Published in final edited form as:
Immunol Allergy Clin North Am. 2022 November ; 42(4): 817–830. doi:10.1016/j.iac.2022.05.008.

Influence of Rural Environmental Factors in Asthma

Jennilee Luedders, MD[1], **Jill A. Poole, MD**[1]
[1]Division of Allergy and Immunology, Department of Internal Medicine, College of Medicine, University of Nebraska Medical Center; Omaha, NE, USA.

Abstract

Purpose: The objective of this article is to review recent literature on the implications of agricultural factors including pesticides, animal/livestock production facilities, agricultural dust, endotoxin, biomass/crop burning, and nutritional factors with respiratory health, particularly in relationship to asthma and wheeze, of rural residents.

Methods: PubMed, Embase, and CINAHL literature searches of years 2016–2021 were conducted with librarian assistance. Terms searched were rural population, rural health, small town, farming, agriculture, environmental pollution, biomass, pesticides, pollution, asthma, pulmonary disease, chronic obstructive pulmonary disease, chronic airflow obstruction, and adult. Articles were selected for inclusion after the literature search based on topic fit by author review.

Results: Several studies suggest increased risk for asthma or wheeze with certain rural exposures, particularly for pesticides, livestock production facilities, agricultural dust, and biomass and crop burning. Endotoxin exposure yields variable consequences and may vary with timing of exposure. Studies also suggest a possible respiratory protective effect for specific nutritional factors, including a high omega-3 fatty acid diet and unpasteurized milk consumption.

Conclusion: A complex network of environmental factors exist which may have detrimental effects on the respiratory health of rural residents. These factors include, but are not limited to, pesticides, livestock and animal production facilities, agricultural dust, endotoxin, and biomass and crop burning. In contrast, several dietary factors have been suggested as potentially protective for respiratory health in rural populations. Further investigations into these agricultural factors to prevent or minimize adverse respiratory effects in rural populations is warranted.

Introduction

When compared to those who live in metropolitan counties, dwellers of rural areas within the United States have increased percentages of preventable deaths from the five leading causes of death (i.e., cancer, heart disease, unintentional injury, chronic lower respiratory disease, stroke), with the largest disparity demonstrated from chronic respiratory disease [1]. It is also recognized that people who reside in rural communities have less access to healthcare and worse health-related outcomes [2]. There are several barriers to care which may contribute to health disparities for those in rural communities including transportation

Corresponding author: Jennilee Luedders, 985990 Nebraska Medical Center Omaha, NE 68198-5990, phone: 402-559-4088, jennilee.luedders@unmc.edu.

issues, cost, language differences, and immigration concerns [3]. In a survey sponsored by the US Department of Labor, it was demonstrated that among farmworkers with asthma the most common reported barriers to healthcare were transportation (60%) and cost (33%) [4]. Pate et al. used data from the National Health Interview Survey to investigate factors relating to asthma and found that asthma mortality rates were significantly higher for persons of all ages in areas with a population <10,000 at 13.4 per 1 million compared to 8.8 per 1 million in large metropolitan areas [2].

Rural environmental exposures and agriculture related work are known to be associated with asthma, both occupational (asthma caused by work) and work-exacerbated (pre-existing asthma that is aggravated at work) [5]. Several studies have suggested that certain farming-related exposures as an adult increase the risk of asthma or asthma-like symptoms development, which contrasts with the hygiene hypothesis concept which suggests that farming and associated microbial exposures are protective against allergic asthma [5, 6]. Farm workers are exposed to a complex working environment with associated disease outcomes dependent on the interplay of many factors including genetics, gender, history of atopy, duration of exposures, livestock, diet, and pesticide exposures [6, 7].

The aim of this article is to review data from the past 5 years pertinent to asthma in rural populations and associated rural risk factors for asthma. PubMed, Embase, and CINAHL literature searches were conducted with the assistance of a librarian. Terms searched were rural population, rural health, small town, farming, agriculture, environmental pollution, biomass, pesticides, pollution, asthma, pulmonary disease, chronic obstructive pulmonary disease, chronic airflow obstruction, and adult. Years searched were 2016–2021 and only studies written in English were utilized. Articles were selected for inclusion after the literature search based on topic fit by author review.

Rural Pesticide Exposure and Impacts on Asthma

There is expanding evidence that suggests that pesticide exposures contribute to allergic and non-allergic asthma and wheeze [8] (Table 1). Agricultural workers can be exposed to pesticides via direct inhalation (during spraying or mixing) or via pesticide-contaminated dust [9]. In 2017 Hoppin and colleagues conducted a comprehensive investigation of the association of pesticides in relationship to wheeze using data from the Agricultural Health Study of male pesticide applicators in North Carolina and Iowa [8]. Associations between pesticide use of 78 different pesticides and wheeze, both allergic (defined as physician diagnosed hay fever and presence of wheeze) and non-allergic (reporting wheeze but no hay fever), were performed [8]. Of the 78 pesticides examined, 51 had not been previously investigated in relation to respiratory health outcomes [8]. Out of >22,000 male pesticide applicator participants, 6% were found to have allergic wheeze and 18% had non-allergic wheeze [8].

Several of these pesticides (N=29) were positively associated with wheeze including non-allergic wheeze (N=21), allergic wheeze (N=19), and both allergic and non-allergic wheeze (N=11) [8]. Seven pesticides had significant ($p < 0.05$) associations with allergic wheeze vs non-allergic wheeze, including 2,4-D and simazine (herbicides), carbaryl, dimethoate, and zeta-cypermethrin (insecticides) [8]. Of the herbicides, 18 of the 43 examined were associated with a wheeze outcome [8]. Clomazone was the only herbicide inversely associated with wheeze (both allergic and non-allergic) [8]. Of those positively associated with wheeze, 14 were associated with non-allergic wheeze and 10 were associated with allergic wheeze [8]. The most popularly used herbicides associated with allergic and non-allergic wheeze included glyphosate (trade name Roundup®) and atrazine while 2,4-D was associated only with allergic wheeze [8]. Of the insecticides, 9 of the 25 examined were positively associated with wheeze [8]. Disulfoton was the only insecticide inversely associated with a wheeze (non-allergic) [8]. Malathion, permethrin, and pyrethrins were associated with both allergic and non-allergic wheeze [8]. Carbaryl, chlorpyrifos, dimethoate, and zeta cypermethrin were associated with allergic wheeze whereas cyfluthrin and Fly Spray were positively associated with non-allergic wheeze [8]. Six fungicides, one fumigant, and one rodenticide were evaluated for association with wheeze and only the rodenticide warfarin was associated with wheeze (allergic) [8]. While non-allergic wheeze was found to be three times as common as allergic wheeze, pesticide associations were stronger with allergic wheeze, potentially implying that pesticides have greater effects in atopic individuals [8].

In addition, Mazurek and Henneberger in 2017 demonstrated greater effects of pesticides with allergic asthma versus non-allergic asthma. Using survey data collected from over 11,000 active US farm workers, farmers with allergic rhinitis were 6.03 times more likely to report current asthma and 1.38 times more likely to report exposure to pesticides as compared to farmers without allergic rhinitis [10]. There was also a positive association between pesticide exposure and comorbid asthma and allergic rhinitis [10]. In contrast, the association with pesticides was not significant in those with current asthma without history of allergic rhinitis [10].

The Farm and Ranch Safety Survey data from >11,000 farmers [11] also found a relationship of pesticide exposures and asthma. Patel et al. demonstrated that insecticide and herbicide use in the last 12 months was associated with current asthma with an adjusted prevalence odds ratio of 1.5 for any pesticide use [11]. Interestingly, glyphosate was not shown to have a significant association to current asthma among farmers which contrasts with the findings from the Agricultural Health Study [11]. The authors hypothesized that this difference could be due to the Agricultural Health Study having a larger number of questions dedicated to pesticide use which could have led to a more thorough assessment of pesticide exposures [11].

In 2018, Cherry and colleagues examined the respiratory health of grain farmers exposed to pesticides in Alberta, Canada to assess pesticide use and respiratory disease and symptoms in >1,300 grain farmers [9]. Phenoxy herbicide exposures were associated with self-reported asthma that increased with duration of exposure demonstrating an adjusted odds ratios of 1.29 for 1–22 years of exposure, 2.52 for 23–34 years of exposure, and 3.18 for >35 years of exposure [9]. After stratification for self-reported allergy, the odd ratios for phenoxy compounds with asthma were higher in those without allergies, suggesting that an irritant mechanism in addition to allergic mechanisms could be considered for this specific pesticide

[9]. Thus, it remains unclear if phenoxy compounds induce a form of reactive airways dysfunction syndrome versus allergic-type immune responses [9].

The mechanisms by which pesticides drive adverse respiratory health consequences remains to be elucidated [12]. To evaluate potential mechanisms, Hoang et al. performed an epigenome-wide association study of blood DNA methylation in relation to specific pesticides utilizing the Agricultural Health Study cohort of >1,000 farmers of European ancestry [12]. They focused on 9 pesticide ingredients for which at least 30 participants had reported past and recent (within the last year) use and 7 organochlorines which have been banned [12]. Comparing the methylation at C-phosphate-G sites among those who were exposed to pesticides to those who had never used pesticides, 162 methylated C-phosphate-G sites across 8 of the 9 pesticide ingredients that are currently available on the market and among one organochlorine were discovered [12]. The differentially methylated C-phosphate-G sites were distinctive for each active ingredient which potentially supports specific methylation patterns for different pesticides [12]. By identifying differential methylation for different pesticide ingredients, this study advances the knowledge of biological mechanisms altered by pesticide exposures [12].

Influence of Livestock and Animal Production Exposures on Asthma

Livestock exposure in agricultural work settings appears to increase the risk of asthma development and asthma exacerbations as well as chronic obstructive pulmonary disease (COPD) [6]. However, it is unclear if asthma symptoms are directly influenced by exposure to the livestock themselves versus influenced by exposure to organic materials (including hay, straw, dust, animal feed) that are handled when working with livestock [6]. In addition, farmers who work in concentrated animal feeding operations (CAFOS) are exposed to gases, organic dusts, fungal spores, and particulate matter which can all contribute to airway inflammation and obstruction [5].

Schultz et al. performed a study in 2019 to evaluate the association between living in residential communities in close proximity to dairy CAFOs and respiratory health effects within a rural Wisconsin population [13]. Survey data was obtained from 2008–2016 of >5,000 adults living in rural areas that included distance to nearest CAFO, prevalence of self-reported physician diagnosed asthma, asthma episodes in the previous 12 months, asthma medication use, allergies, and lung function measured via spirometry [13]. Current asthma was 1.8–1.9 times greater in populations living 1–3 miles from a CAFO vs those living 5 miles from a CAFO and the odds of having allergies were >2 fold when those residing 1–1.5 miles from a CAFO were compared to those who lived 5 miles from a CAFO [13]. In addition, when compared to living 5 miles from a CAFO, the odds of ever having received a diagnosis of asthma were 3.11 (95% CI 1.49, 4.36) for those 1 mile from a CAFO and 2.67 (95% CI: 1.33, 3.08) for those 1.5 miles from a CAFO [13]. The odds of physician diagnosed asthma and asthma-related medication use also decreased as distance from a CAFO increased [13]. Namely, for those within 1, 1.5, 2, and 2.5 miles from a CAFO, asthma medication use was 4, 3, 2.5, and 2 times greater respectively relative to the population that lived 5 miles from a CAFO [13]. In addition, the odds of experiencing an asthma attack were 2 times higher for those living 1–3 miles versus 5 miles from a CAFO

[13]. Correspondingly, lung function measurements were also dependent upon proximity to a CAFO as the predicted forced expiratory volume (FEV1) was 7.72% lower when living 1.5 miles from a CAFO as compared to those living 3 miles from a CAFO [13]. In summary, proximity of residence to animal feeding operations may increase the risk for asthma as well as exacerbate asthma symptoms.

In addition, a case-control study was performed by Rasmussen et al., using electronic health records of a rural Pennsylvania health clinic to investigate residential proximity to swine or dairy/veal industrial food animal productions (IFAP) and the association with asthma exacerbations between groups living <3 miles vs those living >3 miles from an IFAP [14]. They found 11% increased odds of oral corticosteroid prescriptions and 29% increased odds of hospitalizations for asthma among the population living within 3 miles of an IFAP when compared to those living >3 miles from an IFAP [14]. These findings are consistent with other studies on IFAP and asthma exacerbations which suggest IFAP as a risk factor for asthma symptoms and reduced lung function [14–16].

Although asthma was not assessed, a 2019 study by Rinsky and colleagues examined associations between animal operations, COPD diagnoses, and respiratory symptoms in over 22,000 farmers. This study found that raising livestock on medium to large scale operations was positively associated with chronic bronchitis symptoms, both with and without a history of COPD diagnosis, when compared to farmers who did not raise animals [17]. When comparing specific types of livestock, farmers who raised hogs had increased odds of chronic bronchitis symptoms in groups with a history of COPD (OR 1.41, CI: 1.05–1.89) and without a history of COPD (OR 1.25, CI: 1.06–1.47) [17]. In contrast, farmers who raised poultry or beef cattle had increased odds of chronic bronchitis symptoms only in those without a prior diagnosis of COPD (poultry OR 1.29 CI: 0.98–1.70, beef cattle OR 1.29, CI: 0.98–1.70) [17]. In farmers with dairy cattle exposure, there was an increased odds of both COPD diagnosis and chronic bronchitis symptoms (OR 1.63, CI: 0.98–2.70) [17]. This study suggests that raising livestock is associated with increase of chronic bronchitis symptoms, but differences in symptoms may be seen among those raising different types of livestock depending on history of COPD [17]. Future areas of study should consider targeting and investigating these differences as well in association with asthma-COPD overlap.

Rural Dust Exposure on Airway Inflammation

Chronic inhalation of agriculture-related dust has been associated with increased burden of airway inflammatory diseases including asthma, chronic bronchitis, and COPD [18]. Prior studies have suggested endotoxin, peptidoglycans, components of gram-positive bacterial cell walls, (1→3)-β-D-glucans, and fungi as potential components of dust that may be contributors to the inflammatory response [18]. At this time there are no known treatments that can reverse respiratory disease induced by complex environmental dust exposures [19].

To evaluate attributable risk factors for chronic airflow obstruction, including exposure to dusty jobs, the Burden of Obstructive Lung Disease study investigated >28,000 participants to determine prevalence of chronic airway obstruction with various risk factors [20]. Fortyone sites, both rural and urban, across the world were included [20]. Working in a self-reported "dusty job" for >10 years was positively associated with chronic airway obstruction (attributable risk: men: 0.65%; women: 0.29%) of which the highest prevalence for men was in Pakistan (1.6%) and for women was in Austria (0.9%) [20]. The limitation of this study is that the "dusty job" exposure was self-reported and thus errors in interpretation could reduce the estimated relative risk and exposures for of less than 10 years were not examined [20].

In a geographically focused study area of rural Colorado prone to dust storms, James et al. investigated ambient particulate matter concentrations and the effect on emergency visits, urgent care visits, and hospitalizations (EUH) due to asthma [21]. They demonstrated that for each 15 micrograms per cubic meter increase in 3-day ambient particulate matter, there was a 3.1% increase in EUH for patients with asthma [21]. In the events when the 3-day average ambient particulate matter exceeded 50 micrograms per cubic meter, EUH visits increased by 16.8% [21]. Furthermore, when 3-day averages were above 100 micrograms per cubic meter, EUH visits increased by 65.8% [21]. In summary, elevated ambient particulate matter concentrations were associated with increased asthma associated healthcare visits in a rural Colorado community prone to dust storms [21].

The microbiota associated with agriculture exposures and dust also represents an important factor in mediating asthma consequences. For example, Lee et.al., sampled dust from bedrooms of homes of farmers and their spouses in North Carolina and Iowa, of which ~55% reported working with crops and ~50% reported working with livestock, and collected asthma status data [22]. They demonstrated that overall diversity of bacteria in house dust was similar between controlled and uncontrolled asthma, but individual taxon types varied [22]. Specifically, taxa from fusobacteria, cyanobacteria, and Bacteroidetes were more abundant in the homes of those with uncontrolled asthma whereas taxa from Firmicutes were found to be more prevalent in those with controlled asthma [22]. The phylum Firmicutes is known to compose the largest fraction of the gut microbiota and has been previously shown to have a potentially protective association with regards to degree of asthma control in asthmatics [23]. Dysbiosis, or disruption of microbiota homeostasis, of Firmicutes has been associated with respiratory diseases, including asthma [24].

The identification of the key environmental factors and host defense responses would be advantageous to inform potential novel therapeutic strategies for airway inflammatory diseases encountered in rural environments [18]. To investigate potential treatment targets, Poole et al. investigated the role of amphiregulin (AREG), an epidermal growth factor receptor agonist [19]. In the first set of studies, repetitive exposure to swine confinement organic dust extract induced airway inflammatory consequences that persisted after exposure was removed, and in mice receiving an AREG neutralizing antibody, this post-exposure inflammatory response was increased [19]. Conversely, intranasal administration of recombinant AREG for 3 days post-repetitive exposure was found to hasten resolution of dust extract-induced inflammatory cell influx and pro-inflammatory cytokine levels within the airway [19]. Mechanistic studies focused on both murine and human lung fibroblasts also demonstrated that the dust extract increased AREG and inflammatory cytokine release as well as inhibited wound closure and recellularization of lung scaffolds [19]. Whereas these studies suggest that AREG supplementation may be potentially beneficial in improving post-agricultural dust exposure-induced lung disease, additional studies utilizing different rural inflammatory agents (e.g. endotoxin, peptidoglycan) as well as fully characterizing the response over longer time periods is warranted.

Proteases have also been previously implicated in mediating complex agriculture-related organic dust induced airway inflammation [25]. The potential importance of targeting protease activity in complex dusts was recently investigated by Burr et al., centered on an airborne dust collection near an agricultural drainage reservoir in California called the Salton Sea [26]. The Salton Sea dust extract-induced an inflammatory response in mice that was reduced with protease-activity depleted Salton Sea dust extracts [26]. Correspondingly, the Salton Sea dust extract induced pro-inflammatory cytokine release from cultured human bronchial epithelial cells, and this response was reduced with protease activity-depleted dust extract as well as in the setting of protease activated receptor 1 and 2 antagonism [26].

Endotoxin and Asthma Implications

Endotoxin is a type of lipopolysaccharide present on the outer membrane of gram negative bacteria that leads to a pro-inflammatory innate immune system response when released as a free lipopolysaccharide [27]. Endotoxin is also found in higher quantities in dust of homes in rural farming areas when compared to urban or rural non-farming areas [28, 29]. Endotoxin has been previously recognized to play a role in influencing asthma and is associated with inducing asthma exacerbations as well as COPD [30–33].

Carnes et al. examined the association of house dust endotoxin with asthma and pulmonary function in adults [34]. They performed a case-control study utilizing the Agricultural Health Study to evaluate a population of farmers and farmers' spouses and examined 2,485 households with 927 current asthma cases [34]. Dust was collected from the bedrooms of each household and dust endotoxin levels were measured [34]. In addition questionnaires, spirometry, and blood draws of the participants were examined [34]. They found that increasing levels of endotoxin were associated with higher odds of current asthma (OR 1.3, CI 1.14–1.47) irrespective of atopy as there were positive associations with both atopic (OR 1.38, CI 1.09–1.74) and non-atopic asthma (OR 1.24, CI 1.07–1.43) [34]. In addition they investigated whether residence on a farm at birth affected the association between asthma and endotoxin [34]. They demonstrated that associations between endotoxin and asthma were significantly higher for those not residing on a farm at birth (OR 1.67, CI 1.26–2.2) when compared to those who were living on a farm at birth (OR 1.18, CI 1.02–1.37) [34]. Lastly, the investigators demonstrated that increasing endotoxin levels were related to lower FEV_1/FVC in those with asthma (b=21%, SE = 0.5) when compared to those without asthma (b=20.05%, SE = 0.2) (Interaction P = 0.01) [34].

In contrast to the former study by Carnes and colleagues demonstrating an increased odds of asthma in adults with endotoxin exposure, a protective response with endotoxin exposure with farming practices in pediatric populations has been described. In 2017, Stein et al. examined populations of children of two distinct farming communities, the Amish of Indiana and the Hutterites of South Dakota who have similar lifestyles (particularly with respect to factors thought to influence asthma) but vast differences in asthma prevalence

[35]. The Amish follow traditional farming practices and live on single family farms, in contrast to the Hutterites who tend to use industrialized agricultural practices and live on large, communal farms [35]. Asthma prevalence in Amish children was 5.2% while in Hutterite children the prevalence was markedly higher at 21.3% [36, 37]. Moreover, the prevalence of asthma was 4 times lower in the Amish population whereas endotoxin levels were 6.8 times higher when compared to those in Hutterite homes [35]. Using a mouse model, intranasal instillation of Amish dust extract prior to induction of the experimental ovalbumin asthma model led to reduced airway hyperreactivity and eosinophil influx when compared to Hutterite dust extract ($P < 0.001$) [35]. These responses were dependent upon both innate immune MyD88 and Trif signaling pathways [35]. Highlighting the importance of timing of exposure, it has also been demonstrated that exposure to endotoxin-enriched swine confinement organic dust extracts *after* induction of experimental ovalbumin asthma resulted in potentiation (not reduction) of airway inflammatory consequences in mice [38].

Respiratory Effects of Biomass and Crop Burning

The term biomass encompasses recently living plant or animal based material (including wood, crop residue, and animal waste) that can be burned for fuel purposes [39] and represents an important rural area air pollutant that has been associated with airway inflammatory processes of both asthma and COPD [40]. Asthma-COPD overlap (ACO) refers to a heterogeneous entity of chronic respiratory disease with features of both asthma and COPD that tends toward lower quality of life than with either disease alone [29]. Morgan et al. investigated risk factors, including biomass fuels, for ACO amongst adults in various middle and low income countries including Peru, Argentina, Chile, Uruguay, Bangladesh, and Uganda [29]. Biomass fuel smoke exposure was associated with higher odds of having ACO (OR 1.48, 95% CI 0.98–2.23) when compared to those without obstruction or asthma, therefore biomass smoke exposure should be considered as a risk factor for ACO development [29].

Crop burning is another common practice used after harvests to rapidly clear land for shifting cultivation and to remove vegetation to increase agricultural productivity [41]. Prior studies have suggested that crop burning releases air pollutants and has negative impacts on respiratory health [42]. A 2021 study by Rutlen et al. examined the effects of crop burning on emergency department treatments for asthma and COPD in rural Arkansas whereby Craighead county burns approximately half of the acres each year following harvest and Sebastian county does not practice crop burning [43]. Emergency room visits were increased by 20.9% for asthma (95% CI 1.01–1.45, $p = 0.04$) and 16.9% for COPD (95% CI 1.06–1.29, $p = 0.003$) during the fall months in Craighead county when compared to Sebastian county after controlling for sex, age, and race [43]. Correspondingly, PM 2.5 concentrations were significantly ($p=0.005$) elevated in Craighead county relative to Sebastian county only during the fall season [43].

Protective Effects of Diet on Pulmonary Inflammation

Nutrients and dietary components have been considered as potential important factors which may have impacts on chronic lung disease and inflammation [44, 45]. To investigate potential protective effects of diet in those exposed to agricultural dusts, Ulu et al. investigated a potential therapeutic role of docosahexaenoic acid (DHA), a polyunsaturated omega-3 fatty acid, in airway inflammation resolution [45]. Mice were fed either a high DHA diet or control diet and then exposed to swine confinement dust extract for 3 weeks followed by a one week recovery period [45]. Mice on the high DHA diet group showed improved recovery of airway inflammatory markers evidenced by elevated levels of DHA-derived pro-resolvins and decreased levels of airway inflammatory cells and mediators [45]. This study supports a potential protective role for omega-3 fatty acids in reducing airway inflammatory disease with regards to agricultural dust exposures and suggests that additional future studies are warranted to explore translational approaches [45].

In 2018 Wyss et al. examined the effect of consumption of raw or unpasteurized milk practices of children within the Agricultural Lung Health Study [7]. They demonstrated that those who consumed raw milk had higher FEV_1 (β=49.5mL, 95% CI 2.8–96.1mL, p=0.04) and FVC (β=66.2mL, 95% CI 13.2–119.1mL, p=0.01) but not FEV_1/FVC ratio (β=0.4%, 95% CI −0.4–1.1%, p=0.33) as compared to those who did not consume raw milk [7]. Of those who had consumed raw milk as a child, 91% no longer consumed raw milk and only 7.5% had consumed any raw milk within the last 10 years [7]. After accounting for those who had consumed raw milk in the last 10 years the associations were not affected [7]. This study implies that early-life raw milk consumption is associated with higher pulmonary function in adulthood, but the explanation for these findings remain unknown [7]. Potential mechanisms suggested by the authors may be related fat content, micro-organism presence, and interferon γ levels [7].

Implications of Sex Differences on Rural Airway Disease

Sex differences represent an additional variable that is likely important in the understanding of airway inflammatory disease consequences associated with rural exposures as females may be under-represented in studies [46]. In order to explore these associations in asthma, Arroyo et al. used the National Agricultural Workers Survey of US hired crop workers [4]. Interestingly, women in this study were more likely to report lifetime asthma (OR 1.86, CI 1.28–2.72) as well as recent asthma (OR 2.42, CI 1.62–3.61) when compared to men [4].

Similarly, Fix et al. investigated the AGRICOH consortium to examine respiratory disease among farmers and their spouses in 2021 [46]. Over 200,000 participants from both crop and livestock farming operations were included from 6 different continents and 44% of the participants were female [46]. The median prevalence among females for allergic asthma was 5.5% and non-allergic asthma was 3.5% while the median prevalence among men for both allergic and non-allergic asthma was 3.6% [46]. Moreover, females had significantly higher prevalence ratio (PR) of allergic asthma to non-allergic asthma in comparison to their male counterparts (PR 0.76, 95% CI 0.72–0.82) [46]. Future studies are warranted to understand the increased risk of allergic asthma in females exposed to agricultural risk factors [46].

Summary

With increased asthma mortality rates demonstrated in rural areas as compared to urban areas [2], it is increasingly important to develop a more thorough understanding of the environmental risk factors impacting asthma in rural populations and the underlying mechanisms driving airway inflammatory disease. There is a complex network of factors that have potential significant negative implications on the respiratory health of those residing in rural populations. An overview schematic of the beneficial (or protective) influences versus adverse influences is shown (Figure 1). Increased awareness of these factors which include pesticides, livestock and animal production facilities, agricultural dust, endotoxin, and biomass and crop burning may help to limit exposure and decrease the mortality gap that exists in rural populations affected by asthma. Additionally, investigations into nutritional factors and novel strategic approaches to either prevent and/or reduce these adverse health consequences in rural populations are warranted.

Acknowledgments:

We would like to thank Danielle Westmark, librarian at University of Nebraska Medical Center, for her assistance with the literature search used for this review articles.

Funding and Disclosures:

JAP has funding from Department of Defense (PR200793), National Institute for Occupational Safety and Health (U54OH010162 and R01OH012045), and Central States Center of Agricultural Safety and Health (CS-CASH). JAP has received research funding from AstraZeneca and clinical research funding from Takeda and GlaskoSmithKline.

References

1. Garcia MC, et al. , Potentially Excess Deaths from the Five Leading Causes of Death in Metropolitan and Nonmetropolitan Counties - United States, 2010–2017. MMWR Surveill Summ, 2019. 68(10): p. 1–11.
2. Pate CA, et al. , Asthma Surveillance - United States, 2006–2018. Morbidity and mortality weekly report.Surveillance summaries (Washington, D.C.: 2002), 2021. 70(5): p. 1–32.
3. Hoerster KD, et al. , Impact of individual-, environmental-, and policy-level factors on health care utilization among US farmworkers. Am J Public Health, 2011. 101(4): p. 685–92. [PubMed: 21330594]
4. Arroyo AJC, et al. , Occupational exposures and asthma prevalence among US farmworkers: National Agricultural Workers Survey, 2003–2014. The journal of allergy and clinical immunology.In practice, 2018. 6(6): p. 2135–2138.e2. [PubMed: 29626636]
5. Nordgren TM and Bailey KL, Pulmonary health effects of agriculture. Curr Opin Pulm Med, 2016. 22(2): p. 144–9. [PubMed: 26761627]
6. Wunschel J. and Poole JA, Occupational agriculture organic dust exposure and its relationship to asthma and airway inflammation in adults. Journal of Asthma, 2016. 53(5): p. 471–477.
7. Wyss AB, et al. , Raw milk consumption and other early-life farm exposures and adult pulmonary function in the Agricultural Lung Health Study. Thorax, 2018. 73(3): p. 279–282. [PubMed: 28689172]
8. Hoppin JA, et al. , Pesticides are Associated with Allergic and Non-Allergic Wheeze among Male Farmers. Environmental health perspectives, 2017. 125(4): p. 535–543. [PubMed: 27384423]
9. Cherry N, et al. , Pesticide use and asthma in Alberta grain farmers. International Journal of Environmental Research and Public Health, 2018. 15(3).

10. Mazurek JM and Henneberger PK, Lifetime allergic rhinitis prevalence among US primary farm operators: findings from the 2011 Farm and Ranch Safety survey. International archives of occupational and environmental health, 2017. 90(6): p. 507–515. [PubMed: 28341882]
11. Patel O, et al. , Pesticide use, allergic rhinitis, and asthma among US farm operators. Journal of Agromedicine, 2018. 23(4): p. 327–335. [PubMed: 30230435]
12. Hoang TT, et al. , Epigenome-wide dna methylation and pesticide use in the agricultural lung health study. Environmental health perspectives, 2021. 129(9).
13. Schultz AA, et al. , Residential proximity to concentrated animal feeding operations and allergic and respiratory disease. Environment international, 2019. 130: p. 104911. [PubMed: 31238264]
14. Rasmussen SG, et al. , Proximity to Industrial Food Animal Production and Asthma Exacerbations in Pennsylvania, 2005–2012. International journal of environmental research and public health, 2017. 14(4): p. 362. doi: 10.3390/ijerph14040362. [PubMed: 28362334]
15. Schinasi L, et al. , Air pollution, lung function, and physical symptoms in communities near concentrated Swine feeding operations. Epidemiology, 2011. 22(2): p. 208–15. [PubMed: 21228696]
16. Schulze A, et al. , Effects on pulmonary health of neighboring residents of concentrated animal feeding operations: exposure assessed using optimized estimation technique. Arch Environ Occup Health, 2011. 66(3): p. 146–54. [PubMed: 21864103]
17. Rinsky JL, et al. , Animal production, insecticide use and self-reported symptoms and diagnoses of COPD, including chronic bronchitis, in the Agricultural Health Study. Environment international, 2019. 127: p. 764–772. [PubMed: 31029031]
18. Poole JA and Romberger DJ, Immunological and inflammatory responses to organic dust in agriculture. Curr Opin Allergy Clin Immunol, 2012. 12(2): p. 126–32. [PubMed: 22306554]
19. Poole JA, et al. , Amphiregulin modulates murine lung recovery and fibroblast function following exposure to agriculture organic dust. Am J Physiol Lung Cell Mol Physiol, 2020. 318(1): p. L180–l191. [PubMed: 31693392]
20. Burney P, et al. , Prevalence and Population Attributable Risk for Chronic Airflow Obstruction in a Large Multinational Study. American journal of respiratory and critical care medicine, 2020. 203(11): p. 1353–1365.
21. James KA, et al. , Health Services Utilization in Asthma Exacerbations and PM(10) Levels in Rural Colorado. Annals of the American Thoracic Society, 2018. 15(8): p. 947–954. [PubMed: 29979621]
22. Lee MK, et al. , House dust microbiota in relation to adult asthma and atopy in a US farming population. The Journal of allergy and clinical immunology, 2021. 147(3): p. 910–920. [PubMed: 32615170]
23. Ley RE, Peterson DA, and Gordon JI, Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell, 2006. 124(4): p. 837–48. [PubMed: 16497592]
24. Trivedi R. and Barve K, Gut microbiome a promising target for management of respiratory diseases. Biochem J, 2020. 477(14): p. 2679–2696. [PubMed: 32726437]
25. Romberger DJ, et al. , Proteases in agricultural dust induce lung inflammation through PAR-1 and PAR-2 activation. Am J Physiol Lung Cell Mol Physiol, 2015. 309(4): p. L388–99. [PubMed: 26092994]
26. Burr AC, et al. , Lung Inflammatory Response to Environmental Dust Exposure in Mice Suggests a Link to Regional Respiratory Disease Risk. J Inflamm Res, 2021. 14: p. 4035–4052. [PubMed: 34456580]
27. Nijland R, Hofland T, and van Strijp JA, Recognition of LPS by TLR4: potential for anti-inflammatory therapies. Mar Drugs, 2014. 12(7): p. 4260–73. [PubMed: 25056632]
28. Barnig C, et al. , Indoor dust and air concentrations of endotoxin in urban and rural environments. Lett Appl Microbiol, 2013. 56(3): p. 161–7. [PubMed: 23121051]
29. Morgan BW, et al. , Epidemiology and risk factors of asthma-chronic obstructive pulmonary disease overlap in low- and middle-income countries. J Allergy Clin Immunol, 2019. 143(4): p. 1598–1606. [PubMed: 30291842]
30. Kline JN, et al. , Variable airway responsiveness to inhaled lipopolysaccharide. Am J Respir Crit Care Med, 1999. 160(1): p. 297–303. [PubMed: 10390415]

31. Yen YC, et al. , Household airborne endotoxin associated with asthma and allergy in elementary school-age children: a case-control study in Kaohsiung, Taiwan. Environ Sci Pollut Res Int, 2020. 27(16): p. 19502–19509. [PubMed: 32212084]
32. Mendy A, et al. , House Dust Endotoxin Association with Chronic Bronchitis and Emphysema. Environ Health Perspect, 2018. 126(3): p. 037007. [PubMed: 29578323]
33. Thorne PS, et al. , Endotoxin exposure is a risk factor for asthma: the national survey of endotoxin in United States housing. Am J Respir Crit Care Med, 2005. 172(11): p. 1371–7. [PubMed: 16141442]
34. Carnes MU, et al. , House Dust Endotoxin Levels Are Associated with Adult Asthma in a U.S. Farming Population. Annals of the American Thoracic Society, 2017. 14(3): p. 324–331. [PubMed: 27977294]
35. Stein MM, et al. , Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. N Engl J Med, 2016. 375(5): p. 411–421. [PubMed: 27518660]
36. Holbreich M, et al. , Amish children living in northern Indiana have a very low prevalence of allergic sensitization. J Allergy Clin Immunol, 2012. 129(6): p. 1671–3. [PubMed: 22513133]
37. Motika CA, et al. , Rising prevalence of asthma is sex-specific in a US farming population. J Allergy Clin Immunol, 2011. 128(4): p. 774–9. [PubMed: 21840584]
38. Warren KJ, et al. , Ovalbumin-sensitized mice have altered airway inflammation to agriculture organic dust. Respir Res, 2019. 20(1): p. 51. [PubMed: 30845921]
39. Bruce N, Perez-Padilla R, and Albalak R, Indoor air pollution in developing countries: a major environmental and public health challenge. Bull World Health Organ, 2000. 78(9): p. 1078–92. [PubMed: 11019457]
40. Balmes JR, Household air pollution from domestic combustion of solid fuels and health. J Allergy Clin Immunol, 2019. 143(6): p. 1979–1987. [PubMed: 31176380]
41. Cançado JE, et al. , The impact of sugar cane-burning emissions on the respiratory system of children and the elderly. Environ Health Perspect, 2006. 114(5): p. 725–9. [PubMed: 16675427]
42. Agarwal R, et al. , Epidemiological study on healthy subjects affected by agriculture crop-residue burning episodes and its relation with their pulmonary function tests. Int J Environ Health Res, 2013. 23(4): p. 281–95. [PubMed: 23227956]
43. Rutlen C, et al. , Crop burning and the prevalence of asthma and COPD emergency department treatments in a rural Arkansas county. The Journal of asthma : official journal of the Association for the Care of Asthma, 2021. 58(3): p. 293–298. [PubMed: 31858858]
44. Isaak M, et al. , Nutritional Factors in Occupational Lung Disease. Curr Allergy Asthma Rep, 2021. 21(4): p. 24. [PubMed: 33768348]
45. Ulu A, et al. , A high docosahexaenoic acid diet alters lung inflammation and recovery following repetitive exposure to aqueous organic dust extracts. J Nutr Biochem, 2021. 97: p. 108797. [PubMed: 34126202]
46. Fix J, et al. , Gender differences in respiratory health outcomes among farming cohorts around the globe: findings from the AGRICOH consortium. Journal of Agromedicine, 2021. 26(2): p. 97–108. [PubMed: 32182198]

Clinics Care Points

- Rural populations are at risk for unique agriculture-related exposures which likely contribute to worsening asthma and wheeze.
- Pesticide exposures likely contribute to both allergic and non-allergic asthma and wheeze, but these exposures appear to have greater effects in atopic individuals. Considerations should be made by those who work and live in agricultural communities to minimize their risk of pesticide exposure.
- Residential proximity to certain livestock facilities may lead to increased risk for asthma, exacerbation in asthma symptoms, and is associated with reduced lung function. However, differences have been observed according to type of livestock exposure and further investigations into these differences could be the focus of future studies.
- Chronic exposure to agricultural dust is associated with increased airway inflammation but currently there are no treatments to reverse respiratory disease related to these complex dust exposures. AREG supplementation has been identified as potentially beneficial in animal modeling studies.
- Endotoxin has been associated with both asthma exacerbations and COPD, noting differences in airway inflammatory effects may be dependent upon on the timing of exposure.
- Biomass fuel smoke exposure should be considered as a risk factor for asthma-COPD overlap (ACO), and crop burning practices associated with increased particulate matter concentrations may contribute to increased airway inflammation.
- Certain dietary factors, particularly omega-3 fatty acids and unpasteurized milk, may be associated with improved pulmonary function but the underlying mechanisms remain unknown and additional studies are warranted.

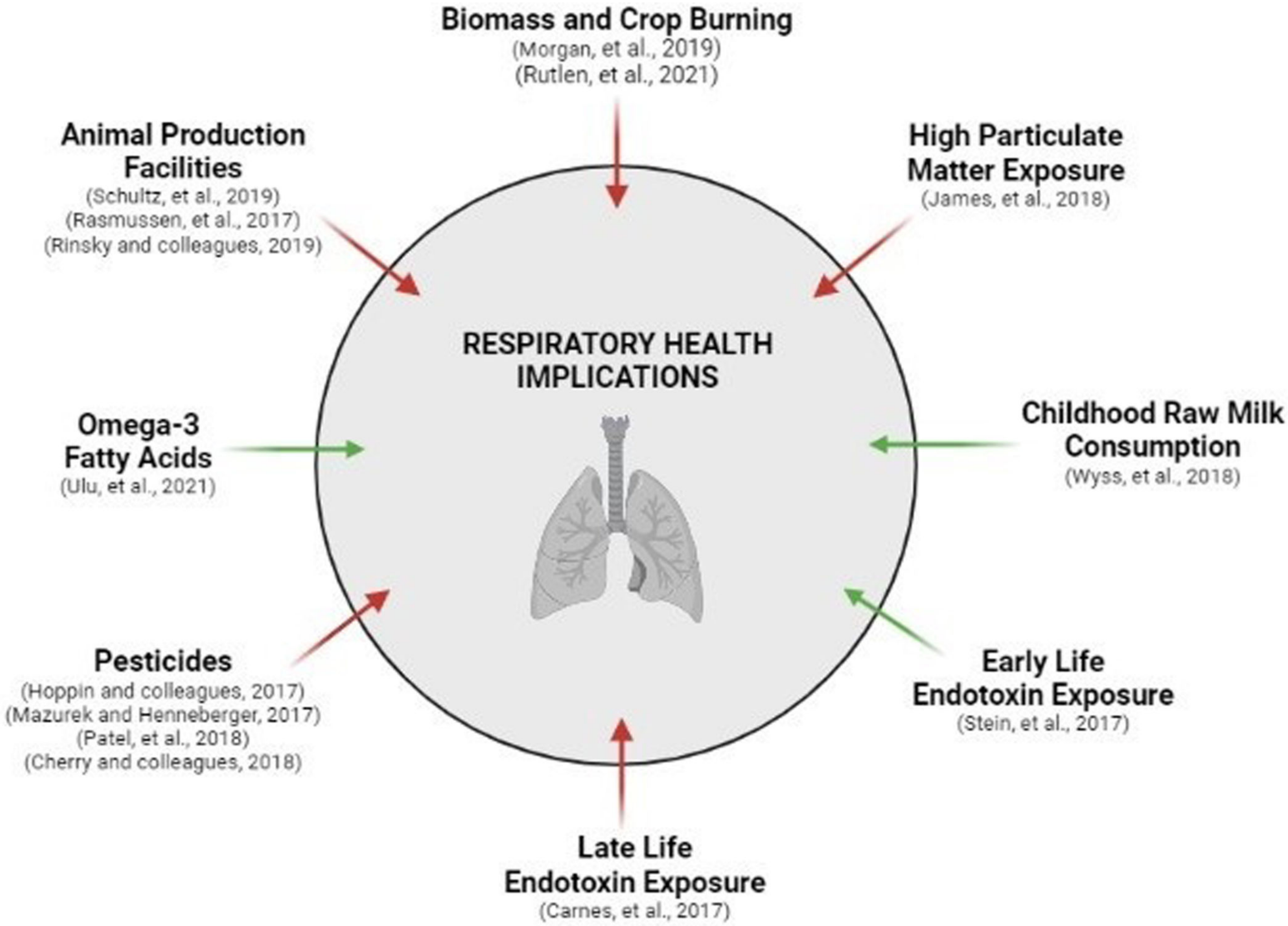

Figure 1. Rural Environmental Factors Influencing Asthma and Wheeze.

Green arrows represent beneficial influences and red arrows represent detrimental influences. Figure created with BioRender.com.

Table 1.

Studies Investigating Pesticides and Asthma and/or Wheeze from 2016–2021.

	PESTICIDE CATEGORY					
	Carbamate	**Phenoxy**	**Pyrethroid**	**Organo-chlorine**	**Glyphosate**[a]	**Malathion**[a]
Cherry, et al.,[9] 2018	No association with asthma	Positive association with asthma	No association with asthma	No association with asthma	Not investigated	No association with asthma
Hoppin, et al.,[8] 2017	Positive association with wheeze	Positive association with wheeze	Positive association with wheeze	No association with wheeze	Positive association with wheeze	Positive association with wheeze
Patel, et al.,[11] 2017	Positive association of insecticides with asthma	No association with asthma	Positive association of insecticides with asthma	Not investigated	No association with asthma	Positive association of insecticides with asthma

[a]Types of organophosphorus herbicide