Influence of Rural Environmental Factors in Asthma

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KEYWORDS

• Rural • Agriculture • Asthma • Wheeze

KEY POINTS

- Rural populations are at risk for unique agriculture-related exposures that likely contribute to worsening asthma and wheeze.
- Exposures to certain pesticides, livestock facilities, agricultural dust, endotoxin (specifically late-life endotoxin exposure), and biomass fuel smoke should be considered as risk factors for asthma and/or wheeze.
- Minimizing exposure to the aforementioned rural risk factors may help reduce negative respiratory effects in agricultural communities and further investigations into these risk factors are warranted.
- Early-life endotoxin exposure and certain dietary factors (particularly omega-3 fatty acids and unpasteurized milk) are potentially protective factors in relation to rural airway inflammation.

INTRODUCTION

When compared with 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 (ie, cancer, heart disease, unintentional injury, chronic lower respiratory disease, and 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 health care 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 issues, cost, language differences, and immigration concerns.[3] In a survey sponsored by the US Department of Labor, it was shown that among farmworkers with asthma, the most commonly reported barriers

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to health care were transportation (60%) and cost (33%).[4] Pate and colleagues[2] 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 less than 10,000 at 13.4 per 1 million compared with 8.8 per 1 million in large metropolitan areas.

Rural environmental exposures and agriculture-related work are known to be associated with asthma, both occupational (asthma caused by work) and work-exacerbated (preexisting 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 that suggests that farming and associated microbial exposures are protective against allergic asthma.[5,6] Farmworkers 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 Cumulative Index to Nursing and Allied Health Literature (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 (COPD), chronic airflow obstruction, and adult. Years searched were 2016 to 2021 and only studies written in English were used. 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 nonallergic 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] Hoppin and colleagues[8] 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. Associations between pesticide use of 78 different pesticides and wheeze, both allergic (defined as physician-diagnosed hay fever and presence of wheeze) and nonallergic (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] Of greater than 22,000 male pesticide applicator participants, 6% were found to have allergic wheeze and 18% had nonallergic wheeze.[8]

Several of these pesticides ($N = 29$) were positively associated with wheeze including nonallergic wheeze ($N = 21$), allergic wheeze ($N = 19$), and both allergic and nonallergic wheeze ($N = 11$).[8] Seven pesticides had significant ($P < .05$) associations with allergic wheeze versus nonallergic 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 nonallergic).[8] Of those positively associated with wheeze, 14 were associated with nonallergic wheeze and 10 were associated with allergic wheeze.[8] The most popularly used herbicides associated with allergic and nonallergic wheeze included glyphosate (trade name Roundup) and atrazine, whereas 2,4-D was associated only with allergic wheeze.[8] Of the insecticides, 9 of the 25 examined were positively associated with

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Table 1
Studies investigating pesticides and asthma and/or wheeze from 2016 to 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] 2018	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.

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wheeze.[8] Disulfoton was the only insecticide inversely associated with a wheeze (nonallergic).[8] Malathion, permethrin, and pyrethrins were associated with both allergic and nonallergic wheeze.[8] Carbaryl, chlorpyrifos, dimethoate, and zeta cypermethrin were associated with allergic wheeze, whereas cyfluthrin and Fly Spray were positively associated with nonallergic 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] Although nonallergic 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[10] showed greater effects of pesticides with allergic asthma versus nonallergic 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 with farmers without allergic rhinitis. 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 a history of allergic rhinitis.[10]

The Farm and Ranch Safety Survey data from greater than 11,000 farmers[11] also found a relationship between pesticide exposures and asthma. Patel and colleagues[11] showed 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. It is interesting to note that glyphosate was not shown to have a significant association with current asthma among farmers, which contrasts with the findings from the Agricultural Health Study.[11] The authors hypothesized that this difference could be because of 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]

Cherry and colleagues[9] examined the respiratory health of grain farmers exposed to pesticides in Alberta, Canada, to assess pesticide use and respiratory disease and symptoms in greater than 1300 grain farmers. Phenoxy herbicide exposures were associated with self-reported asthma that increased with duration of exposure showing an adjusted odds ratio of 1.29 for 1 to 22 years of exposure, 2.52 for 23 to 34 years of exposure, and 3.18 for greater than 35 years of exposure.[9] After stratification for self-reported allergy, the odds 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 remain to be elucidated.[12] To evaluate potential mechanisms, Hoang and colleagues[12] performed an epigenome-wide association study of blood DNA methylation in relation to specific pesticides using the Agricultural Health Study cohort of greater than 1000 farmers of European ancestry. They focused on nine pesticide ingredients for which at least 30 participants had reported past and recent (within the last year) use and seven organochlorines that 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 eight of the nine 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 that potentially supports specific methylation patterns for different pesticides.[12] By identifying differential

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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 seems to increase the risk of asthma development and asthma exacerbations as well as 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, and 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 that can all contribute to airway inflammation and obstruction.[5]

Schultz and colleagues[13] 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. Survey data were obtained from 2008 to 2016 of greater than 5000 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 to 1.9 times greater in populations living 1 to 3 miles from a CAFO versus those living 5 miles from a CAFO and the odds of having allergies were greater than 2fold when those residing 1 to 1.5 miles from a CAFO were compared with those who lived 5 miles from a CAFO.[13] In addition, when compared with 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 the 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 to 3 miles versus 5 miles from a CAFO.[13] Correspondingly, lung function measurements were also dependent on 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 with those living 3 miles from a CAFO.[13] In summary, proximity of residence to animal feeding operations may increase the risk for asthma and exacerbate asthma symptoms.

In addition, a case-control study was performed by Rasmussen and colleagues,[14] 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 less than 3 miles versus those living greater than 3 miles from an IFAP. 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 with those living greater than 3 miles from an IFAP.[14] These findings are consistent with other studies on IFAP and asthma exacerbations that suggest IFAP as a risk factor for asthma symptoms and reduced lung function.[14–16]

Although asthma was not assessed, a study by Rinsky and colleagues[17] examined associations between animal operations, COPD diagnoses, and respiratory symptoms in more than 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 with farmers who

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did not raise animals. 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 the increase of chronic bronchitis symptoms, but differences in symptoms may be seen among those raising different types of livestock depending on the history of COPD.[17] Future areas of study should consider targeting and investigating these differences as well in association with asthma–COPD overlap (ACO).

RURAL DUST EXPOSURE TO AIRWAY INFLAMMATION

Chronic inhalation of agriculture-related dust has been associated with an 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, $(1 \rightarrow 3)$-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 greater than 28,000 participants to determine the prevalence of chronic airway obstruction with various risk factors.[20] Forty-one sites, both rural and urban, across the world were included.[20] Working in a self-reported “dusty job” for greater than 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 of less than 10 years were not examined.[20]

In a geographically focused study area of rural Colorado prone to dust storms, James and colleagues[21] investigated ambient particulate matter concentrations and the effect on emergency visits, urgent care visits, and hospitalizations (EUH) due to asthma. They showed that for each 15 μg 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 μg per cubic meter, EUH visits increased by 16.8%.[21] Furthermore, when 3-day averages were greater than 100 μg per cubic meter, EUH visits increased by 65.8%.[21] In summary, elevated ambient particulate matter concentrations were associated with increased asthma-associated health care 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 and colleagues,[22] 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. They showed that the 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

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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 regard to the 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 and colleagues[19] investigated the role of amphiregulin (AREG), an epidermal growth factor receptor agonist. 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 postexposure inflammatory response was increased.[19] Conversely, intranasal administration of recombinant AREG for 3 days post-repetitive exposure was found to hasten the 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 showed that the dust extract increased AREG and inflammatory cytokine release as well as inhibited wound closure and recellularization of lung scaffolds.[19] Although these studies suggest that AREG supplementation may be potentially beneficial in improving post-agricultural dust exposure-induced lung disease, additional studies using different rural inflammatory agents (eg, endotoxin, peptidoglycan) and fully characterizing the response over longer time periods are 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 and colleagues,[26] centered on an airborne dust collection near an agricultural drainage reservoir in California called the Salton Sea. 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 the dust of homes in rural farming areas when compared with urban or rural nonfarming areas.[28,29] Endotoxin has been previously recognized to play a role in influencing asthma and is associated with inducing asthma exacerbations and COPD.[30–33]

Carnes and colleagues[34] examined the association of house dust endotoxin with asthma and pulmonary function in adults. They performed a case-control study using the Agricultural Health Study to evaluate a population of farmers and farmers' spouses and examined 2485 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

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positive associations with both atopic (OR 1.38, CI 1.09–1.74) and nonatopic 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 showed 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 with those who were living on a farm at birth (OR 1.18, CI 1.02–1.37).[34] Last, the investigators showed that increasing endotoxin levels were related to lower FEV_1/Forced vital capacity (FVC) in those with asthma (b = 21%, SE = 0.5) when compared with those without asthma (b = 20.05%, SE = 0.2) (interaction $P = .01$).[34]

In contrast to the former study by Carnes and colleagues showing 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. Stein and colleagues[35] examined populations of children of two distinct farming communities, the Amish of Indiana and the Hutterites of South Dakota who have similar lifestyles (particularly for factors thought to influence asthma) but vast differences in asthma prevalence. 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%, whereas 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 with those in Hutterite homes.[35] Using a mouse model, intranasal instillation of Amish dust extract before induction of the experimental ovalbumin asthma model led to reduced airway hyperreactivity and eosinophil influx when compared with Hutterite dust extract ($P < .001$).[35] These responses were dependent on both innate immune MyD88 and Trif signaling pathways.[35] Highlighting the importance of timing of exposure, it has also been shown 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] 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 and colleagues[29] investigated risk factors, including biomass fuels, for ACO among adults in various middle- and low-income countries including Peru, Argentina, Chile, Uruguay, Bangladesh, and Uganda. Biomass fuel smoke exposure was associated with higher odds of having ACO (OR 1.48, 95% CI 0.98–2.23) when compared with 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 and colleagues[43] 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

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burning. Emergency room visits were increased by 20.9% for asthma (95% CI 1.01–1.45, $P = .04$) and 16.9% for COPD (95% CI 1.06–1.29, $P = .003$) during the fall months in Craighead county when compared with Sebastian county after controlling for sex, age, and race.[43] Correspondingly, particulate matter (PM) 2.5 concentrations were significantly ($P = .005$) 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 potentially important factors which may have an impact on chronic lung disease and inflammation.[44,45] To investigate the potential protective effects of diet in those exposed to agricultural dusts, Ulu and colleagues[45] investigated a potential therapeutic role of docosahexaenoic acid (DHA), a polyunsaturated omega-3 fatty acid, in airway inflammation resolution. Mice were fed either a high-DHA diet or a control diet and then exposed to swine confinement dust extract for 3 weeks followed by a 1-week recovery period.[45] Mice in 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 regard to agricultural dust exposures and suggests that additional future studies are warranted to explore translational approaches.[45]

Wyss and colleagues[7] examined the effect of consumption of raw or unpasteurized milk practices of children within the Agricultural Lung Health Study. They showed that those who consumed raw milk had higher FEV_1 ($\beta = 49.5$ mL, 95% CI 2.8–96.1 mL, $P = .04$) and FVC ($\beta = 66.2$ mL, 95% CI 13.2–119.1 mL, $P = .01$) but not FEV_1/FVC ratio ($\beta = 0.4\%$, 95% CI -0.4%–1.1%, $P = .33$) as compared with 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 remains unknown.[7] Potential mechanisms suggested by the authors may be related to fat content, microorganism 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 women may be underrepresented in studies.[46] To explore these associations in asthma, Arroyo and colleagues[4] used the National Agricultural Workers Survey of US hired crop workers. It is interesting to note that women in this study were more likely to report lifetime asthma (OR 1.86, CI 1.28–2.72) and recent asthma (OR 2.42, CI 1.62–3.61) when compared with men.[4]

Similarly, Fix and colleagues[46] investigated the A Consortium of Agricultural Cohort Studies (AGRICOH) consortium to examine respiratory disease among farmers and their spouses in 2021. More than 200,000 participants from both crop and livestock farming operations were included from six different continents and 44% of the participants were women.[46] The median prevalence among women for allergic asthma was 5.5% and nonallergic asthma was 3.5%, whereas the median prevalence among men for both allergic and nonallergic asthma was 3.6%.[46] Moreover, women had a

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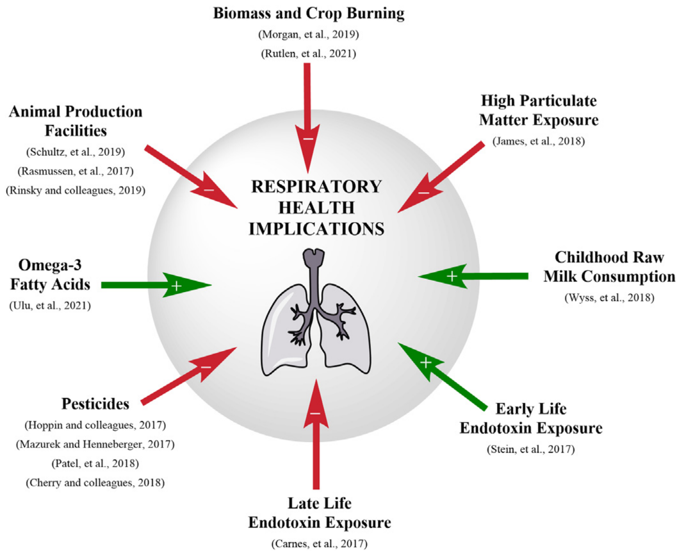

Fig. 1. Rural environmental factors influencing asthma and wheeze. Green arrows represent beneficial influences and red arrows represent detrimental influences. (Figure created with ChemDraw.)

significantly higher prevalence ratio (PR) of allergic asthma to nonallergic 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 women exposed to agricultural risk factors.[46]

SUMMARY

With increased asthma mortality rates shown in rural areas as compared with 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 potentially 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 (**Fig. 1**). Increased awareness of these factors that 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. In addition, investigations into nutritional factors and novel strategic approaches to either prevent and/or reduce these adverse health consequences in rural populations are warranted.

CLINICS CARE POINTS

- Pesticide exposures likely contribute to both allergic and nonallergic asthma and wheeze, but these exposures seem 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.

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- 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 the 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. Amphiregulin supplementation has been identified as potentially beneficial in animal modeling studies.
- Endotoxin has been associated with both asthma exacerbations and chronic obstructive pulmonary disease (COPD), noting differences in airway inflammatory effects may be dependent on the timing of exposure.
- Biomass fuel smoke exposure should be considered as a risk factor for asthma–COPD overlap, 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.

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