



Review

Respiratory and allergic health effects in children living near agriculture: A review



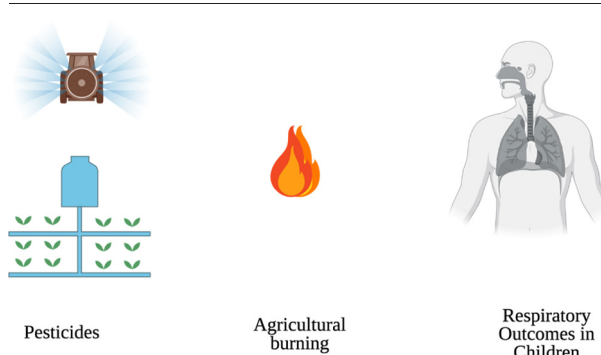
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HIGHLIGHTS

- Pesticide and agricultural burning can impact respiratory health outcomes in children.
- There is heterogeneity in the exposure metrics for pesticides and agricultural burning.
- Most common health outcomes reported are wheezing, coughing, and lung function.
- Lack of joint-effect studies to understand cumulative impact on children.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Exposure to pesticides and agricultural burning are likely to co-occur in agricultural communities, but these exposures have remained distinct bodies of research. We reviewed epidemiological studies to identify the respiratory health effects of children exposed to pesticides and agricultural burning through a systematic evaluation of peer-reviewed publications of children living in industrial agricultural areas.

Methods: Two academic search databases (PubMed and Scopus) were queried for all available studies published in English before May 31st, 2021. The initial search combining both exposure metrics (pesticides and agricultural burning) yielded zero publications and thus the queries were performed and presented separately.

Results: Studies were categorized based on main exposure of interest (i.e., pesticides or agricultural burning) and by respiratory health outcome assessment (i.e., self-reported asthma, acute respiratory symptoms, and lung function measurements). In total we identified 25 studies that focused on pesticide exposures and children's respiratory health, and 12 studies that focused on exposure to agricultural burning and children's respiratory health. A majority of the pesticide studies (18/25) reported a positive association between exposure to pesticides and adverse childhood respiratory health effects. Similarly, most (11/12) of the agricultural burning studies also reported a positive association between exposure to agricultural burning and adverse respiratory health effects.

Conclusion: The most frequently studied health outcomes in these publications were acute respiratory symptoms ($n = 11$ pesticides, $n = 3$ agricultural burning), followed by asthma ($n = 9$ pesticides, $n = 3$ agricultural burning), and lung function measurements ($n = 5$ pesticides, $n = 6$ agricultural burning). Although health outcome assessment differed between pesticide studies and agricultural burning studies, similar adverse respiratory health effects were observed across the majority of studies.

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1.	Introduction	2
2.	Methods	2
2.1.	Search strategy	3
2.2.	Data collection.	3
3.	Results	3
3.1.	Study characteristics	3
3.2.	Exposure metric characteristics	3
3.3.	Self-reported and symptoms-based asthma.	4
3.4.	Respiratory symptoms	8
3.4.1.	General acute respiratory symptoms	8
3.4.2.	Wheezing.	10
3.4.3.	Allergies	10
3.4.4.	Respiratory tract infections	13
3.5.	Lung function	13
4.	Discussion	14
5.	Conclusion.	15
	Funding	16
	CRedit authorship contribution statement	16
	Declaration of competing interest	16
	References	16

1. Introduction

Recent investigations suggest that the prevalence of rural pediatric asthma and asthma-like symptoms is similar to urban counterparts (Fedele et al., 2016; Malik et al., 2012; Ownby et al., 2015; Pesek et al., 2010; Valet et al., 2011); and is correlated with socioeconomic and environmental factors (Buescher and Jones-Vessey, 1999; Chrischilles et al., 2004; Keet et al., 2015; Perry et al., 2018). While earlier research has suggested that living on a small (“family”) farm may provide a protective benefit for children’s respiratory health (Depner et al., 2017; Karvonen et al., 2012; Lawson et al., 2012; Normand et al., 2011; Wells et al., 2014), with the rise of industrial agriculture, it is not clear whether this trend persists (Estrada and Ownby, 2017; Harun and Ogneva-Himmelberger, 2013; Loftus et al., 2016; Pavilonis et al., 2013). Such activities may impact the health of the communities living nearby and contribute to observed rural health disparities. Rural communities are disproportionately exposed to environmental hazards related to industrial agriculture (Kelly-Reif and Wing, 2016). Reduced lung capacity and increased asthma and respiratory symptoms have been reported among agricultural workers (Choma et al., 1998; Dalphin et al., 1998; Gamsky et al., 1992; Hernández et al., 2008; J. A. Hoppin et al., 2009; Jane A. Hoppin et al., 2002), however there remains a gap in understanding the impacts of industrial agricultural activities on the respiratory health of children in nearby communities (W. Benka-Coker et al., 2020; Mora et al., 2020; Raanan et al., 2015, 2016, 2017; P. Salameh et al., 2006). While environmental exposures in occupational rural settings among adults such as agricultural workers have been extensively documented (Chakraborty et al., 2009; Faria et al., 2005; Negatu et al., 2017), less is known about the exposures experienced by children in rural communities. Exposure to organophosphate (OP) pesticides in children has been associated with higher risk of asthma morbidity (W. O. Benka-Coker et al., 2019), decreased lung function (Raanan et al., 2015, 2016), and wheezing (Huq et al., 2020). While data gaps in mechanistic models remain, some preclinical models have suggested that OP pesticide exposures can induce airway hyperactivity via neurogenic inflammation, oxidative stress, and altered neuronal plasticity (Chakraborty et al., 2009; Hernández et al., 2011; Shaffo et al., 2018).

Approximately 50% of earth’s habitable land is dedicated to agricultural usage, of which, 23% is utilized for agricultural crop production (Friedl et al., 2002; Ritchie and Roser, 2019). Industrial agriculture contributes to numerous forms of environmental degradation, including air and water pollution, soil depletion and reduction in biodiversity, which can all in turn impact the health and well-being of nearby communities (Horriagan et al., 2002). Globally, the largest agricultural producers (i.e., European Union, United States (US), Brazil, and China) are also the largest consumers of pesticides, each using over 500 million pounds of pesticides annually

(Donley, 2019; Food and agriculture organizations of the United Nations, 2019; US Geological Survey USGS NAWQA, 2017). In the US alone, the agricultural sector accounts for nearly 90% of the total pesticide usage (U.S. EPA, 2017). In addition to regular exposure to pesticides (von Glascoe and Schwartz, 2019), rural communities are also impacted by pollution generated through agricultural burning (Jenkins et al., 1992), particulate matter (James et al., 2018), and biomass burning (Oluwole et al., 2017). Open burning of agricultural fields to remove crop residue left after harvesting continues to be a common agricultural practice that remains an understudied source of air pollution exposure worldwide (Jenkins et al., 1992). Agricultural burning is widespread, accounting for nearly half as much biomass burned as wildfires (Rangel and Vogl, 2019), and for approximately 10% of the annual fire activity (Korontzi et al., 2006). Across the continental US, agricultural burning amounts to an estimated ~3–5.8 million acres burned annually (McCarty et al., 2009). Each year nearly 50,000 tons of PM 2.5 are attributable to crop burning in the US (Pouliot et al., 2017), potentially affecting 15.5 million people (McCarty, 2011). While prior research has identified adverse health impacts from wildfire events (Holstius et al., 2012) and domestic biomass burning (Naeher et al., 2007), there is a paucity of research on the specific impact of particulate matter (PM 2.5 and PM 10) resulting from agricultural burning on health, despite evidence that it is a widespread practice and associated with the generation of toxic air pollutants (PM 2.5 and PM 10) (He et al., 2020; Jimenez et al., 2006; Johnston et al., 2019; Pasukphun, 2018; Rangel and Vogl, 2019; Reinhardt et al., 2001; Reisen et al., 2011).

The objective of this review was to identify the respiratory health effects (e.g., self-reported asthma, acute respiratory symptoms (e.g., coughing, wheezing, pneumonia), impairment of lung function) of children exposed to pesticides and agricultural burning through a systematic evaluation of peer-reviewed epidemiological publications on children living in agricultural areas. Exposure to pesticides can occur through hand-to-mouth behaviors, time spent outside, exposures from diet, take-home pathways, and pesticide drift. Additionally, rural agricultural communities are also disproportionately exposed to emissions from agricultural burning (Coronado et al., 2011). As emissions of PM 2.5 and 10 from agricultural burning are rising globally and pesticide usage continues to be a growing concern, it is imperative to consider the compounding effects of both pesticides and agricultural burning, particularly in rural communities, which are more likely to be dually impacted by these environmental pollutants.

2. Methods

For this review, we focused on studies investigating the respiratory health effects from exposures to pesticides and agricultural burning, in

children residing in communities near industrial agricultural activities. To be included in this review, publications had to meet the following criteria: a) be focused on children under 18 years of age (or present analyses stratified by age), b) had a respiratory health as the outcome of measure (e.g., asthma, pneumonia, bronchitis), c) taken place in an agricultural or rural area, and d) focused on pesticides and/or agricultural burning as the exposure measure. Only epidemiological studies were included in this review. We excluded studies conducted in urban areas, those focused on residential (i.e., domestic) pesticide exposure such as those concentrated on the application of pesticides to the lawn, or pest management. As particulate matter is likely to have multiple sources (e.g., traffic, proximity to highway, industrial), we only included studies that considered agricultural burning as the exposure. We reviewed and report on the evidence from each exposure (i.e., pesticide or agricultural burning) to each respiratory health effect separately. The focus of this review was to identify published scientific articles on 1) respiratory and allergic health effects in children exposed to pesticides and 2) respiratory and allergic health effects in children exposed to agricultural burning.

2.1. Search strategy

Two academic search databases (PubMed and Scopus) were queried for all available studies published in English before March 31st, 2021, with no limitations on initial cut-off date. The initial search combining both exposure metrics (pesticides and agricultural burning) yielded zero publications and thus the queries were performed and presented separately.

For articles where the exposure metric was pesticides the following terms were searched: (pesticide* OR agrochemical* OR fumigant* OR fungicide* OR insecticide* OR herbicide* OR acaricide* OR nematocide AND (child* OR pregnant* OR prenatal OR offspring OR newborn OR early-life OR infant* OR preschool*) AND (respiratory* OR pulmonary* OR asthma* OR allergy* OR hypersensitivity* OR rhinitis)). This yielded 1257 in PubMed and 853 in Scopus. After excluding studies not published in English, animal, or cell model studies, and removing duplicates, 188 articles remained for abstract screening. From the 50 selected for full-text screening to ensure eligibility, we also excluded reviews and commentaries, 40 were selected for full-text assessment. A total of 15 studies were excluded due to the following reasons: study with only adults as subjects, protocol description, exposure study with no health effects, study focused on indoor exposures, and study took place in an urban only environment. A total of 25 studies met the inclusion criteria.

For articles where the exposure metric was agricultural burning the following terms were searched: (agriculture burn* OR crop residue burn* OR crop burn* OR agricultural burn*) AND (child* OR pregnant* OR prenatal OR offspring OR newborn OR early-life OR infant* OR preschool*) AND (respiratory* OR pulmonary* OR asthma* OR allergy* OR hypersensitivity* OR rhinitis)). This yielded 198 in PubMed and 81 in Scopus. Studies not published in English, animal, or cell model studies and duplicates were excluded, yielding 59 articles for abstract screening. From the 53 selected for full-text screening to ensure eligibility, we also excluded reviews and commentaries, a total of 46 were selected for full-text assessment. A total of 34 studies were excluded due to the following reasons: studies with adults as subjects and no stratified analyses, exposure studies with no health effects. Finally, a total of 12 studies met the inclusion criteria. Due to the relatively small body of literature on this topic, all study designs were considered. The flow chart of the study selection process is shown in Fig. 1a and b.

2.2. Data collection

Information from the selected publications was extracted, including the following from each paper: 1) basic information such as first author, country, and year of publication; 2) study information such as study design, sample size, age of participants, and race/ethnicity of participants; 3) exposure assessment, health outcome assessment, and conclusions. To better understand research gaps, and need for assessment of cumulative impacts, the

following information was also extracted 4a) do agricultural-burning studies mention pesticides as a concern?, and do pesticide studies mention agricultural burning as a concern?; 4b) do studies adjust for other air pollutant exposures?; 4c) are policies and/or structural changes discussed?; and 4d) do studies suggest further research is needed? The articles were organized by exposure of interest (pesticides or agricultural burn) and by health outcome assessment: 1) self-reported asthma; 2) acute respiratory symptoms (e.g., general respiratory symptoms, wheezing, allergies, upper/lower respiratory tract infections; pneumonia, bronchitis) and 3) lung function.

3. Results

3.1. Study characteristics

We identified 25 studies that focused on exposure to pesticides and 12 focused on agricultural burning and respiratory health in children published before March 31st, 2021. The majority of the studies focused on pesticides were conducted in the US ($n = 12$). Other countries with more than one pesticide study included Germany ($n = 2$), Sri Lanka ($n = 2$), and Lebanon ($n = 2$). The oldest pesticide study included in this review was published in 2001 (Karmaus et al., 2001) with over half of the pesticide studies included in this review being published since 2017 ($n = 14$). Of those focused on agricultural burning exposure, most of the published studies were conducted in India ($n = 6$) and Brazil ($n = 4$). Other countries with at least one agricultural burning study included Thailand ($n = 1$), and Japan ($n = 1$). The oldest agricultural burning study included in this review was published in 2000 (Torigoe et al., 2000).

The sample size of each study varied, with a majority of the pesticide studies having less than 1000 participants ($n = 15/25$), and of those, most ($n = 13/15$) had less than 500 participants. Among the pesticide studies, a cohort study in Australia had the largest sample size with $N = 3985$ (Pape et al., 2020). The smallest pesticide study was a subset of the Aggravating Factors of Asthma in a Rural Environment (AFARE) study in 2020 with 16 participants (W. Benka-Coker et al., 2020). For studies focused on agricultural burning, most had less than 1000 participants ($n = 7/12$), of those 4/7 had less than 500 participants. The largest sample size among the agricultural burning studies was from a study in Thailand that utilized Moderate-Resolution Imaging Spectroradiometer satellite data on fire hotspots for a total of $N = 5,641,107$ (Uttajug et al., 2021); the smallest study had 50 participants (R. Agarwal et al., 2010). For studies focused on pesticides, a cohort study design was employed in 24.0% ($n = 6/25$) of the studies included in this review, and of these a majority ($n = 4/6$) were birth-cohorts. A cross-sectional study design was used in 60.0% of the pesticide studies ($n = 15/25$), as well as in half ($n = 6/12$) of the agricultural burning studies included in this review. Hospital records (e.g., hospitalizations or outpatient visits) were utilized to obtain outcome information in four pesticide studies, as well as in four agricultural burning studies.

3.2. Exposure metric characteristics

Pesticide studies that met inclusion criteria for this review were varied, with some focusing on exposure to a single agent (e.g., Dichlorodiphenyltrichloroethane (DDT)) and others focusing on general exposure to pesticides (e.g., proximity to agricultural fields) (Tables 1–6). When we categorized the studies by class of pesticides, we found that more than half ($n = 13/25$) of the studies focused on a single class of pesticides (e.g., organochlorine (OC), organophosphate (OP), or pyrethroid (PYR)), with OCs ($n = 4/25$) and OPs ($n = 5/25$) being the most studied. However, several studies reported assessing exposure to multiple pesticides (e.g., OPs and PYR) ($n = 6/25$), while some did not specify the pesticides of interest ($n = 7/25$) (Tables 1–3). Similarly, we categorized the agricultural burning studies by exposure assessment method (Tables 4–6). The majority ($n = 7/12$) of the studies focused on direct ambient measurements (e.g., PM₁₀, PM_{2.5}, total suspended particles (TSP)), three studies reported assessing exposure to agricultural

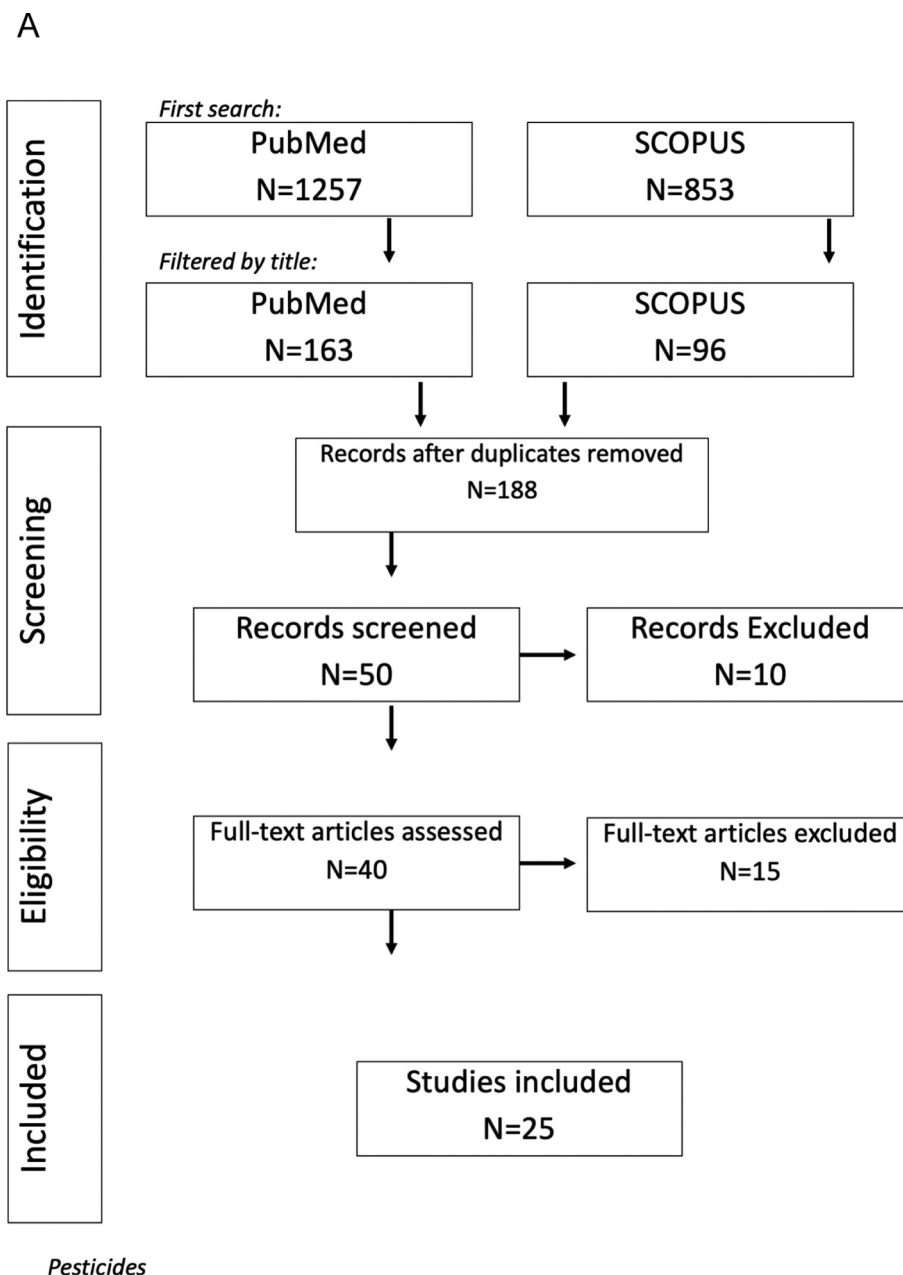


Fig. 1. a.: Flow chart presenting the selection of studies of the association between respiratory and allergic health effect outcomes and pesticides. **b.:** Flow chart presenting the selection of studies of the association between respiratory and allergic health effect outcomes and agricultural burning.

burning through categorization of the surrounding area (e.g., burning vs non-burning season), and two utilized newer satellite-based approaches to quantify exposures.

3.3. Self-reported and symptoms-based asthma

In total, nine studies investigated the association between pesticide exposures and self-reported and symptoms-based asthma (Table 1). Of these studies, two reported using a child self-reported questionnaire and two used a parental self-reported questionnaire to ascertain asthma status, with only one using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (Asher et al., 1995). A total of three

studies reported using biomarkers (i.e., leukotriene E4 in urine (uLTE4) or Th1/Th2 in blood) to assess asthma exacerbations or allergic asthma, (W. Benka-Coker et al., 2020; W. O. Benka-Coker et al., 2019; Duramad et al., 2006) and two utilized emergency department (ED) records for asthma-related visits (Gharibi et al., 2020a, 2020b).

Overall, the research consistently reported associations between exposure to pesticides and asthma (W. Benka-Coker et al., 2020; W. O. Benka-Coker et al., 2019; Duramad et al., 2006; Gharibi et al., 2020a, 2020b; Karmaus et al., 2001). In the two hospital records-based studies, researchers relied on ED visits and defined asthma by utilizing the International Classification of Diseases, 9th Revision (ICD-9) code 493 for asthma (Gharibi et al., 2020a, 2020b). In one study, ED visits in Central

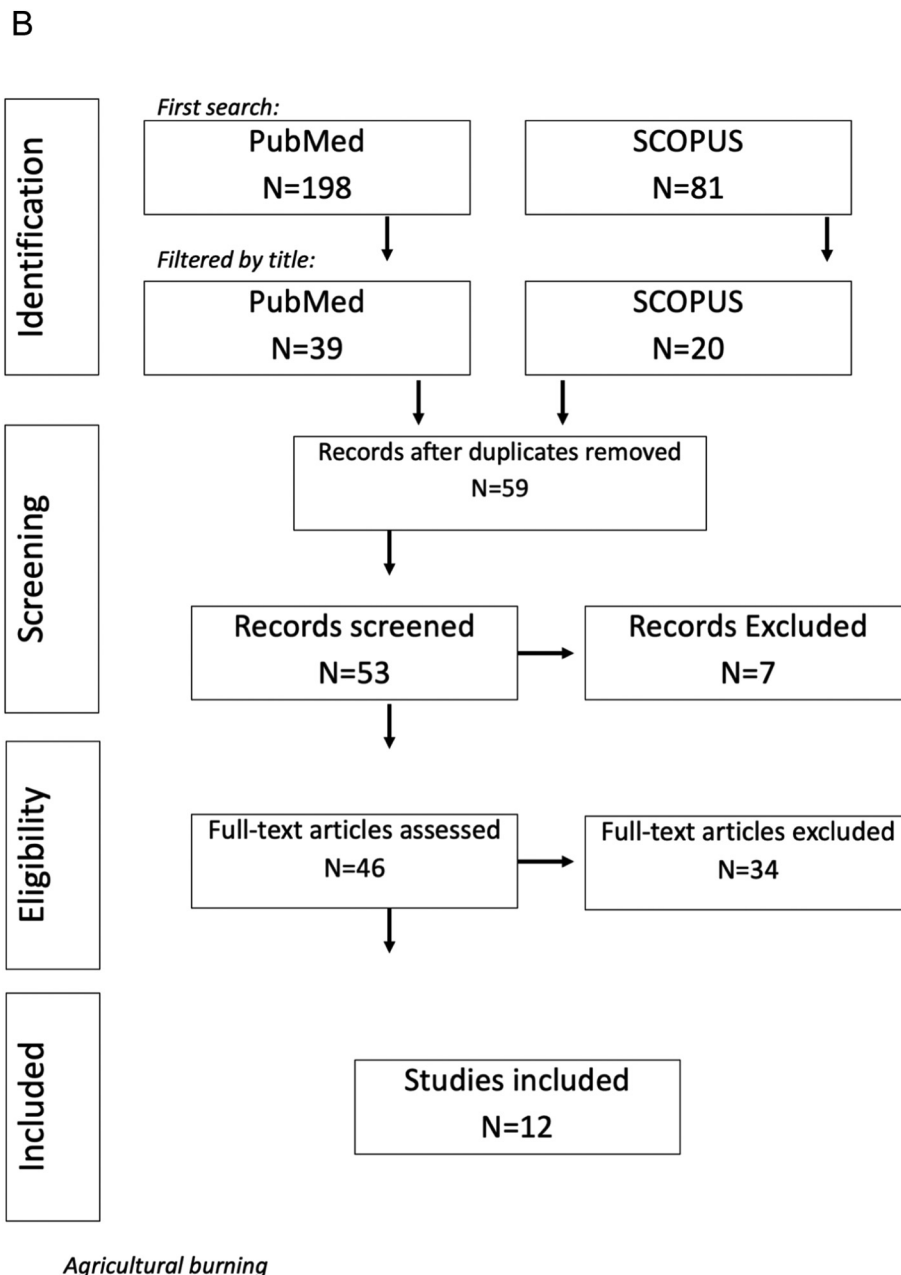


Fig. 1 (continued).

and Southern California were matched with pesticide data from ambient air monitors managed by the U.S. EPA. A 0.01 ppb increase in the ambient concentration of methyl bromide (MBR) was found to be associated with 7.1% (OR 1.071, 95% CI: 1.029–1.108) increased odds of having an asthma ED visit after adjusting for 1,3-Dichloropropene (1,3-D), PM 2.5, nitrogen dioxide (NO₂), temperature, and relative humidity (Gharibi et al., 2020b). However, when stratified by age, MBR was positively associated with asthma ED visits (OR 1.071, 95% CI: 1.016–1.125) only among those children aged 6 to 18 years. Similarly, a 0.01 ppb increase in the ambient concentration of 1,3-D (adjusted for MBR, PM_{2.5}, NO₂, temperature, and relative humidity) was associated with 13.5% (OR 1.135, 95% CI: 1.123–1.149) increase in the odds of having an asthma ED visit (Gharibi et al., 2020a). Additionally, positive associations between ambient 1,3-D and asthma ED visits were found when stratified for children ages 2 to 5 (OR 1.065 95% CI: 1.020–1.133), and 6 to 18 (OR 1.142, 95% CI: 1.086–1.196) (Gharibi et al., 2020a).

Of the studies that measured pesticides using biomarkers, most reported an association between exposure to pesticides and asthma and/or biomarkers of asthma (W. Benka-Coker et al., 2020; W. O. Benka-Coker et al., 2019; Karmaus et al., 2001, 2003; Perla et al., 2015). Among 6 to 16-year old's with asthma in the rural Yakima Valley of Washington, USA, dimethyl alkylphosphate (EDM) (median: 58.3 nmol/g creatine), diethyl alkylphosphate (EDE) (median: 71.2 nmol/g creatine), and all dialkylphosphate pesticides (EDAP) (142.9 nmol/g creatine) levels in urine were positively associated with leukotriene E₄ (uLTE₄) ((β_{EDM} : 1.1 (95% CI: 0.5–1.7)); (β_{EDE} : 8.7 (95%CI: 2.8–14.6)); (β_{EDAP} : 4.1 (95%CI: 0.7–7.5))), a measure of asthma exacerbations (W. Benka-Coker et al., 2020). An association between total urinary DAP metabolites (median: 142.9 nmol/g creatine) persisted (β_{EDAP} : 53.5 (95%CI: 24.2–82.8 pg/mg) in multi-pollutant models accounting for air pollution (PM 2.5 and ozone) (W. O. Benka-Coker et al., 2019). Similarly in Germany, dichlorodiphenyldichloroethane (DDE) (median 0.29 μ g/L) was measured in the blood of 7–10 year old

Table 1
Pesticide studies on self-reported and symptoms-based asthma.

Exposure metric	Author	Location	Study design	N	Age	Race/ethnicity	Pesticide(s) & exposure assessment	Health outcome measure	Results (Strengths of association)
Ambient concentrations	Gharibi et al., 2020a	USA, CA	ED visits 2005–2011	n = 4262	Adults (n = 2579) and kids (n = 1502) visits	White, Black, Hispanics	Methyl Bromide Ambient concentrations Mean(SD) ppb: 0.02(0.05)	Emergency Department visits	†asthma ED visits OR 1.07 _{1e-18} ys 95% CI: 1.016–1.125
	Gharibi et al., 2020b	USA, CA	ED visits 2005–2011	n = 3878	adults (n = 2403) and kids (n = 1331) visits	White, Black, Hispanics	1,3-dichloropropene (1,3-D) Ambient concentrations Mean(SD) ppb: 0.06(0.03)	Emergency Department visits	†asthma ED visits OR 1.06 _{5e-5} ys 95% CI: 1.02–1.133 OR 1.14 _{2e-18} ys 95% CI: 1.086–1.196
Parental Occupation	Duramad et al., 2006	USA	Cross sectional of the CHAMACOS study	n = 414	0 to 24 months	–	Mothers working in agricultural fields where Organophosphate (OP) and Pyrethroids (PYR) are used	Blood samples were collected at 12 and 24 months of age and analyzed for Th1/Th2, biomarkers of allergic asthma.	↑ Th2 allergic asthma Mother working in field 25.9% increase in Th2 levels (95% CI: 0.8–57.3%) ∅ asthma OR _{father} 0.74; 95% CI: 0.52–1.40 OR _{mother} 0.46; 95% CI 0.14–1.51
Proximity to fields	Pape et al., 2020	Australia	population-based cohort study	n = 3985	0 to 15 (diagnosis)	–	Parental exposed to pesticides through occupation	Asthma qx child self-report as adults	∅ asthma OR _{father} 0.74; 95% CI: 0.52–1.40 OR _{mother} 0.46; 95% CI 0.14–1.51
	Bukalasa et al., 2018	Netherlands	Cross-sectional of the PIAMA birth cohort study	n = 1473	age 14	n = 1315/1443 Dutch nationality	General Presence Presence of individual crops at 100, 500, and 1000 m of residences	Asthma qx parent self-report	100, 500 and 1000 m ∅ asthma OR _{100m} : 0.36; 95% CI: 0.09–0.55 OR _{500m} : 0.98; 95% CI: 0.60–1.62 OR _{1000m} : 0.86; 95% CI: 0.52–1.40
Biomarkers	Benka-Coker et al., 2019	USA, Yakima Valley of Washington State	Cross-sectional	n = 16	mean 12	Latino n = 15	OP Urinary metabolites summed to total dialkyl phosphate (EDAP) dimethylphosphate, dimethyl thiophosphate, dimethyl dithiophosphate, diethyl phosphate, diethyl thiophosphate, and diethyl dithiophosphate PM 2.5 and Ozone ambient U.S. EPA monitors EDAP Median (IQR): 142.9 (197.3) nmol/g creatine	Asthma exacerbation (leukotriene E4 (uLTE4)) was assessed in urine samples	↑ asthma exacerbations β _{EDAP} : 53.5; 95%CI: 24.2–82.8 pg/mg creatine
	Benka-Coker et al., 2020	USA, Yakima Valley of Washington State	Case-control of the Aggravating Factors of Asthma in a Rural Environment (AFARE) study cohort	n = 16	6–16	Latino n = 15	OP Urine samples total dimethyl alkylphosphate (EDM) median (IQR): 58.3 (77.5) nmol/g creatine total diethyl alkylphosphate (EDE) median (IQR): 71.2 (79.9) nmol/g creatine total dialkylphosphate (EDAP) median (IQR): 142.9 (197.3) nmol/g creatine	Asthma exacerbation (leukotriene E4 (uLTE4)) in urine samples	↑ asthma exacerbations β _{EDM} : 1.1; 95%CI: 0.5–1.7 μg/g creatine β _{EDE} : 8.7; 95%CI: 2.8–14.6 μg/g creatine β _{EDAP} : 4.1; 95%CI: 0.7–7.5 μg/g creatine
	Karmaus et al., 2001	Germany	Cross-sectional	n = 343	7–10	–	Organochlorines (OCs) Children's blood (at 7–10 years): metabolites DDE (median 0.29 μg/L)	Asthma qx (ISAAC) parents self-report	↑ asthma OR _{OC} 3.30 _{0.33} DDE 3.71; 95% CI: 1.10–12.56
	Petia et al., 2015	USA	cross sectional NHANES	N = 1484	6–16	n = 453 white, n = 571 Mexican American, n = 514 Black	Organophosphate (OP) and Organochlorine (OC) Dialkylphosphate (DAP) dichlorophenyl/dichloroethylene (DDE) serum DAP GM _{age6-11} : 87.7 nmol/g creatine DAP GM _{age12-16} : 57.7 nmol/g creatine DDE GM _{age12-16} : 105 ng/g	Asthma qx child self-report	RR _{OC} 1.94 _{0.33} DDE 6-11: 1.16; 95%CI: 0.62–2.17 RR _{OC} 1.94 _{0.33} DDE 12-16: 1.20; 95%CI: 0.66–2.20 RR _{OC} 1.94 _{0.33} DDE 12-16: 0.81; 95%CI: 0.33–2.00

↑ = increased effect, ↓ = decreased effect, ∅ = no effect.

Table 2
Pesticide studies on acute respiratory symptoms (wheeze, respiratory infections, respiratory health emergency visits, allergies).

Exposure Metric	Author	Location	Study design	N	Age	Race/ethnicity	Pesticide(s) & exposure assessment	Health outcome	Results
Parental Occupation	Runkle et al., 2014	USA	Cross sectional	n = 170	0–1	n = Mother Hispanic 150	Mothers working as farmworkers in femeries or nurseries	Respiratory condition qx parents self-report	↑respiratory condition respiratory conditions higher in infants born to femery workers (17.6%) compared to nurseries (6.4%)
	Tagiyeva et al., 2010	England	Birth Cohort	n = 13,971	0–8.5		maternal postnatal occupation exposure to biocides and fungicides derived ratings (high, medium, low and zero) for the intensity of exposure based on questionnaires on occupation	wheeze, asthma qx parents self-report	Medium/high exposure ↑ wheezing & ↑asthma OR _{wheeze} 1.22, 95% CI: 1.02–2.05 OR _{asthma} 1.47, 95% CI: 1.1–1.88
Clinical diagnosis	Dayasiri et al., 2017	Sri Lanka	Hospital admissions	n = 1621, n = 155 acute pesticide poisoning	9 months to 12 yrs.	–	Children admitted for pesticide poisoning herbicides, rodenticides, insecticides and fungicides and organophosphates (OPs)	respiratory symptoms qx parents self-report	About 8.6%–10.8% of children poisoned presented respiratory symptoms
Questionnaire	Wesjak et al., 2007	Canada	Retrospective cohort	n = 3405	0–12		Questionnaire on pesticides used in agriculture	allergies or hay fever qx parents self-report	Herbicides, insecticides, or any pesticides ↑ allergies or hay fever in >12 OR _{herbicides} 1.98, 95% CI: 1.30–3.01 OR _{insecticides} 1.70, 95% CI: 1.07–2.70 OR _{pesticides} 1.82, 95% CI: 1.24–2.67
	Salameh et al., 2004	Lebanon	Cross-sectional	n = 3291	5–16	–	Questionnaire of pesticide exposure	respiratory disease, asthma, chronic phlegm, recurrent wheezing, and ever wheezing qx (ISAAC)parents self-report	Any exposure ↑ respiratory disease, asthma, chronic phlegm, recurrent wheezing, and ever wheezing OR _{respiratory disease} 1.71, 95% CI: 1.20–2.43 OR _{chronic phlegm} 1.9, 95% CI: 1.26–2.87 OR _{recurrent wheezing} 1.99, 95% CI: 1.39–3.18 OR _{ever wheeze} 1.99, 95% CI: 1.43–2.78
Proxy measure for proximity to fields	Kudagammana and Mohotti, 2018	Sri Lanka	Cross-sectional	n = 182	6–7	–	Conventional vs Organic farm Proximity to a conventional vs organic farm	Allergies qx (ISAAC) children self-report	Allergic conditions were higher (75.2% vs 49.4%) in children with environmental exposure to agrochemicals and chemical fertilizers when compared to that of organic cultivation systems. 10-fold increase in DAP, DE, DM ↑ respiratory symptoms, exercise-induced coughing
Biomarkers	Raanan et al., 2015	USA	Cross-sectional study in CHAMACOS	n = 364	0–7	maternal country of birth Mexico n = 314/364	OP Urine samples Dialkyl phosphate (DAP), specifically diethyl (DE) and dimethyl (DM) phosphate (area under curve (AUC)) DAP median: 1636 (Range:118–18,297) nmol/year/g-creatinine DE median: 251 (Range: 14–16,580) nmol/year/g-creatinine DM median: 1244 (Range: 79–15,460) nmol/year/g-creatinine	respiratory symptoms, exercise-induced coughing qx (ISAAC) parents self-report	OR _{DAP} 2.53, 95%CI: 1.32–4.86 OR _{DE} 5.40, 95%CI: 2.10–13.91 OR _{DM} 2.35, 95%CI: 1.27–4.34 OR _{DE} 3.62, 95%CI: 1.38–9.55 OR _{DM} 2.17, 95%CI: 1.19–3.98 OR _{DM} 4.46, 95%CI:1.81–10.98
	Karmaus et al., 2003	Germany	Cross-sectional	n = 338	7–10	–	OCs Children's blood (at 7–8 years): DDE (median 0.29 µg/L – 1)	ever asthma and allergic symptoms qx (ISAAC) parents self-report	○ ever asthma, allergic symptoms (atopic eczema, hay fever) OR _{asthma} 3.04, 95%CI 0.53–22.3 OR _{eczema} 1.74, 95%CI 0.73–4.27
	Huq et al., 2020	Vhembe district of Limpopo, South Africa	Birth cohort	n = 658	3.5 yrs.	–	OCs Maternal peripartum serum in dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyltrichloroethane (DDT) DDE median 57.2 ng/g lipid (Range: <0.03–15.027) DDT median 249.2 ng/g lipid (Range: 4–22,613)	wheezing qx (ISAAC) parents self-report	OR _{hayfever} 2.74, 95%CI: 0.58–15.83 p,p'-DDT ↑ wheezing p,p'-DDE ○ wheezing OR _{DDT} 1.5, 95% CI: 1.0–2.3 OR _{DDE} 1.4, 95% CI: 0.8–2.4

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Table 2 (continued)

Exposure Metric	Author	Location	Study design	N	Age	Race/ethnicity	Pesticide(s) & exposure assessment	Health outcome	Results
	Cupul-Uicab et al., 2014	Mexico	Birth Cohort	n = 747 boys	0–21 months	–	OCs Maternal Serum Samples p,p'-DDE and p,p'-DDT p,p'-DDE median(IQR): 0.27 (0.67) µg/g lipid p,p'-DDT median(IQR): 2.70 (4.50) µg/g lipid Fungicides, OP pyrethroids, herbicides Urine samples Metabolites: ETU, TCPy 3PBA, 2,4-D, DCCA, OH-PYR, 5-OH-TBZ throughout pregnancy average ng/mL specific gravity adjusted median (range) ETU 3.35(0.81–127.38) TCPy 1.75 (0.41–62.96) 3PBA 0.79 (0.10–16.96) 2,4-D 0.33 (0.09–79.76) DCCA 1.30 (0.15–26.56) OH-PYR 0.56 (<LOD–368.55) 5-OH-TBZ 0.11 (<LOD–339)	pneumonia, bronchitis or LRTI qx parents self-report	Ø LRTI IRR _{IQ} increase in DDE: 0.92, 95%CI: 0.78–1.10 IRR _{IQ} increase in DDT: 0.95, 95%CI: 0.86–1.04
	Mora et al., 2020	Costa Rica	Birth cohort	n = 355 LRTI, Wheezing n = 272	0 to 1	Maternal country of birth CR n = 266/355	ETU, TCPy 3PBA, 2,4-D, DCCA, OH-PYR, 5-OH-TBZ Ø LRTI, wheezing ETU OR _{wheez} 0.69, 95%CI: 0.37–1.28; OR _{LRTI} 1.50, 95%CI: 0.70–3.19 TCPy OR _{wheez} 0.86, 95%CI: 0.48–1.54; OR _{LRTI} 0.84, 95%CI: 0.36–1.95 3PBA OR _{wheez} 1.07, 95%CI: 0.60–1.90; OR _{LRTI} 1.64, 95%CI: 0.78–3.47 2,4-D OR _{wheez} 0.87, 95%CI: 0.48–1.59; OR _{LRTI} 1.48, 95%CI: 0.69–3.14 DCCA OR _{wheez} 0.74, 95%CI: 0.39–1.38; OR _{LRTI} 1.07, 95%CI: 0.49–2.36 OH-PYR OR _{wheez} 0.83, 95%CI: 0.45–1.53; OR _{LRTI} 1.49, 95%CI: 0.70–3.18 5-OH-TBZ OR _{wheez} 0.80, 95%CI: 0.45–1.45; OR _{LRTI} 0.98, 95%CI: 0.45–2.16	physician or nurse diagnosis of LRTIs and wheeze (ISAAC) parents self-report	

↑ = increased effect, ↓ = decreased effect, Ø = no effect.
LOD = limit of detection.

children, those with DDE ≥ 0.3 µg/L had higher odds of asthma (OR 3.71, 95% CI: 1.10–12.56) compared to those with DDE < 0.3 µg/L (Karmaus et al., 2001).

In contrast, four studies did not observe significant associations between pesticide exposures and asthma (Bukalasa et al., 2018; Karmaus et al., 2003; Pape et al., 2020; Perla et al., 2015). In a study from Northern Europe, Spain, and Australia parental occupational exposure to pesticides was not associated (OR_{father occupation}: 0.74 (95%CI: 0.40–1.37); OR_{mother occupation}: 0.46 (95%CI: 0.14–1.51)) with asthma in children 0–15 years old (Pape et al., 2020). In the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, there was no association (OR_{100m}: 0.36 (95%CI: 0.09–0.55); OR_{500m}: 0.98 (95%CI: 0.60–1.62); OR_{1000m}: 0.86 (95%CI: 0.52–1.40)) between living within 100, 500 and 1000 m of agricultural fields likely treated with pesticides and symptoms of asthma at age 14 (Bukalasa et al., 2018). Additionally, there was no significant association between DDE measured in children's serum (median: 0.29 µg/L) in Germany and children's ever asthma (OR: 3.04 (95% CI: 0.53–22.3)) (Karmaus et al., 2003) (Table 2). Furthermore, there was no significant association between concentrations of biomarkers of pesticide exposure (urinary DAP (OP)) (GM_{age6–11}: 87.7 nmol/g creatine; GM_{age12–16}: 57.7 nmol/g creatine) or serum DDE (OC) (GM_{age12–16}: 105 ng/g) and asthma diagnosis among 6–16-year-olds enrolled in the US-based National Health And Nutrition Examination Survey (NHANES) (RR_{75%DAP 6–11}: 1.16 (95%CI: 0.62–2.17); RR_{75%DAP 12–16}: 1.20 (95%CI: 0.66–2.20); RR_{80%DDE 12–16}: 0.81 (95%CI: 0.33–2.00)) (Perla et al., 2015) (Table 1).

We identified three studies that investigated and found an association between exposure to agricultural burning and asthma (Table 4). Two studies relied on asthma hospitalization records, defining asthma by utilizing the International Classification of Diseases, 9th Revision (ICD-9) or 10th Revision (ICD-10) codes (Cançado et al., 2006; Uriarte et al., 2009). Increased monthly incidence in fire occurrence from sugarcane cultivation were associated with respiratory morbidity among children 10 years of age and younger (estimate 0.195, SE 0.08, p -value < 0.0001) (Uriarte et al., 2009). Similarly, in Japan, during the rice straw burning season there was an increase in visits to the ED for asthma attacks among 0–25-year olds (7.1 ± 3.9 vs 4.5 ± 3.9 p -value < 0.001) (Torigoe et al., 2000). One study from Brazil investigated the association between emissions from sugarcane burning and respiratory health by measuring PM 10 and PM 2.5 (Cançado et al., 2006). An increase of 10.2 µg/m³ in PM 2.5 was associated with a 21.4% (95% CI: 4.3–38.5) increase in respiratory hospital admissions, and an increase in 42.9 µg/m³ in PM10 was associated with a 24.5% (95% CI: 4.3–47.5) increase in asthma hospitalizations in children under 13 years of age (Cançado et al., 2006).

3.4. Respiratory symptoms

A total of 11 studies were identified that examined the association between pesticide exposures and acute respiratory symptoms (e.g., coughing, wheezing, allergies, and respiratory tract infections) (Table 2). Overall, the majority suggest an association between pesticide exposures and increased respiratory symptoms, wheezing, and respiratory tract infections in children. Similarly, the three studies focusing on exposure to agricultural burning and acute symptoms (e.g., respiratory infections, respiratory health hospitalizations) identified in this review ($n = 3$) report a positive association (Table 5).

3.4.1. General acute respiratory symptoms

In a multi-center study in Sri Lanka investigating clinical manifestations of pesticide poisoning, 9.4% of the children presented with respiratory symptoms (Dayasiri et al., 2017) (Table 2). Similarly, a 10-fold increase exposures to OP pesticides, measured as total DAP metabolites in urine (median: 1636 (Range: 118–18,297) nmol/year/g-creatinine), were associated with respiratory symptoms (OR_{per 10-fold increase} 2.53, 95% CI: 1.32–4.86) and exercise-induced coughing (OR_{per 10-fold increase} 5.40, 95% CI: 2.10–13.91) in 5 to 7-year-old children (Raanan et al., 2015) (Table 2). Maternal occupational exposure to pesticides was also reported as a risk factor

Table 3
Pesticide studies on lung function measurements.

Exposure metric	Author	Location	Study design	N	Age	Race/ethnicity	Pesticide(s) & exposure assessment	Health outcome measure	Results
Proximity to fields	Raanan et al., 2017	USA, CA	Cross-sectional study in CHAMACOS	n = 347	age 7	maternal country of birth Mexico n = 208/237	Elemental sulfur (kg) applications within 0.5, 1, and 3 km of a residence one year Median (25th–95th) 0.5 km: 0 (0–442.1) Median (25th–95th) 1.0 km: 73.4 (0–2235) Median (25th–95th) 3.0 km: 6229 (2295–14,877)	Questionnaire and Spirometry, (FEV ₁), (FVC), (FEF _{25–75}) (Two acceptable blows)	Sulfur 1 km ↓ FEV ₁ , ∅ FEF _{25–75} , FVC, FEV ₁ /FVC 10-fold increase sulfur 1 km: FEV ₁ (β = −0.143, 95%CI −0.248 to −0.039), FVC (β = −0.127, 95%CI −0.230 to −0.024), FEF _{25–75} (β = −0.165, 95%CI −0.338 to 0.007), FEV ₁ /FVC (β = −0.005, 95%CI −0.017 to 0.007) Sulfur 0.5 km ↓ FEV ₁ , ∅ FEF _{25–75} , FEV ₁ /FVC, FVC Sulfur 3 km ∅ FEV ₁ , FVC, FEF _{25–75} , FEV ₁ /FVC prenatal exposure: chloropiricin, metan sodium or 1,3-dichloropropene at 8 km ∅ FEV ₁ , FVC, FEF _{25–75} 10-fold increase chloropiricin 8 km: FEV ₁ (β = 0.04, 95%CI: −0.01 to 0.09); FVC (β = 0.05, 95%CI: −0.01 to 0.11) 10-fold increase metan sodium 8 km: FEV ₁ (β = −0.03, 95%CI: −0.08 to 0.02); FVC (β = −0.02, 95%CI: −0.04 to 0.04); FEF _{25–75} (β = −0.08, 95%CI: −0.18 to 0.03) 10-fold increase 1,3-dichloropropene 8 km: FEV ₁ (β = −0.02, 95%CI −0.07 to 0.02); FVC (β = −0.03, 95%CI: −0.09 to 0.03); FEF _{25–75} (β = −0.08, 95%CI: −0.18 to 0.02) methyl bromide at 8 km ↑ FEV ₁ , FEF _{25–75} , ∅ FVC 10-fold increase methyl bromide 8 km: FEV ₁ (β = 0.06, 95%CI 0.00 to 0.12); FEF _{25–75} (β = 0.15, 95%CI: 0.03 to 0.27); FVC (β = 0.06, 95%CI: 0.01 to 0.13) chloropiricin at 8 km ↓ FEF _{25–75} 10-fold increase chloropiricin 8 km: FEF _{25–75} (β = 0.11, 95%CI: 0.00 to 0.21)
							Agricultural fumigants (kg) Methyl bromide, chloropiricin, metan sodium and 1,3-dichloropropene applications within 8 km of residences mean (SD) Prenatal pesticide use methyl bromide 13,380 (10437) chloropiricin 8665 (6816) metan sodium 466 (1451) 1,3-dichloropropene 867 (1770) Postnatal pesticide use methyl bromide 88,449 (59061) chloropiricin 97,869 (67513) metan sodium 10,166 (9558) 1,3-dichloropropene 6073 (45929)	Questionnaires and Spirometry, (FEV ₁), (FVC), (FEF _{25–75})	Postnatal exposure: Methyl bromide, chloropiricin, metan sodium or 1,3-dichloropropene at 8 km ∅ FEV ₁ , FEF _{25–75} , FVC 10-fold increase methyl bromide 8 km: FEV ₁ (β = −0.10, 95%CI: −0.28 to 0.08); FVC (β = −0.04, 95%CI: −0.25 to 0.18); FEF _{25–75} (β = −0.14, 95%CI: −0.51 to 0.23) 10-fold increase chloropiricin 8 km: FEV ₁ (β = −0.01, 95%CI: −0.16 to 0.13); FVC (β = 0.00, 95%CI: −0.17 to 0.18); FEF _{25–75} (β = 0.05, 95%CI: −0.25 to 0.35) 10-fold increase metan sodium 8 km: FEV ₁ (β = 0.04, 95%CI: −0.04 to 0.13); FVC (β = 0.05, 95%CI: −0.05 to 0.16); FEF _{25–75} (β = 0.05, 95%CI: −0.12 to 0.23) 10-fold increase 1,3-dichloropropene 8 km: FEV ₁ (β = 0.00, 95%CI: −0.15 to 0.14); FVC (β = 0.04, 95%CI: −0.13 to 0.22); FEF _{25–75} (β = −0.01, 95%CI: −0.31 to 0.29) ∅ for 3 and 5 km Total DAP, ∅ FEV ₁ Total DAP, ∅ FVC or FEF _{25–75} DE ↓ FEF _{25–75} or FVC DM ∅ FEV ₁ , FVC or FEF _{25–75} (10-fold increase total DE: FEV ₁ (β = −0.18, 95%CI −0.32 to −0.05); FVC (β = −0.18, 95%CI −0.34 to −0.02); FEF _{25–75} (β = −0.36, 95%CI −0.64 to −0.08)) (10-fold increase total DAPs: FEV ₁ (β = −0.14, 95%CI: −0.29 to 0.00); FVC (β = −0.12, 95%CI: −0.29 to 0.05); FEF _{25–75} (β = −0.18, 95%CI: −0.49 to 0.12)) (10-fold increase total DM: FEV ₁ (β = −0.10, 95%CI: −0.23 to 0.04); FVC (β = −0.08, 95%CI: −0.24 to 0.09); FEF _{25–75} (β = −0.09, 95%CI: −0.37 to 0.23))
Biomarkers	Raanan et al., 2016	USA	Cross sectional of the CHAMACOS study	n = 279	6 to 60 months	maternal country of birth Mexico n = 237/279	OPs Urine Samples DEs: diethylphosphate, diethylthiophosphate and diethylthiophosphate) and three dimethyl (DMs: dimethylphosphat, dimethylthiophosphate and dimethylthiophosphate) phosphates GM DAP: 145 nmol/L specific gravity-adjusted GM DE: 22 nmol/L specific gravity-adjusted GM DM: 105 nmol/L specific gravity-adjusted	Spirometry FVC, FEV ₁ , and FEF 25–75 (1–3 acceptable blows)	

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Table 3 (continued)

Exposure metric	Author	Location	Study design	N	Age	Race/ethnicity	Pesticide(s) & exposure assessment	Health outcome measure	Results
	Raherison et al., 2019	France	Cross-sectional	n = 281	3–10 yrs	-	56 pesticides in the ambient outdoor air around schools and dithiocarbamates & pesticides measured in urine ethylenethiourea (ETU) concentrations in urine in a subsample of children (n = 96) and Phyto Index ETU range (0.01–12.42) µg/g creatinine Pyrethroids (PYR) Urine Samples 3-phenoxybenzoic acid GM: 0.50 µg/g creatinine	Questionnaire and peak expiratory flow (PEF).	Pesticides in air or ETU ϕ PEF (OR _{air} 0.73, 95%CI: 0.20 to 2.72) (OR _{ETU} 1.52, 95%CI: 0.24 to 9.55)
	Hu et al., 2021	USA NHANES	cross sectional	n = 1174	6–17	White, Mexican American, Black, other		Spirometry FVC, FEV ₁ , and PEF 25–75	↓ FEV ₁ , FVC, PEF ϕ FEF _{25–75} , FEV ₁ /FVC FEV ₁ (β = -0.01, 95%CI -0.02 to -0.002) FVC (β = -0.01, 95%CI -0.02 to -0.004) PEF (β = -0.01, 95%CI -0.02 to -0.01) FEF _{25–75} (β = -0.01, 95%CI: -0.02 to 0.01) FEV ₁ /FVC (β = 0.002, 95%CI: -0.001 to 0.01)

↑ = increased effect, ↓ = decreased effect, ϕ = no effect.
GM = geometric mean.

among infants born in the US (J. Runkle et al., 2014). Infants born to mothers working in ferneries had a higher rate of diagnosis of respiratory conditions (17.6%) compared to infants born to mothers working in nurseries (6.4%) (J. Runkle et al., 2014). While pesticides were not measured among infants, previous research among the mothers reported higher OP exposures (measured as DAP, DMP, DEP, DMTP, DETP, DMDTP in urine) among nursery than fernery workers (J. D. Runkle et al., 2013). Two agricultural burning studies relied on hospitalization records, with both defining respiratory disease by utilizing the International Classification of Diseases, 10th Revision (ICD-10) codes (Paraiso and Gouveia, 2015; Uttajug et al., 2021) (Table 5). Monthly increases in fire occurrences were positively associated (standardized morbidity ratio mean(SD): 0.0008 (0.003), p-value = 0.008) with hospitalizations for respiratory disease in those under five (Paraiso and Gouveia, 2015). One study incorporated measures of ambient air pollutants from agricultural burning into their exposure assessment (Uttajug et al., 2021). On burning days mean concentrations of PM 10 were higher and ranged from 122.9 to 165.1 µg/m³, compared to non-burning days 18.0 to 30.4 µg/m³. Among 0–15-year old's in Thailand a 10 µg/m³ increase in PM 10 on burning days was associated with a respiratory disease-related hospital visits (OR: 1.01, 95% CI: 1.00–1.02) (Uttajug et al., 2021) (Table 5).

3.4.2. Wheezing

In a cross-sectional study of 5–16-year-olds in Lebanon, any type of pesticide exposure (i.e., regional exposure (proximity to a field), household use, or occupational exposure) was associated with respiratory disease (OR 1.71, 95% CI: 1.20–2.43), chronic phlegm (OR 1.9, 95% CI: 1.26–2.87), recurrent wheezing (OR 2.1, 95% CI: 1.39–3.18), and ever wheeze (OR 1.99, 95% CI: 1.43–2.78) (P. R. Salameh et al., 2004) (Table 2). Within the same study, residential pesticide exposure (i.e., regional or proximity to a treated field) was also associated with respiratory disease (OR 1.82, 95% CI: 1.28–2.59), chronic phlegm (OR 1.59, 95% CI: 1.03–2.45), recurrent wheezing (OR 2.73, 95% CI: 1.85–4.05), and ever wheezing (OR 2.55, 95% CI: 1.84–3.52) (P. R. Salameh et al., 2004). The authors did not partition data by pesticide type (e.g., OPs, OCs, PYR). In participants of the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE) birth cohort study in South Africa, maternal peripartum serum p,p'-DDT concentrations (median: 57.2 ng/g lipids) were associated (OR 1.5, 95% CI: 1.0–2.3) with wheezing in 3.5-year-old children (Huq et al., 2020). Additionally, two studies examined children's respiratory health in relation to maternal pesticide exposures (Mora et al., 2020; Tagiyeva et al., 2010). In the Avon Longitudinal Study of Parents and Children (ALSPAC), an English birth cohort study, among children up to 7 years of age, maternal levels of postnatal occupational exposure to biocides/fungicides were associated with increased odds of wheezing (OR 1.22, 95% CI: 1.02–2.05) and asthma (OR 1.47, 95% CI: 1.1–1.88) (Tagiyeva et al., 2010). In contrast, in the infants' Environmental Health (ISA) study, pesticide metabolites (specific gravity-adjusted, ng/mL) were measured in urine samples of mothers in Costa Rica (ethylenethiourea (ETU) (median: 3.35); 3,5,6-trichloro-2-pyridinol (TCPy) (median: 1.75); 3-phenoxybenzoic acid (3-PBA) (median: 0.79); 2,4-dichlorophenoxyacetic acid (2,4-D) (median: 0.33); 3-(2,2-di-chlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (DCCA) (median: 1.30); 3-hydroxypyrimetanil (OH-P) (median: 0.56); and 5-hydroxythiabendazol (5-OH-TBZ) (median: 0.1)). No significant association between pesticides and wheezing at one year of age were found (ETU (OR 0.69, 95%CI: 0.37–1.28); TCPy (OR 0.86, 95%CI: 0.48–1.54); 3PBA (OR 1.07, 95%CI: 0.60–1.90); 2,4-D (OR 0.87, 95%CI: 0.48–1.59); DCCA (OR: 0.74, 95%CI: 0.39–1.38); OH-PYR (OR 0.83, 95%CI: 0.45–1.53); 5-OH-TBZ (OR 0.80, 95%CI: 0.45–1.45) (Mora et al., 2020) (Table 2).

3.4.3. Allergies

Among children living in Salinas Valley, CA, US, serum Th2 levels (a biomarker of allergy/atopy) at 24 months of age were higher for those who lived with an agricultural worker or whose mother worked in the agricultural fields (Duramad et al., 2006) (Table 1). In Canada, children

Table 4
Agricultural burning studies on self-reported and symptoms-based asthma.

Exposure metric	Author	Location	Study design	N	Age	Race/ethnicity	Crop	Exposure assessment	Health outcome assessment	Results
Burning or fire occurrence	Torigoe et al., 2000	Niigata, Japan	Ecological	700	0–25	–	Rice	Ambient PM ₁₀ and burning vs non-burning months Range 100 to 400 µg/m ³ per hr. Ambient TSP (<50 µm), PM _{2.5} & fire occurrence through satellite images TSP range 40–90 µg/m ³ PM _{2.5} range 10–35 µg/m ³	Outpatient records on asthma attacks 1994–1998 Asthma hospitalizations 2003 ICD-10, codes J00–J99	burning months ↑ emergency room visits and hospitalizations for asthma attacks (7.1 ± 3.9 vs 4.5 ± 3.9 p-value <0.001) fire occurrence ↑ asthma hospitalizations β = 0.195; SE 0.08, p-value < 0.0001
Particulate Matter	Uriarte et al., 2009	Brazil	Ecological time-series	N = 18,052; <10 N = 5196; > 60	Under 10 and >60	–	Sugarcane	Ambient PM _{2.5} , PM ₁₀ , black carbon, burning vs non-burning Mean(SD) PM _{2.5} : burning 22.8 (14.7) µg/m ³ vs. non-burning 10.0 (4.6) µg/m ³ Mean(SD)PM ₁₀ : burning 87.7(57.9) µg/m ³ vs. non-burning 28.9(12.8) µg/m ³	Asthma hospitalizations 1997–1998 (International Classification of Diseases, revision 9, ICD-9, codes 460–519; revision 10, ICD-10, codes J00–J99)	PM _{2.5} & PM ₁₀ ↑ asthma hospitalizations 10.2 µg/m ³ increase in PM _{2.5} 21.4% (95% CI: 4.3–38.5) 42.9 µg/m ³ increase in PM ₁₀ 24.5% (95% CI: 4.3–47.5)

↑ = increased effect, ↓ = decreased effect, Ø = no effect.

Table 5
Agricultural burning studies on acute respiratory symptoms (wheeze, respiratory infections, emergency visits).

Exposure metric	Author	Location	Study design	N	Age	Race/ethnicity	Crop (s)	Exposure assessment	Health outcome assessment	Results
Burning or fire occurrence	Chakrabarti et al., 2019	India	Cross-sectional	N = 252,539 N = 18,688	0+ Sub: < 5	–	Fire occurrences	Moderate-Resolution Imaging Spectroradiometer satellite data on fire occurrence between 2013 and 2014 Monthly burning outbreaks through satellite images	Questionnaire on acute respiratory infections between 2013 and 2014 hospitalizations for respiratory diseases 2010 ICD-10, codes not mentioned	ACRB ↑ acute respiratory infections among <5 RR 3.65, 95% CI: 3.06–4.34 burning outbreak ↑ hospital admissions for respiratory disease under 5 standardized morbidity ratio mean (SD): 0.0008(0.003), p-value = 0.008 PM ₁₀
Particulate Matter	Paraiso and Gouveia, 2015	Brazil	Ecological	645 municipalities and 2010, N missing	Under 5 and > 65	–	Sugarcane	Ambient PM ₁₀ , NASA-MODIS fire hotspots Burning days mean PM ₁₀ range: 122.9–165.1 µg/m ³ non-burning days mean PM ₁₀ range: 18.0–30.4 µg/m ³	Outpatient hospital visits 2014–2018 (ICD-10: J00–J99.8)	↑ Respiratory disease hospital visit 10 µg/m ³ increase in PM ₁₀ OR: 1.01, 95% CI: 1.00–1.02

↑ = increased effect, ↓ = decreased effect, Ø = no effect.

ACRB = Acute Crop Residue Burning.

Table 6
Agricultural burning studies on lung function measurements.

Exposure metric	Author	Location	Study Design	N	Age	Race/ethnicity	Crop	Exposure assessment	Health outcome assessment	Results
Burning or Fire occurrence	Gupta et al., 2016	India	Cross-sectional	N = 150	10–16	–	Rice & wheat	PM _{2.5} , PM ₁₀ , burning vs non-burning period Burning PM _{2.5} 43–107 µg/m ³ PM ₁₀ 71–167 µg/m ³ Non-burning Below 60 µg/m ³ for PM _{2.5} and 100 µg/m ³ for PM ₁₀	FVC, PEF	FVC and PEF decreased more during burning period vs (non-burning) Decrease in FVC (5%–7%) and PEF (4%–6%)
Particulate Matter	Awasthi et al., 2010	India	Cross-sectional	Total N = 40 N = 23 N = 17	10–13 20–35	–	Rice and wheat	SPM Before: 170 ± 48 µg/m ³ SPM During: 456 ± 13 µg/m ³ SPM After: 227 ± 30 µg/m ³ PM _{2.5} Before: 47 ± 1.1 µg/m ³ PM _{2.5} During: 98 ± 1.5 µg/m ³ PM _{2.5} After: 65 ± 4.9 µg/m ³ PM ₁₀ Before: 84 ± 1.1 µg/m ³ PM ₁₀ During: 160 ± 1.3 µg/m ³ PM ₁₀ After: 106 ± 8.4 µg/m ³	FVC, FEV ₁ , PEF, FEF _{25–75}	SPM, PM _{2.5} , PM ₁₀ ↓FVC, FEV ₁ , PEF, and FEF _{25–75} SPM (increment 10 µg/m ³) FVC: –0.151(95%CI: –0.260to-0.041); FEV ₁ : –0.192(95%CI: –0.323to-0.062); PEF: –0.092(95%CI: –0.168to-0.017); FEF _{25–75} -0.122(95%CI: –0.260to0.016) PM _{2.5} (increment 10 µg/m ³) FVC: –0.943(95%CI: –1.718to-0.169); FEV ₁ : –1.251(95%CI: –2.149to-0.353); PEF: –0.725(95%CI: –1.152to-0.299); FEF _{25–75} -0.939(95%CI: –1.068to-0.181) PM ₁₀ (increment 10 µg/m ³) FVC: –0.625(95%CI: –1.068to-0.181); FEV ₁ : –0.804(95%CI: –1.326to-0.281); PEF: –0.433(95%CI: –0.706to-0.163); FEF _{25–75} -0.584(95%CI: –1.107to-0.061)
	Agarwal et al., 2010	India	Cross-sectional	N = 51	13–53	–	Wheat	SPM Before: 291 ± 71 µg/m ³ SPM During: 366 ± 152 µg/m ³ SPM After: 181 ± 66 µg/m ³ PM _{2.5} Before: 291 ± 71 µg/m ³ PM _{2.5} During: 366 ± 152 µg/m ³ PM _{2.5} After: 181 ± 66 µg/m ³ PM ₁₀ Before: 291 ± 71 µg/m ³ PM ₁₀ During: 366 ± 152 µg/m ³ PM ₁₀ After: 181 ± 66 µg/m ³	FVC, FEV ₁ , PEF, FEF _{25–75}	During ↓FVC, FEV ₁ , PEF, and FEF _{25–75} During FVC -4.1 (95%CI: –1.7to-6.5); FEV ₁ -3.5 (95%CI: –0.7to-6.4); PEF -3.3 (95%CI: 1.1to-5.6); FEF _{25–75} -3.6 (95%CI: –1.6to-5.5) After ↓FVC, FEV ₁ , PEF, and FEF _{25–75} After FVC -1.1 (95%CI: –1.9to-4.2); FEV ₁ -0.9 (95%CI: –2.9to-4.8); PEF -0.08 (95%CI: –5.8to-5.6); FEF _{25–75} -0.6 (95%CI: –5.7to-7.0) SPM ↓FVC, FEV ₁ , PEF, and FEF _{25–75} SPM (increment 126 µg/m ³) FEF _{25–75} -3.0 (95%CI: –7.2 to 1.0); FVC -1.4 (95%CI: –4.7to1.8); FEV ₁ -1.1 (95%CI: 4.3to2.1); PEF -3.5 (95%CI: –5.8to –1.3) PM ₁₀ (increment 36 µg/m ³) FEF _{25–75} -3.2 (95%CI: –6.6 to –0.2); FVC -2.1 (95%CI: –4.1 to –0.12); FEV ₁ -2.0 (95%CI: –3.9 to –0.16); PEF -3.3 (95%CI: –5.5 to –1.1) PM _{2.5} ↓FVC, FEV ₁ , PEF, and FEF _{25–75} PM _{2.5} (increment 19 µg/m ³) FEF _{25–75} -3.7 (95%CI: –6.8 to –0.5); FVC -2.2 (95%CI: –4.4 to 0.02); FEV ₁ -2.1 (95%CI: –4.2 to 0.0); PEF -3.6 (95%CI: –5.7 to –1.5)
	Riguer et al., 2011	Brazil	Cross-sectional	N = 817 QX N = 131 PFT	10–14	–	Sugarcane	Ambient black carbon, PM _{2.5} Mean (SD) PM _{2.5} : 17.1 (7.4), range (8.7–39.2) µg/m ³ Mean (SD) Black carbon: 1.44 (0.64), range (0.09–2.98)	Questionnaire and PEF	PM _{2.5} & BC ↓ PEF Difference between daily prevalence's of PEF below 20% (0 prevalence, 0.01% to 4.9% or ≥ 5%) was not different by PM _{2.5} levels (p = 0.18) or black carbon levels (p = 0.05)

Agarwal et al., 2013	India	Cross-sectional	N = 50 (N = 10)	13-53 (<18)	Rice and wheat	SPM, PM ₁₀ - PM _{2.5}	FVC, FEV ₁ , PEF, FEF ₂₅₋₇₅	SPM ↓FVC, FEV ₁ , PEF, and FEF ₂₅₋₇₅ PM ₁₀ ↓FVC, FEV ₁ , PEF, and FEF ₂₅₋₇₅ PM _{2.5} ↓FVC, FEV ₁ , PEF, and FEF ₂₅₋₇₅
	India	Cross-sectional	N = 150	10-12	Rice & wheat	PM was greater in rice seasons than in wheat seasons.	FVC, FEV ₁ , PEF, FEF ₂₅₋₇₅	Wheat & Rice period PM ₁₀ ↓FVC, FEV ₁ , PEF, and FEF ₂₅₋₇₅ Wheat & Rice period PM 2.5 ↓FVC, FEV ₁ , PEF, and FEF ₂₅₋₇₅ 10 µg/m ³ PM _{2.5} ~ FVC -5.27% to -7.53% vs. (-2.57% to -5.02%); FEV ₁ -4.27% to -5.11% vs. (-2.54 to -3.58%); PEF -4.89% to -7.12% vs. -(3.47% to -4.41%); FEF ₂₅₋₇₅ -2.04% to -4.63% vs. (-2.29% to -3.78%) 10 µg/m ³ PM ₁₀ ~ FVC -2.84% to -3.91% vs. (-2.12 to -2.57); FEV ₁ -1.42% to -2.43% vs. (-1.36% to -2.47%); PEF -3.28% to -4.69% vs. (-1.92% to -2.26%); FEF ₂₅₋₇₅ -0.89% to -3.98% vs. (-1.36% to -1.75%)
Gupta et al., 2018	India	Cross-sectional	N = 150	10-12	Rice & wheat	Rice season	PM _{2.5} 48 ± 9 to 107 ± 15 µg/m ³	
							PM ₁₀ 71 ± 23 to 167 ± 37 µg/m ³	
						Wheat season	PM _{2.5} 43 ± 9 to 81 ± 19 µg/m ³	
							PM ₁₀ 72 ± 17 to 81 ± 19 µg/m ³	

↑ = increased effect, ↓ = decreased effect, ∅ = no effect.
a = Suspended Particulate Matter, PM_{2.5}, and PM₁₀ levels not provided.

over 12 reported higher odds of having allergies or hayfever if they were exposed in utero to herbicides (OR 1.98, 95% CI: 1.30–3.01), insecticides (OR 1.70, 95% CI: 1.07–2.70), or any pesticides (OR 1.82, 95% CI: 1.24–2.67) (Weselak et al., 2007). Furthermore, in Sri Lanka allergies were higher in children living in environments exposure to pesticides from conventional agricultural vs those exposed to organic systems (75.2% vs. 49.4% p-value<0.001) (Kudagammana and Mohotti, 2018). In contrast, no significant associations were found between DDE (median: 0.29 µg/L) in blood of 7–8 year old's and atopic eczema (OR 1.74, 95%CI: 0.73–4.27) or hay fever (OR 2.74, 95%CI: 0.58–15.83), in a study based in Germany (Karmaus et al., 2003) (Table 2).

3.4.4. Respiratory tract infections

Respiratory tract infections were also investigated in the Costa Rican ISA study, similar to wheezing, no significant association between pesticides and lower respiratory tract infections at one year of age were found (ETU (OR 1.50, 95%CI: 0.70–3.19); TCPy (OR 0.84, 95%CI: 0.36–1.95); 3PBA (OR 1.64, 95%CI: 0.78–3.47); 2,4-D (OR 1.48, 95%CI: 0.69–3.14); DCCA (OR: 1.07, 95%CI: 0.49–2.36); OH-PYR (OR 1.49, 95%CI: 0.70–3.18); 5-OH-TBZ (OR 0.98, 95%CI: 0.45–2.16) (Mora et al., 2020) (Table 2). Similarly, there was no significant association between maternal serum DDE and DDT concentrations (median: 2.70 µg/g lipid, and 0.27, respectively) and lower respiratory tract infections in 0–21 month old Mexican children (IRR_{IQ} increase in DDE: 0.92, 95%CI: 0.78–1.10; IRR_{IQ} increase in DDT: 0.95, 95%CI: 0.86–1.04) (Cupul-Uicab et al., 2014). In one agricultural burning study, information from India's fourth District Level Health Survey on acute respiratory tract infections were combined with Moderate-Resolution Imaging Spectroradiometer satellite data on fire occurrence (Chakrabarti et al., 2019) (Table 5). Those living in areas with intense agricultural burning had a 3-fold higher risk (RR: 2.99, 95% CI: 2.77–3.23) of reporting an acute respiratory infection (Chakrabarti et al., 2019). The risk for acute respiratory tract infections were even greater (RR: 3.65, 95% CI: 3.06–4.34) among children under five years of age (Chakrabarti et al., 2019).

3.5. Lung function

Based on the available peer-reviewed literature included in this review, there is an inverse association between pesticide exposures and children's lung function measurements. Lower forced expiratory volume during the first second (FEV₁) measurements were the most consistently reported significant association with exposure to pesticides (Table 3). A total of five studies conducted lung function measurements to evaluate the association between pesticide exposures and respiratory health outcomes in children (Gunier et al., 2018; Hu et al., 2021; Raanan et al., 2016, 2017; Raherison et al., 2019). Among children living in an agricultural community in CA, US, urinary diethyl phosphate (DE) and total dialkyl phosphate (DAP) concentrations were associated with decreased lung function at age 7 (Raanan et al., 2016). Specifically, a 10-fold increase in urinary DE, resulted in lower FEV₁ (β = -0.18, 95%CI -0.32 to -0.05); lower forced vital capacity (FVC) (β = -0.18, 95%CI -0.34 to -0.02); and lower forced expiratory flow at 25–75% of FVC (FEF_{25–75}) (β = -0.36, 95%CI -0.64 to -0.08). Additionally, Raanan et al., 2016 also reported that a 10-fold increase in total DAPs, resulted in lower FEV₁ (β = -0.14, 95%CI -0.29 to 0.00) and lower FEF_{25–75} (β = -0.17, 95%CI -0.34 to 0.01), but not FVC. No association was found between dimethyl phosphate (DM) concentrations and FEV₁, FVC, or FEF_{25–75} (Raanan et al., 2016).

In children 6 to 17 years old who participated in the US National Health and Nutrition Examination Survey, urinary 3-Phenoxybenzoic acid (3-PBA) concentrations were associated with reduced FEV₁ (β = -0.01, 95%CI -0.02 to -0.002), FVC (β = -0.01, 95%CI -0.02 to -0.004), and peak expiratory flow (PEF) (β = -0.01, 95%CI -0.02 to -0.01), but not FEV₁/FVC or FEF_{25–75} (Hu et al., 2021). Among children of a cohort in rural Salinas Valley, CA, US, a 10-fold increase in sulfur applied to agricultural soils within 1000 m of a child's residence was associated with a decrease in FEV₁ (β = -0.143, 95%CI -0.248, -0.039), and FVC (β =

−0.127, 95%CI −0.230, −0.024) but not FEF_{25-75} (Raanan et al., 2017). However, in the same population but assessing other fumigants no associations were found between a 10-fold increase in wind-adjusted fumigant use (kg) (i.e., chloropicrin, metam sodium, 1,3-dichloropropene, or methyl bromide) and lung function measurements (i.e., FEV_1 , FVC or FEF_{25-65}) at 7 years of age (Gunier et al., 2018). While an association between pesticide concentrations measured in urine as ethylenethiourea (ETU) in children ages three to ten living in rural France and asthma symptoms was reported (OR 3.56, 95%CI 1.04–12.12); no association was found with lung function (Raherison et al., 2019).

Similar to the overall findings among pesticide studies, lower lung function has been consistently associated with exposure to agricultural burning. A total of six studies have conducted lung function measurements to understand the association between agricultural burning exposures and respiratory health outcomes (Table 6). Of these, all ($n = 6$) measured FVC and/or PEF, a total of three measured FEV_1 and FEF_{25-75} , and no studies reported the FEV_1/FVC ratio. In India, four studies among children observed that PM 2.5 levels from agricultural burning were associated with significant decreases in FVC, FEV_1 , PEF, and FEF_{25-75} (R. Agarwal et al., 2010; Ravinder Agarwal et al., 2013; Awasthi et al., 2010; Gupta et al., 2018). Similar decreases in FVC, FEV_1 , PEF, FEV_1/FVC , and FEF_{25-75} were observed for studies focusing on PM 10 emissions from agricultural burning in India and Iran (R. Agarwal et al., 2010; Ravinder Agarwal et al., 2013; Awasthi et al., 2010; Gupta et al., 2018). Furthermore, exposure to suspended particulate matter from agricultural burning in India was associated with decreases in FVC, FEV_1 , PEF, and FEF_{25-75} (Ravinder Agarwal et al., 2013; Awasthi et al., 2010; Gupta et al., 2016). Only one study among 10–14-year old's in Brazil found no association between PM 2.5 levels from sugarcane burning and lung function measured by PEF (Riguera et al., 2011).

4. Discussion

In this review we summarized the available peer-reviewed literature to evaluate the association between pesticides and agricultural burning exposures and children's respiratory health. Rural communities face multiple factors that can impact respiratory health including housing quality, access to healthcare along with exposure to environmental pollutants from agricultural activities (Depner et al., 2017; Estrada and Ownby, 2017; Karvonen et al., 2012; Loftus et al., 2016; Malik et al., 2012; Pavilonis et al., 2013; Pesek et al., 2010). While there is a small but growing body of literature on the relationship between pesticides and children's respiratory health, information on the potential role of agriculture burning, and its co-occurrence remains scarce. Exposure to pesticides and agricultural burning are likely to co-occur in agricultural communities, but these exposures have remained distinct bodies of epidemiological research. Examining the impacts of these co-exposures in tandem is key to understanding the cumulative impacts when assessing children's respiratory health. In this review we summarized the available peer-reviewed literature to evaluate the association between.

Among the pesticide studies, concentrations in human specimens are either reported among urine or blood/serum samples. Among children residing in Washington, USA median (IQR) levels of total dialkylphosphate (DAP), diethyl alkylphosphate (DE), and dimethyl alkylphosphate (DM), 142.9 (197.3) nmol/g creatine, 71.2 (79.9), and 58.3 (77.5), respectively, were associated with increased asthma exacerbations (W. Benka-Coker et al., 2020; W. O. Benka-Coker et al., 2019). Compared to children in Washington, those residing in California had higher median DAP: 1636 nmol/year/g-creatinine, DE: 251, and, DM:1244 levels (Raanan et al., 2015). A 10-fold increase in DAP, DE, or DM levels was associated with increased respiratory symptoms, exercise-induced coughing, or lower FEV_1 (Raanan et al., 2015, 2016). One mechanism by which OPs interact is by their ability to inhibit acetylcholinesterase (AChE) (Pope, 1999). Inhibition of AChE has been linked with development of asthma (Banks and Lein, 2012; Shaffo et al., 2018). Even with no significant inhibition of AChE, some OPs can cause asthma hyperactivity, suggesting that at levels which

are encountered in environmental settings, OPs could contribute to asthma pathogenesis (Fryer et al., 2004; Lein and Fryer, 2005). In addition to OPs, pyrethroids (PYR) may also impact respiratory health. In NHANES, 3-phenoxybenzoic acid (3-PBA (PYR)) levels (GM: 0.50 $\mu\text{g/g}$ creatinine) were associated with lower FEV_1 , FVC, and PEF (Hu et al., 2021). As OPs and PYR are both insecticides and widely used in agriculture their potential to impact children is high (Babina et al., 2012), especially since the interaction between OPs and PYRs may lead to greater than additive toxicity (Hernández et al., 2013). For studies using blood/serum, children's DDE levels (median 0.29 $\mu\text{g/L}$) were associated with asthma (Karmaus et al., 2001). Among mothers, maternal serum DDT levels median (range) 249.2 (4–22,613) ng/g lipid were associated with an increase in reported wheezing (Huq et al., 2020). Furthermore, in a meta-analysis of 10 European birth cohorts where DDE was measured in cord-serum samples (geometric mean range: 52.4–1067.7 ng/L), the risk of bronchitis or wheeze (combined outcome) increased with DDE exposure (RR 1.03 95% CI: 1.00–1.07) in children under 18 months of age (Gascon et al., 2014). Spraying of DDT was outlawed in 1970 and thus these levels are unlikely to be due to current spraying, however as DDT is still used indoors for malaria control which potentially explains levels seen in Huq, 2020, which takes place in Africa. As concentration units are not consistent across studies it is difficult to make conclusions on the overall levels of pesticide residues in human specimens resulting in adverse health effects.

Although health outcome assessment differed between pesticide studies and agricultural burning studies, similar adverse respiratory health effects were observed across the majority of studies. In total we identified 25 studies that focused on pesticide exposures and children's respiratory health, and 12 studies that focused on exposure to agricultural burning and children's respiratory health. A majority of the pesticide studies (19/26) reported a positive association between exposure to pesticides and adverse childhood respiratory health effects. Similarly, most (11/12) agricultural burning studies reported a positive association between exposure to agricultural burning and adverse respiratory health effects. Studies were categorized based on main exposure of interest (i.e., pesticides or agricultural burning) and by respiratory health outcome assessment (i.e., asthma, acute symptoms, and lung function measurements). The most frequently studied health outcomes in these publications were acute respiratory symptoms ($n = 11$ pesticides, $n = 3$ agricultural burning), followed by asthma ($n = 9$ pesticides, $n = 3$ agricultural burning), and lung function ($n = 5$ pesticides, $n = 6$ agricultural burning). A total of 17 pesticide studies implemented questionnaires for gathering respiratory health information, but only two agricultural burning studies employed this data collection method. In addition to the utilization of hospital records, studies focusing on agricultural burning could employ a similar approach to collect more detailed information about acute respiratory symptoms and asthma exacerbations. One of the limitations among studies using questionnaires to assess asthma is the inconsistent use of the ISAAC questionnaire (Asher et al., 1995). While some studies state that a “standardized” questionnaire was utilized it is not clear how these questions compare to the validated ISAAC survey, limiting comparison across studies. Additionally, while some studies state that the question “has your child ever been diagnosed by a doctor as having asthma “as the main definition for asthma based on the ISAAC questionnaire others do not state which question(s) were utilized. Furthermore, there is a gap in children's own self-assessment of asthma and asthma morbidity as a majority of the studies rely on parent's completing the questionnaire.

In addition to studies focusing on asthma and respiratory symptoms, pulmonary function in children have been investigated in the context of these agricultural exposures. Overall, lower lung function are consistently reported to be associated with both exposure to agricultural burning and to pesticides. Lung function is objectively assessed using a spirometer and usually overseen by trained personnel. In the studies included, there were various lung function measures reported, including FVC, FEV_1 , FEF_{25-75} , and FEV_1/FVC , with variability in number and or type of lung function measures reported. It is not clear whether studies did not obtain these measurements, either due to study limitations of differences in spirometers, or if

certain measures were omitted from results potentially creating bias by only reporting statistically significant results. Among the five pesticides studies in this review utilizing lung function measurements, two utilized proximities to pesticide applications (i.e., distance to agricultural fields sprayed with pesticides) as the main exposure metric, while three utilized metabolites in urine. Among the two studies assessing exposure through a geospatial approach, only those living in close proximity (i.e. within 0.5 and 1 km) to agricultural fields sprayed with sulfur were associated with lower FEV₁ (Raanan et al., 2017). In contrast, proximity to fumigant (i.e., methyl bromide, chloropicrin, metam sodium and 1,3-dichloropropene) applications assessed at 3, 5, and 8 km were not associated with lower FEV₁ or FVC measurements (Günier et al., 2018). Future studies utilizing a geospatial approach should assess various distances and provide a clear explanation as to what close versus far categorization of proximity to pesticide applications entails. Among the three studies assessing pesticide exposure through biomarkers, only two found an association with lower FEV₁, (Hu et al., 2021; Raanan et al., 2016) FVC, (Hu et al., 2021; Raanan et al., 2016) and PEF (Hu et al., 2021). However, each focused on metabolites of different pesticide classes: Raanan et al. (2016) focused on metabolites of OPs, Hu et al. (2021) focused on 3-PBA, a metabolite of pyrethroids, and Raherison et al. (2019) measured ETU concentrations, a marker of dithiocarbonates fungicides. There are many limitations to the usage of metabolites such as difficulty deciphering between the exposure to the pesticide or an environmental degradant, low correlation between ambient and urinary metabolites, and large within person variations (Barr et al., 2007; Sudakin and Stone, 2011). These limitations should be taken into consideration in future studies investigating the association between pesticide exposures and lung function measurements.

Among the agricultural studies, the PM 2.5 and PM 10 levels exceed the World Health Organization (WHO) guidelines (PM 2.5 and PM 10 annual average 5 µg/m³ and 15 µg/m³, respectively). In Japan, PM 10 levels ranging 100 to 400 µg/m³ per hr resulting in increased emergency room visits and hospitalizations for asthma (Torigoe et al., 2000). Similarly in Brazil mean (sd) PM 10 levels 87.7(57.9) µg/m³ were also associated with asthma hospitalizations (Cançado et al., 2006). In Thailand similar ranges of PM 10 (122.9–165.1 µg/m³) were associated with respiratory disease hospital visits (Uttajug et al., 2021). Additionally, PM 2.5 levels in Brazil ranging from 10 to 35 µg/m³ during fire occurrences also resulted in asthma hospitalizations (Uriarte et al., 2009) and mean(sd) PM 2.5: 22.8 (14.7) µg/m³ were also associated with increased asthma hospitalizations (Cançado et al., 2006). For studies focusing on lung function, PM 2.5 levels ranging from 43 to 107 µg/m³ (Gupta et al., 2016, 2018), mean (sd) 98(1.5) µg/m³ (Awasthi et al., 2010) and mean (sd) 291(71) µg/m³ (R. Agarwal et al., 2010) were all associated with decreases in various lung function measurements. For studies focusing on PM 10 and lung function, reduced lung function measurements were observed in studies reported PM 10 levels ranging from 71 to 167 µg/m³ (Gupta et al., 2016, 2018), mean 160(1.3) µg/m³ (Awasthi et al., 2010), and 366 (152) µg/m³ (R. Agarwal et al., 2010).

There is a wide range of methods used in assessing exposure to pesticides and agricultural burning. In pesticide studies proximity to agricultural fields (Bukalasa et al., 2018; Günier et al., 2018; Raanan et al., 2017), ambient concentrations (Gharibi et al., 2020a), and biomarkers in urine were utilized (W. Benka-Coker et al., 2020; Cupul-Uicab et al., 2014). Biomarkers of pesticide exposure are a measure of whole-body burden and do not differentiate between the source of exposure. Urinary pesticide concentrations could represent exposure from consumption of food with pesticide residues, non-dietary ingestion of pesticides, and potentially ambient exposure. In contrast, among agricultural burning studies, a majority rely on ambient measurement of emissions from agricultural burning for their exposure assessment (Ravinder Agarwal et al., 2013; Awasthi et al., 2010; Gupta et al., 2018). The shared route of exposure between agricultural burning and pesticide studies is through inhalation. This is especially a concern for agricultural communities, which could be exposed to both pesticides and the emissions from agricultural burning during clearing of the fields. Additionally, children are also exposed to pesticides through other non-drift pathways (e.g., proximity to agricultural fields), such as the

take-home pathway (e.g., having a parent working in the fields that can have remaining residue on their clothes), eating or drinking food with pesticide residue, and at home residential pesticide usage (Deziel et al., 2017; López-Gálvez et al., 2019). Similarly, while exposure to agricultural burning is the focus of this review, children in rural areas can also be exposed to particulate matter through proximity to traffic and highways, agricultural equipment, trash burning, wildfires, or windblown dust.

We observed heterogeneity in reporting of race/ethnicity, age, and windows of exposure, which challenge our ability to carry out comparisons. Studies focusing on pesticide exposures in the United States tend to include race and ethnicity information, however, those in other countries rarely provide this information in their reporting. Among the agricultural burning studies included in this review, none provided race/ethnicity information, however as these took place outside of the US it may not be common practice to report. Most studies focus on assessing pesticide exposures postnatally (e.g., once child is birthed), with only a few focusing on prenatal periods of exposure (Günier et al., 2018; Huq et al., 2020). Additionally, the timing of exposure is varied, with some studies assessing pesticide exposures years before health outcome assessments (Raanan et al., 2017), and others on recent exposures such as cross-sectional studies (Hu et al., 2021). This inconsistent or lack of reporting makes potential analysis looking at disparities and varying windows of exposure difficult. Additionally, pesticide and agricultural burning practices vary greatly across countries, which further hinders analysis and comparisons across different groups and by geographic locations.

Exposure to multiple pollutants in non-occupational agricultural settings is likely to occur, yet only 34.6% (n = 9/26) of pesticide studies and 8.3% (n = 1/12) of agricultural studies adjusted for other air pollutants. Furthermore, only one agricultural burning study mentioned that pesticides could potentially affect respiratory health among children. While all pesticide studies included in this review mention that further research is needed, only 19.2% (n = 5/26) discuss potential policy or interventions that could be implemented to reduce exposure to pesticides such as ingestions of organic food or setbacks for pesticide applications. In contrast, 58.3% (n = 7/12) of agricultural burning studies suggest policy changes such as banning of agricultural burning as a method for clearing fields. Geographically, most pesticide studies identified in this review were carried out in the US (n = 12), yet no agricultural burning studies were conducted in the US. In contrast, India and Brazil led in agricultural burning studies, but no studies focusing on pesticides and respiratory health in children were identified from them. As pesticide regulations in low- and middle-income countries such as India and Brazil are subject to different practices (e.g., monitoring and registration procedures, less protective equipment, and different regulating agencies) (Schreinemachers and Tipraqsa, 2012; Utyasheva and Bhullar, 2021; Valbuena et al., 2021), pesticide exposures may disproportionately affect children those residing in these communities (Zikankuba et al., 2019).

Our review only included peer reviewed literature written in English, and thus publication bias could be a potential source of error as studies that had null results and were not published are excluded from these findings. We identified several limitations on the reporting of windows of susceptibility, timing and length of exposure assessment, age of health outcome assessment, potential role of co-exposures, few objective health measures such as lung function or fractional exhaled nitric oxide (FENO), and lack of reporting on demographic variables. Nevertheless, pesticide and agricultural burning studies were consistent in their findings reporting adverse respiratory health outcomes in children. While there is less data on the effects between pesticide or agricultural burning exposures to lung function in children, evidence is growing (Gharibi et al., 2020b; Huq et al., 2020).

5. Conclusion

The top class of pesticide investigated in studies identified in this review were OPs, however their usage in the agricultural sector in the US has been declining (U.S. EPA, 2017). This decline is mainly due to a shift in usage of other classes of pesticides (e.g., pyrethroids, fumigants) and thus focusing

on other classes of pesticides and their possible impact on respiratory health is of utmost importance. Although health outcome assessment differed between pesticide studies and agricultural burning studies, similar adverse respiratory health effects (e.g., self-reported asthma, acute respiratory symptoms, and lower lung function) were observed across the majority of studies. Additionally, as pesticide and agricultural burning practices vary globally, additional studies in low- and middle-income countries are needed. Future studies should also focus on multi-pollutant assessments, investigate usage of different asthma medications, utilize objective outcome measures such as FENO or pulmonary function test, and integrate satellite advances into the exposure assessment. Furthermore, future studies should integrate an intersectionality framework and focus on assessing different risk factors, such as medically underserved areas, race and ethnicity, poverty index, and access to asthma management programs. Moreover, as the industrialization of agriculture perpetuates environmental injustice in rural communities, (Kelly-Reif and Wing, 2016) policy changes aimed at reducing the reliance on crop burning, and aerial application of pesticides near sensitive locations (e.g., schools, daycares) should be prioritized.

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CRediT authorship contribution statement

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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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