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Farming-Associated Environmental Exposures and Atopic Diseases

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Abstract

Objective—To review important farming related environmental factors and host immunologic features with resulting impact on atopic and non-atopic upper and lower respiratory diseases.

Data Sources—PubMed databases were searched for relevant articles pertaining to farming practices, organic dust exposure, immunology, atopy, rhinitis, asthma, bronchitis and respiratory disease.

Study Selections—Articles were selected based on relevance to the topic of the review.

Results—Overall, farming exposures, particularly in children, appears protective against developing IgE-mediated diseases. However, upper and lower respiratory diseases, which tend to be non-allergic marked by enhanced neutrophilic influx, are prevalent in the farming community. These environments are complex and heterogeneous and a large number of environmental factors including dust particles, Gram-negative and Gram-positive bacteria components, peptidoglycans, endotoxins, fungi, gases, pesticides, and allergens are important mediators. Pattern recognition receptors such as Toll-like receptors and nucleotide oligomerization domain-like receptors play key roles in the host defense response. An allergy evaluation tailored to the subjects' environmental history remains important. Therapeutic interventions are limited and attempts to reduce personnel exposure are recommended.

Conclusion—Upper and lower respiratory adverse health effects, particularly non-IgE mediated, are common to agriculture work and represent a substantial concern for farmers, workers, and their families. Regional and international differences in farming practice in addition to type, timing, duration, and intensity of the exposure are important considerations in the evaluation of symptomatic subjects.

Keywords

Farm; Organic dust; rhinitis; asthma; allergy; pattern recognition receptor

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Introduction

Farming is a major industry for the United States and many countries worldwide, and the potential for adverse health effects from chronic exposure to various farming practices are often respiratory-related. These diseases include rhinitis, sinusitis, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), and hypersensitivity pneumonitis. Moreover, individuals with established allergic respiratory disorders will experience worsening symptoms following various types of farming exposures[1]. However, it is now recognized that farming exposures are also often associated with protection against the development of allergic, IgE-mediated diseases[2]. This interesting paradigm of high rates of farming exposure-associated non-allergic upper and lower respiratory diseases, but yet lower rates of allergic-mediated diseases provide an opportunity to review recent advances in our understanding of how farming exposures may modulate atopic diseases.

Exposure agents within farming environments are inherently complex and heterogeneous, and it is increasingly appreciated that exposure to the diversity of microbial-rich components as opposed to one single agent in the farming environment is likely responsible for the immunologic response. Whereas endotoxin remains an important factor, peptidoglycans, Gram-positive bacteria cell wall components, β(1→3)-glucan, and fungi are all emerging as critical players. With focus on the innate immune response to these agents, studies have also yielded important roles for host genetic factors and pattern recognition receptors and sensors. This review will highlight these advances in our understanding of how farming exposures broadly impact allergic and non-allergic respiratory disease manifestations.

Epidemiological Studies

It was proposed by Strachan in 1989 that limited exposure to bacterial and viral pathogens during early childhood results in a predisposition to allergy[3]. Subsequently, numerous studies have repeatedly found that environmental exposures to microbes are inversely related to various atopic diseases with many of these studies focused on the protective effect of farm living in children[2]. Namely, data from several European cohort studies that focus on the health of farm children and allergy and asthma outcomes including the European Allergy and Endotoxin (ALEX) the Prevention of Allergy Risk Factors of Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL), and the multidisciplinary study to identify the genetic and environmental causes of asthma in the European community (GABRIEL) studies largely support that children living on farms have significantly lower prevalence of doctor-diagnosed [4-6]. However, the difference between children living on farms and the reference groups is more striking for atopy as defined by specific IgE antibody measurements[4]. However, even within these cohorts, there can be substantial heterogeneity across study regions and farming practices[7]. It also appears that the protective effect of childhood contact to farm animals will continue into adulthood, but with the caveat that self-selection out of farming or under-reporting of symptoms may occur[8]. Interestingly, initiating exposure to farm animals as an adult may actually increase the risk of allergic sensitization[8].

In contrast to these European cohorts, others have not found that farming is protective against the development of atopic respiratory disorders[9, 10]. In a United States (US) Iowan cohort (Keokuk County Rural Health Study), there was a high prevalence of asthma health outcomes among children living on farms that raise swine (~44% prevalence)[11]. Interestingly, if antibiotics were added to the swine feed, the prevalence for childhood asthma was even higher (~56%)[11]. These findings were demonstrated despite lower rates of atopy and personal histories of allergy[11]. It has also been reported that farm living increases the risk of reporting allergic disease (i.e. rhinitis, hayfever, asthma, and wheeze) in New Zealand, but rates of skin prick test positivity were not increased[12]. These studies highlight that regional and international differences in farm practices are important.

Although farming exposures appear protective against developing IgE-mediated diseases, upper and lower respiratory diseases represent a substantial health problem for the farming community. Although children are affected, respiratory disorders have been best described in adults, which might be explained by chronicity, intensity, and duration of exposure. The prevalence of airways disease, particularly chronic bronchitis ranges from 6 to 32% in adult farmers[1]. Moreover, adult farmers with atopy appear more susceptible to develop farming-related COPD[1] and wheeze[13]. The types of farming and regional differences in farming practices are also important considerations. Animal farming practices (i.e. livestock, dairy, sheet, goats, swine, poultry) have been associated with the greatest risk of developing airways disease as compared to crop farmers in Europe[1]. Similar findings were found in the US Agricultural Health Study (AHS) in that animals and animal-related exposures were important triggers for wheeze among adult farmers[13]. The importance of animal farming exposures, particularly in the US, might be attributable to the rise in large-scale, concentrated, closed, animal-feeding operations that can generate significant amounts of organic dust.

Although rhinitis has long been recognized as the most common respiratory disorder associated with agricultural work, there is a scarcity of recent studies and/or reliable estimates as to the true prevalence of rhinitis or sinusitis related to farming. Nasal symptoms have been reported in up to 64% of grain handlers, whereas the prevalence of sensitization to grain dust antigens ranges from 2-18% in earlier studies[14]. In the Agricultural Health Study, approximately two-thirds of all farmers reported rhinitis symptoms[15]. Others have found that breeding and handling of livestock, dairy production, swine barn exposures, and grain farming all increased nasal inflammation and symptoms[14, 16].

Environmental Agents in Farming Practices

There are a large number of environmental factors in farming practices that could lead to adverse respiratory effects, and include dust particles, Gram-negative and Gram-positive bacteria cell components, fungi/mold, archeabacteria, ammonia, hydrogen sulfide, quaternary ammonium compounds, pesticides, and allergens. In agriculture studies, the exposure environment and respiratory health effects are best described with swine confinement farming. Endotoxin (cell wall component of Gram-negative bacteria; lipopolysaccharide/LPS) is a well-characterized inflammatory agent routinely measured and often linked to respiratory outcomes in agriculture workers[17]. Moreover, earlier work from a cross-sectional survey of rural areas of Austria, Germany, and Switzerland found that higher endotoxin exposure was associated with an increased risk of non-atopic wheeze in children[5]. However, in agriculture-associated adult respiratory disease, a universal dose-response relationship has not been established for endotoxin since studies have reported high exposure without symptoms or lower exposures with a possible dose-response relationship[18, 19].

To understand the nature of airborne microorganisms in farming environments, applied molecular approaches and gas chromatography-mass spectrometry (GC/MS) methods have been recently employed. In the bioaerosols of swine confinement facilities, phylogenetic analysis has revealed large number of sequences (>90%) related to Gram-positive anaerobic bacteria [20] and methanogenic archaea [21]. Mass spectrometry methods revealed high concentration of muramic acid, a marker of peptidoglycan (PGN) derived predominately from Gram-positive bacteria (i.e.~85% of cells wall), but also Gram-negative bacteria (i.e.~5% of cell wall), in settled dust samples from swine confinement facilities and dairy barns [22, 23]. Levels of muramic acid/PGN have been associated with respiratory inflammatory outcomes in humans following swine barn exposure in Europe [24].

Fungi, which are ubiquitous in soil, are also important exposure agents because mold (and bacteria) can reach high levels in hay, grain, or straw, particularly in high humidity storage conditions. The relative concentration of ergosterol, a marker of fungi, is greatly increased in grain elevators as compared to swine and dairy barns in Colorado and Nebraska[22]. Importantly, fungi (and bacteria) inhalation in agricultural environments can result in a hypersensitivity pneumonitis (HP) commonly referred to as Farmer’s lung because the first cases of HP were associated with moldy grain and hay handling in farmers[25].

Pesticides are commonly used in various farming practices, and may be important contributors to the risk of respiratory disease. As recently reviewed by Hernandez, et al, many pesticides are sensitizers or irritants capable of directly damaging the bronchial mucosa, resulting in an airway environment that may be sensitive to allergens or other stimuli[26]. Data from the Agriculture Health Study found that pesticide use is associated with wheeze and atopic and non-atopic asthma among farmers[13, 27]. Further studies from this cohort found that pesticides may contribute to atopic asthma among farm females (wives of farmers)[28]. Specific pesticides may also contribute to rhinitis in US farmers, particularly petroleum oil, malathion, permethrin and the herbicides glyphosate and metolachlor[15]. Thus, pesticide exposure may be playing an important contributory role to asthma and rhinitis risk among adult farmers. Data in children is lacking.

Farming Exposure-Induced Inflammatory Response

As opposed to an eosinophilic and Th2-cytokine response, exposure to farming environments is commonly associated with a neutrophilic response in both the upper and lower airway. For example, naïve persons exposed once to swine barns (i.e. three hour exposure) demonstrate a marked increase in systemic and airway inflammation. The systemic inflammatory response is marked by fevers and increases in serum TNF-α, IL-6, and IL-1β and increased bronchial hyper-responsiveness to methacholine[17]. There is also evidence neutrophil influx, and IL-1β, IL-6, IL-8, and TNF-α levels in broncholaveloar lavage fluid and/or nasal lavage fluid compared to non-exposed persons[17]. While less is known about the inflammatory response with chronic exposures, there is evidence of increased concentration of total cells, granulocytes, albumin, fibronectin, and hyaluronan in the lavage fluid of swine workers as compared to non-exposed persons[17, 29]. Symptomatic swine confinement workers also have epithelial basement membrane thickening by bronchial biopsy[17]. Interestingly, repetitive farming exposure results in a “chronic inflammatory adaptation response.” This response describes the well-recognized observation that there is significant attenuation of the initial, robust inflammatory response following repetitive exposures, but yet, up to one-third of exposed workers will develop chronic lung disease and significant decline in lung function over time[30, 31]. Animal models have been recently described to study this chronic inflammatory adaptation response[32, 33].

The mechanisms understanding this adaptation response are not entirely clear, but may also be important in understanding the protective effect against allergic development. Studies reveal that repetitive swine facility organic dust exposures impair macrophage responses and prevent full maturation of dendritic cells *in vitro*[34, 35]. Specifically, when monocytes are differentiated into macrophages in the presence of dust extract or it components (i.e. endotoxin, peptidoglycan, endotoxin-depleted extract), cell-surface marker expression (HLA-DR, CD80, CD86), phagocytosis, intracellular bacterial killing, and cytokine responsiveness are significantly diminished [35]. Moreover, the organic dust-induced responses *in vitro* appear best paralleled to peptidoglycan plus endotoxin as compared to each agent alone[35], highlighting potential synergist activity amongst components. Although the phenotype of the infiltrating leukocytes is not clear, there is a suggestion of a Th17-polarized response in adults because exposure to swine confinement organic dust environments increases IL-17A in lavage fluid cells, mainly in lymphocytes[36]. Finally, earlier work demonstrated that swine workers have increased levels of soluble L-selectin, which may serve as a protective role against atopy because soluble L-selectin is associated with decreases in inflammatory cell migration [37].

Role of Innate Immune Pattern Recognition Receptors and Sensors

Since farming environments are microbial-rich, studies have focused on the role of specific host pattern recognition receptors (PRRs) and sensors that could be responsible for mediating immune responses to farming environment. Toll-like receptors (TLRs) are one family of PRRs responsible for recognizing highly conserved microbial motifs. Overall, gene expression of several TLRs and CD14 tend to be increased in farm children[2, 38]. Of the 11 human TLRs, TLR4 forms a complex with CD14 and LPS-binding protein (LBP) to recognize endotoxin and elicit inflammatory responses. Whereas corn dust-induced airway inflammation can be profoundly reduced in endotoxin-resistant mice [39], animal farming dust-induced airway inflammation is not completely dependent on the TLR4 pathway[40]. In humans, those with the TLR4 variant (299/399) demonstrated a decrease in cross-shift change in lung function (FEV_1) following a high endotoxin swine barn exposure challenge, but no difference was observed after a low endotoxin swine barn exposure challenge [41]. Moreover, in a cohort study (Iowa Keokuk county), CD14 polymorphorisms (CD14/-159T and CD14/-1610G) were associated with increased prevalence of wheezing among farmers [42]. In general, polymorphisms in TLR4 and CD14 have been associated with various allergy phenotypes[43]. These studies highlight the important role of endotoxin and its TLR4 signaling pathway in mediating respiratory consequences.

Since Gram-positive bacteria appear highly abundant in animal farming environments, several recent studies have focused on the TLR2 pathway because TLR2 recognizes peptidoglycans, lipoteichoic acid, and lipoproteins from Gram-positive bacteria. Indeed, airway epithelial cell TLR2 increases following swine confinement facility dust extract exposure [44], and dust-induced proinflammatory cytokine release from epithelial cells is reduced when TLR2 is blocked *in vitro* [45] In addition, airway neutrophil influx, cytokine release, and lung parenchymal inflammation is significantly reduced, but not completely abrogated, in TLR2 deficient mice following organic dust extract intranasal inhalation challenges [46]. However, as observed with TLR4 deficient mice[40], TLR2 deficient animals retained their airway hyper-responsiveness following dust exposures[32]. Lastly, there may be a role for TLR2 gene variants because children of farmers with polymorphism in TLR2/-16934 were less likely to have asthma and allergic symptoms compared to children of non-farmers with same polymorphism[47]. The importance of TLR2 genetic polymorphisms in agriculture workers is not known.

Another innate immune PRR group that senses microbial motifs is the NACHT-LRR protein family. Of this large family of intracellular proteins, nucleotide oligomerization domain 1 (NOD1) senses peptidoglycan containing D-glutamyl-meso-diaminopimelic acid (iE-DAP) predominately from Gram-negative bacteria and NOD2 senses muramyl dipeptide that is a component of virtually all types of bacterial-derived peptidoglycan. Dust extracts from swine barns as well as endotoxin and peptidoglycan products alone upregulate NOD2 expression in mononuclear phagocytes [48]. The loss of NOD2 resulted in an enhancement of inflammatory outcomes following swine barn dust extract[48] and peptidoglycan challenges[49], suggestive of a negative regulatory role. In contrast, others have found that in the absence of NOD2, pro-inflammatory cytokine production is reduced after stimulation with various TLR agonists [50], favoring a positive regulatory role. Thus, there may be an important regulatory role for NOD2, but further studies are needed. Although genetic variants in NOD2 have not been described in agricultural workers, NOD2 polymorphisms have been implicated in atopic diseases [51]. NOD1 has been associated in several studies with asthma susceptibility and development [51]. Furthermore, children of farmers with NOD1 variant (CARD4/-21596) were strongly protected from allergy and asthma[52]. Thus, understanding the role of these intracellular protein sensors is necessary as they may be important modifiers in farming exposure-induced respiratory diseases.

Allergens

While the protective effect of farm life on atopy has received considerable attention in recent years, allergens remain important players and should not be overlooked in the evaluation of agriculture workers and their family members with respiratory disease. Although rates of allergic sensitization appear lower as compared to non-farm subjects, farm subjects and their children can manifest significant IgE-mediated disease. The prevalence of skin prick test (SPT) reactions to common allergens (i.e. grass, tree, weed, dust mite, mold, cat, and dog) has been reported as high as 25-30% in farm subjects[11, 12]. Skin testing to all the appropriate allergens is also an important consideration. For example, Remes, et al found that the proportion of non-farmers' children with one positive SPT reaction to common allergens was 13.4% as compared to 10.1% in farmers' children[53]. However, they found no difference in SPT positive rates when testing for "other" allergens that included cockroach, horse, storage mite, and cow[53]. There may also be limitations in our current commercially available skin test reagents because Heutelbeck et al reported that approximately 60% of German cattle farmers reported both asthma and rhinitis when working with cattle, but yet positive reactivity to commercially available cow allergen extracts was low[54]. Moreover, the same group found that supplementing skin tests using extracts of the hair of the farmers' own cattle improved positive responses[55]. Diet may also play a role in interpreting studies as obese farm subjects may have a greater prevalence of allergic sensitization as compared to non-obese farm subjects and thus, obesity may negate the protective effect of farming exposures[56]. Another important factor is gender because case series have reported new onset occupational asthma and atopy in female workers in the swine industry[57]. Thus, complete history evaluations with testing to environmental allergens tailored to the subject's environment is recommended.

Preventative and therapeutic options

For individuals exposed to agricultural environments experiencing adverse respiratory health outcomes, the therapeutic options are somewhat limited. At present, there is a paucity of studies to strongly recommend specific therapies for the treatment of rhinitis in farmers or farm children. Nonetheless, clinicians should follow best practice guidelines for the general treatment of allergic and non-allergic rhinitis. There is evidence that intranasal fluticasone propionate may be beneficial because when it was administered prior to swine barn exposure, plasma protein leakage, IL-8, and TNF-α response was reduced[58].

There are several studies that have investigated the effect of various pharmacologic interventions and their effect on agricultural-based organic dust-induced airway inflammation. Inhaled sodium cromoglycate has been shown to reduce neutrophilic influx and pro-inflammatory indices in bronchoalveolar fluid following exposure to dust in pig farms[59]. Pre-treatment with inhaled corticosteroids results in a mild dampening of pro-inflammatory indices, but no effect on bronchial responsiveness[58]{{}}. The benefit of adding long-acting beta agonist like salmeterol is less clear as early work found no protection against bronchial hyper-responsiveness induced by pig barn exposure[60], but yet the same group later found that salmeterol offered partial protection alone[61]. There does not appear to be a role for ibuprofen or anti-leukotriene modifers (i.e. 5-lipoxygenase inhibitors)[61, 62].

Non-pharmacologic interventions are an attractive alternative given the relative low success rate with pharmacologic interventions to date. Of these non-pharmacologic interventions, the use of N-95 disposable respirators is recommended. Studies show that these respirators can dampen the acute adverse respiratory health effects in individuals, but unfortunately the routine and regular use of dust masks is low [63]. Efforts to reduce dust levels by sprinkling canola oil in swine barn did find lower mean shift changes in pulmonary function, lower white blood cell counts, lower total cells in nasal lavage fluid, and improvement in bronchial-hyper-responsiveness[64]. Finally, the use of robot (high-pressure) pre-cleaning of swine barns resulted in a reduction in bronchial responsiveness and nasal lavage cellularity, neutrophils, and IL-8 levels as compared to pre-cleaning without a robot[65].

CONCLUSION

It is now well appreciated that there is a protective effect of growing up on the farm from the subsequent development of IgE-mediated allergic disorders. However, upper and lower respiratory adverse health effects, particularly non-IgE mediated, are common to agriculture work and represent a substantial concern for farmers, workers, and their families. It is important to understand that the farming environmental exposure is heterogeneous and complex and that regional and international variation in farming practice should be considered. Exposure to the wide diversity of microbial rich components, which include Gram-positive peptidoglycans, Gram-negative endotoxins and fungi, are all potent and potential activators of host defense response. TLRs and intracellular sensors (i.e. NODs) are important pathways involved in mediating disease. The timing, type, duration and intensity of the farming environmental exposures plus host genetic factors are likely responsible for determining the development of non-allergic respiratory diseases or protection against allergy. Pesticides, chemicals, gases, dust particles, and allergens are also important in the evaluation of these subjects. In general, there is a paucity of rhinitis and sinusitis studies in this population to make definitive conclusions on the magnitude of disease or recommendations for preventative and therapeutic strategies. Lower respiratory disease such as asthma and bronchitis are also prevalent and future studies are needed to address the primary non-allergic nature of these disease in children and adults exposed or working on the farm.

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