma. To our knowledge, our findings are consistent with the only existing study to date that has also assessed pesticide exposures and respiratory morbidity in children with established asthma. In a sample of predominantly Black children (7–12 years) with asthma living in low-income, urban housing in Boston, Cincinnati, and New Orleans, Werthmann et al. reported positive associations, albeit not statistically significant, between urinary concentrations of PNP, a biomarker of parathion, and asthma-related healthcare utilization [61]. While we observed significant associations between urinary TCPY concentrations and asthma-related hospitalizations, instead of PNP, both biomarkers reflect exposure to organophosphorus (OPs) insecticides. As a class of insecticides, OPs may contribute to asthma through multiple mechanisms, including cholinergic overstimulation, airway hyperreactivity, inflammation, and oxidative stress [73,74]. Emerging evidence suggests both acute and chronic effects, with potential long-term consequences for respiratory health, particularly in vulnerable populations like children [73–76]. Although non-significant, Werthmann et al. also reported suggestive evidence that a mixture of multiple pesticide biomarkers (TCPY, 2,4-D, 3PBA, and PNP), which were assessed in our study, was positively associated with asthma-related healthcare utilization

[61], but did not assess exposure to glyphosate, which was positively associated with emergency department visits for asthma in our study. While we did not observe consistent associations for the other pesticide biomarkers, there is still the potential for associations, as larger sample sizes may be needed to elucidate these relationships. Higher prevalence and higher exposures to select pesticides in our sample may have provided more variation in exposure as well as more asthma exacerbation events, thereby increasing our power to identify the observed associations [77].

While evidence synthesized from NHANES (1999–2008) reported generally null associations between asthma prevalence and exposure to organophosphorus insecticides among U.S. children, positive associations were observed among non-Hispanic Blacks, who experienced the highest rates of asthma prevalence [78]. Studies of children from agricultural areas, where pesticide exposures are often high, have also reported positive associations between organophosphorus pesticide exposures and decreased lung function [79], respiratory symptoms [80], and urinary concentrations of leukotriene E4, a marker of the cysteinyl leukotriene pathway implicated in asthma pathophysiology [81]. Although we did not observe statistically significant changes in lung function or inflammation in the present study, our results are consistent with previous studies that reported positive associations between endocrine disrupting chemicals and asthma symptoms [46,58]. Still, it is possible that pesticide exposures may potentiate asthma morbidity through other mechanisms, which do not directly correspond to increases in FeNO or changes in spirometry [73,74].

The present study has some limitations. First, we were able to conduct longitudinal assessment of pesticide exposures using urinary biomarkers, which are considered the gold standard, but the relatively short half-lives of these biomarkers limit the precision of exposure assessment over longer time periods [16,17,64,85]. Although analysis of biobanked samples serves as an efficient use of existing resources, our exposure assessment was constrained to the timing of clinical visits, which occurred every three months in the parent study. For highly detected pesticide biomarkers, low ICCs confirmed the high temporal variability of urinary concentrations within children over the study period. While we collected repeated urine samples to characterize acute exposures, it is also possible that our acute exposures do not directly correspond to the outcome periods assessed (e.g., symptoms in the prior two weeks, healthcare utilization in the prior three months). However, we expect that non-differential measurement error (independent of asthma morbidity status) would attenuate the effect estimates observed [86], making it plausible that the true magnitude of associations identified are larger. We also observed consistent association trends across different outcomes and in our sensitivity analyses with TCPY and AMPA, providing suggestive evidence that our findings are not coincidental. Other limitations include our sample size, which restricted our capacity to examine sexually dimorphic effects. Additionally, the potential for spurious findings and unmeasured confounding remains possible, and the large number of biomarkers examined raises the opportunity of random variation causing the statistical significance of some associations. Finally, our study captures exposures from 2007–2009, and there is the potential that pesticide exposures have declined over time. However, we still observed associations with asthma morbidity at levels comparable to recent estimates for select pesticide biomarkers. Additionally, we

observed detectable concentrations of select biomarkers despite multiyear bans on their parent pesticides, revealing persistent exposures and the need to investigate present day exposure disparities.

While acknowledging its limitations, the present study has several strengths. Notably, our efforts focused on an understudied population of predominantly urban, Black children with established asthma. To our understanding, the current study is the first to characterize exposure variability for glyphosate and AMPA, in addition to several other pesticide biomarkers, among children. Our prospective study design leveraged repeated measures to enhance the accuracy of both exposure and outcome characterization while decreasing the risk of recall bias. Few studies have examined associations between pesticides and asthma morbidity and our findings highlight the importance of conducting epidemiologic studies among populations with pre-existing health conditions to identify potential points of intervention. Finally, we were able to evaluate the robustness of our results by adjusting for meaningful confounders (e.g., race, education, season), and co-exposures to other contaminants previously linked to asthma morbidity (PM_{2.5}, NO₂, BPA, and phthalates) when examining the independent effects of target pesticide biomarkers on asthma morbidity.

Conclusions

This study on a group of predominantly Black children in a low-income setting provides evidence of pesticide exposure disparities and positive associations with asthma symptoms in children. We observed elevated concentrations of select pesticides comparable to pre-ban levels for biomarkers of chlorpyrifos and 2,4,5-T, in our population of Black children with asthma. We also detected concentrations of the most widely used herbicide globally, glyphosate, at a higher frequency than the general population of US children. These findings suggest that exposures to select pesticides are associated with asthma morbidity among children with established asthma, but the existing body of evidence remains quite limited. Future studies should continue to characterize pesticides as exposures may vary over time, especially in racially and ethnically diverse populations to elucidate pesticide exposure disparities and inform interventions aimed at reducing asthma morbidity in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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not imply endorsement by the CDC, the Public Health Service, or the U.S. Department of Health and Human Services.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author on reasonable request.

Abbreviations

aOR	adjusted odds ratio
BMI	body mass index
BPA	bisphenol A
CDC	Centers for Disease Control and Prevention
CI	confidence Interval
DF	detection frequency
ED visit	emergency department visit
FEV1	forced exhaled volume in the first second
FeNO	fractional exhaled nitric oxide
FVC	forced vital capacity
GEE	generalized estimating equation
GM	geometric mean
GSD	geometric standard deviation
ICC	intraclass correlation coefficient
LOD	limit of detection
MAACS	Mouse Allergen and Asthma Cohort Study
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
QC	quality control
SABA	short-acting beta agonist

Pesticide Biomarkers

2,4-D	2,4-dichlorophenoxyacetic acid
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4F-3PBA	4-fluoro-3-phenoxybenzoic acid
IMPY	2-isopropyl-4-methyl-pyrimidinol
MDA	2-[(dimethoxyphosphorothioyl) sulfanyl] succinic acid
3PBA	3-phenoxybenzoic acid
PNP	4-nitrophenol
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
TCPY	3,5,6-trichloro-2-pyridinol
AMPA	Aminomethylphosphonic acid
GPS	Glyphosate

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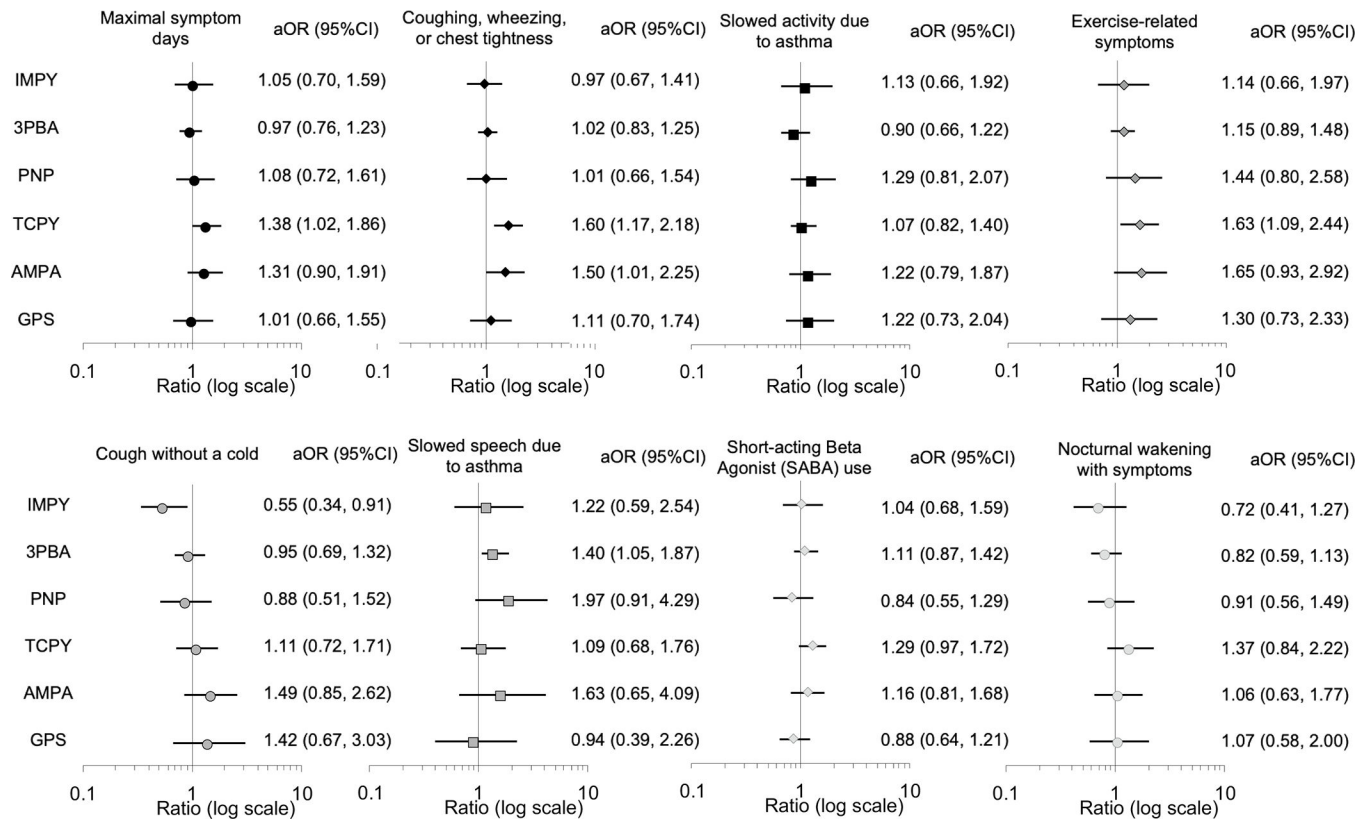
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Highlights

- Black children in urban areas may face disproportionate exposure to pesticides.
- Pesticides may be associated with respiratory morbidity in children with asthma.
- Chlorpyrifos may increase odds of asthma symptom exacerbation and hospitalization.
- Results support the importance of pesticide biomonitoring among Black children.

**Figure 1.**

Forest plots of associations between asthma symptoms and urinary pesticide concentrations in 148 asthmatic inner-city children (n=650).

Asthma symptom variables were treated as dichotomous outcomes using binomial regression models with generalized estimating equations and log link to obtain ORs; pesticide concentrations were modeled as continuous variables (log-10 transformed concentrations); nocturnal awakening with asthma symptoms missing on 2 children; cough without a cold missing on 1 child. Multivariable models were adjusted for age, sex, race, caregiver education, season, and presence of smokers in the home as a proxy for environmental tobacco smoke exposure (n=148). Abbreviations: aOR=Adjusted odds ratio; 95%CI: 95% Confidence Interval.

Table 1.Baseline demographic characteristics for MAACS children ages 5–17 years (n=148).^a

Demographic Characteristic	n (%)	
Age ^b		
5–7 years	41	(27.7)
8–10 years	35	(23.7)
11–13 years	26	(17.6)
14–17 years	46	(31.1)
Sex		
Male	85	(57.4)
Female	63	(42.6)
Child’s race		
Black/African American	135	(91.2)
Other ^c	13	(8.8)
Child body mass index (BMI)		
Underweight (<5th percentile)	6	(4.1)
Normal Weight (5th–<85th percentile)	77	(52.7)
Overweight (85th–<95th percentile)	22	(15.1)
Obese (≥ 95th percentile)	41	(28.1)
Caregiver’s Education Level		
Less than high school	42	(28.4)
High school graduate	51	(34.5)
Some college or more	55	(37.2)
Annual household income		
<\$35,000	92	(68.7)
>\$35,000	42	(31.3)
Insurance		
Private/self-pay	20	(13.7)
Government-based (public)	126	(86.3)
Smoker lives in child’s home		
No	64	(43.2)
Yes	84	(56.8)

^aInformation reported is for 148 MAACS children. Information was missing for select demographic characteristics at baseline (BMI: n=2; Annual household income: n=14; Health insurance: n=2).

^bThe mean(SD) age of MAACS children was 11.2(4.0) years.

^c“Other” race category includes White (n=6); American Indian or Alaska Native (n=5); Other Pacific Islander (n=1); and Unknown (n=1).

Table 2.Baseline clinical characteristics for MAACS children ages 5–17 years (n=148).^a

Allergic sensitization characteristics		n (%)		
Atopic (≥1 Positive skin prick test response)		134(91.2)		
Skin test sensitivities				
	Cat	96(65.3)		
	Cockroach	91(61.9)		
	Dust mite	85(57.8)		
	Mouse	78(53.1)		
	Dog	26(17.7)		
Total IgE (kU/L)	Median (p25,p75)	190(55.7, 458)		
Asthma Symptoms in the prior 2 weeks		n (%)		
Number of days with symptoms		[0 – 4]	[5 – 9]	[10 – 14]
Coughing, wheezing, or chest tightness		114 (77)	18 (12)	16 (11)
Nocturnal waking with symptoms		126 (88)	14 (10)	4 (3)
Exercise-related symptoms		129 (88)	8 (5)	9 (6)
Cough without a cold		118 (85)	8 (6)	13 (9)
Slowed activity due to asthma		124 (84)	13 (9)	11 (7)
Maximal symptom days		103 (70)	23 (16)	22 (15)
Short-acting Beta Agonist (SABA) use		101 (68)	17 (11)	30 (20)
Slowed speech due to asthma		147 (99)	1 (1)	0 (0)
Lung function				
FEV1 (% predicted);	Mean (SD)	91.3(15.6)		
FVC (% predicted);	Mean (SD)	100.2(13.5)		
FEV1/FVC%;	Mean(SD)	80.6(9.6)		
Bronchodilator reversibility ^b	n /total (%)	37/130(28.5)		
FeNO, ppb;	Median (p25,p75)	33(16.0, 62.0)		
Asthma-related health care utilization in the prior 3 months		n (%)		
Acute health care visit ^C	93(62.8)			
ED visit	68(46.0)			
Hospitalization	14(9.5)			
Unscheduled doctor’s office visit	35(23.7)			
Controller medication use ^d	106(71.6)			

^a. Information was missing on some participants (atopic status and skin sensitivities: n=1; IgE: n=3; FVC % predicted: n=16; FEV1 % predicted: n=16; FEV1/FVC%: n=16; bronchodilator reversibility: n=18; FENO: n=17).

^b. Bronchodilator reversibility is defined as an increase in FEV1 of 12% or greater following treatment with a short-acting β -agonist or SABA.

^c. Acute health care visits consists of a composite measure of any unscheduled healthcare visit for asthma-related symptoms (e.g., ED visits, hospitalization, and/or unscheduled doctor's visits for asthma).

d. Inhaled corticosteroid or leukotriene inhibitor.

Abbreviations: FEV1: Forced exhaled volume in the first second; FVC: Forced vital capacity; FeNO: fractional exhaled nitric oxide; ED visit: Emergency department visit for asthma.

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Abbreviations: LOD: Limit of detection; %>LOD: Percent of samples with concentrations above the limit of detection; GM: geometric mean; GSD: geometric standard deviation; 95%CI: 95% confidence interval; ICC: intraclass correlation coefficient; OP: organophosphorus.