Review

Asthma and Atopy in Rural Children: Is Farming Protective?

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ABSTRACT

The prevalence of asthma and other atopic diseases has recently increased, especially in urban and modernized regions of the world. The majority of published prevalence surveys report that asthma and atopy are less common among children living in rural areas. While many exposures differ in rural and urban areas of the world, several recent studies have suggested that agricultural exposures in early childhood may decrease the risk of developing atopic disease. Livestock exposure, in particular, seems to be important, but additional research is needed to pinpoint the underlying mechanisms behind this apparent protective effect of rural and farm living. Additionally, prospective studies are needed to more closely examine the timing of farm exposures in relation to the onset of asthma and atopy, and to determine if the apparent protective effects of farming persist into adulthood.

INTRODUCTION

The prevalence of asthma and other atopic diseases, such as hay fever and atopic dermatitis, appears to have increased among children worldwide in recent years, but the reasons behind this increase are currently unknown. The increase has been relatively rapid and dramatic, suggesting that changing environmental factors rather than changing genetic factors have contributed to the increase.^{1,2} Although the definition and diagnosis of these conditions are frequently difficult, the increase in prevalence has been consistently reported and appears to be a real increase rather than just a reflection of changing diagnostic trends.

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The prevalence of atopic conditions is lower in rural and less-developed areas of the world and higher in areas that are rapidly urbanizing or are modernized.² The reasons for these observed prevalence gradients are currently not well understood. Interestingly, atopic conditions have become more prevalent at the same time that childhood infectious diseases have become less prevalent worldwide, and some researchers have speculated that early life exposures to bacteria and viruses may prevent the development of asthma and atopy in children.^{1,3,4}

Children living in rural or developing areas often have different infectious disease exposures than urban children, but they are also more likely to reside on farms or engage in farm work. Several recent studies from Europe, Canada, and Australia have suggested that agricultural exposures may protect children from developing asthma and atopy.⁵⁻¹⁷ However, these findings are not all consistent, and research has not yet identified the underlying mechanisms of this association. Further, this suggested protection in children contrasts with a host of studies from the occupational literature that suggest adult farmers are at increased risk of respiratory disease.^{8,18,19} Respiratory symptoms in adult farmers have been associated with agricultural exposures such as grain dust, soybean dust, endotoxin, and pesticides.²⁰⁻²⁵

This review highlights findings from several recent studies of asthma and atopy among rural and farm children. Many of these studies hypothesize about the apparent protective effect of rural living and farming, yet they still leave critical questions for future research.

ASTHMA AND ATOPY IN RURAL POPULATIONS

In general, the reported prevalence of asthma and atopic conditions among children is lower in rural areas than in urban areas (table 1). These differences in observed prevalence can be partially explained by urban and rural differences in environmental exposures, such as air pollution and home heating, and allergens, such as pollens, cockroaches, and house dust mites.²⁶⁻³¹ Other urban-rural lifestyle differences could affect the prevalence of asthma and atopy. Rural children typically have more siblings,^{11,29,30} are exposed to less tobacco smoke at home,^{27-29,32} and are more likely to own pets or be exposed to animals than are urban children.^{11,27,29,31,32} Studies have also looked at urban-rural differences in exercise and diet.³³ Although many of these exposures are frequently associated with asthma and atopy, several studies have reported that the protective effect of rural living persists after adjusting for these exposures.^{11,27,33}

ASTHMA AND ATOPY IN FARMING POPULATIONS

Many children living in rural areas are exposed to agriculture by residing, working, and playing on farms. Agricultural exposures that may affect respiratory health and atopy include endotoxin, grain dust, soybean dust,

pesticides, livestock, and zoonotic pathogens.^{19,20,22-25} Several recent studies from Europe and Canada suggest that farm children are less likely to develop asthma and other atopic conditions than non-farm children (table 2). Ernst and Cormier evaluated 1,199 rural children 12 to 19 years of age in Quebec, Canada.⁷ The odds ratio for being raised on a farm and having a diagnosis of asthma was 0.59 (95% confidence interval (CI): 0.37-0.95) after adjusting for gender and smoking. Children raised on a farm also had reduced atopic sensitization (odds ratio (OR)=0.58; 95% CI: 0.46-0.75). Airway hyperresponsiveness and hay fever were also less common among children with farm exposures. The associations noted in this study were more pronounced for girls than for boys.

Von Ehrenstein et al. conducted a cross-sectional survey of 10,163 school children in southern Germany.¹⁰ Children of farmers had a lower prevalence of asthma (OR=0.65; 95% CI: 0.39-1.09), hay fever (OR=0.52, 95% CI: 0.28-0.99), and wheeze (OR=0.55; 95% CI: 0.36-0.86) compared to children not living on farms. In Switzerland, Braun-Fahrlander and colleagues examined 1,620 children and report an adjusted odds ratio of 0.31 (95% CI: 0.13-0.73) for the association between atopic sensitization in children and farming as a parental occupation.⁵ No significant associations were noted for hay fever (OR=0.89; 95% CI: 0.49-1.59), eczema (OR=1.15; 95% CI: 0.74-1.81), or asthma (OR=1.17; 95% CI: 0.64-2.13).

A number of studies have found that a decreased prevalence of atopy and asthma is associated not just with farm residence but with livestock exposure in particular. In a cross-sectional survey of 2,283 children in Austria, Riedler et al. report a decreased prevalence of asthma, hay fever, and atopic sensitization among children 8 to 11 years of age living on farms.⁹ Regular contact with livestock was associated with a decreased prevalence of atopic sensitization. This association was even noted for children who did not live on a farm but reported regular contact with livestock.

Remes et al. examined 7,981 children 13 to 14 years of age in Finland.¹⁶ Living on a farm was associated with a decreased prevalence of allergic rhinoconjunctivitis (OR=0.79, 95% CI: 0.63-0.99), but was not associated with asthma (OR=1.01; 95% CI: 0.72-1.41), wheeze (OR=1.09; 95% CI: 0.75-1.56), or eczema (OR=1.07; 95% CI: 0.90-1.28). Models were adjusted for gender, age, geographic region, parental atopy, parental education, smoking, and number of siblings. A trend in the prevalence of allergic rhinoconjunctivitis was observed when farm families were stratified by livestock ownership. Children living on farms with livestock had the lowest prevalence (OR=0.70), followed by children living on farms without livestock (OR=0.89) and non-farm children (*P*-value for trend=0.02). No such trend was observed for asthma, wheeze, or eczema.

Table 1. Prevalence of asthma and other atopic conditions among children in rural regions.

Study	Population	Sample size		Asthma		Wheeze		Airway hyperreactivity		Atopic sensitization*		Hay fever/allergic rhinitis		Eczema/atopic dermatitis	
		Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban
Gergen et al. 1988 ⁴⁹	United States 3 to 17 year olds	7399		5.7%	7.1% ^a										
Crockett and Alpers 1992 ⁴⁷	Australia 5 to 15 year olds	825	1261			24.1%	27.6%					21.3%	45.9% ^a	10.0%	16.2% ^a
AddoYobo et al. 1997 ⁴⁸	Ghana 9 to 16 year olds	276	819					2.7%	3.4%	1.5%	5.6% ^a				
Yemaneberhan et al. 1997 ⁵²	Ethiopia all ages	3032	9844	1.3%	3.6% ^a	1.2%	3.7% ^a								
Nilsson et al. 1999 ²⁷	Sweden 13 to 14 year olds	1878		4.5%	11%							20%	23%	24%	29%
Barnes et al. 2001 ¹¹	Crete 11 to 19 year olds	438	559							9.6%	19.6% ^a				
Bibi et al. 2002 ²⁸	Israel 9 to 12 year olds	85	363	7.1%	6.8%					45.5%	63.3% ^a				
Perzanowski et al. 2002 ⁵⁰	Kenya 9 to 13 year olds	136	129	3.9%	11.2% ^a					4%	14% ^a				
Dagoye et al. 2003 ³⁰	Ethiopia 1 to 4 year olds	2862	4293			2.0%	4.4%								
Sudhir and Prasad 2003 ³¹	India 7 to 15 year olds	200	200	7%	12.5%	5.5%	12.5% ^a	10.1%	13.2%			15.5%	23.5%		

* assessed with skin prick testing or serum IgE.

^a statistically significant prevalence difference: rural vs. urban.**Table 2.** Prevalence of asthma and other atopic conditions in farm children.

Study	Population	Sample size		Asthma		Wheeze		Airway hyperreactivity		Atopic sensitization*		Hay fever/allergic rhinitis		Eczema/atopic dermatitis	
		Farm	Control	Farm	Control	Farm	Control	Farm	Control	Farm	Control	Farm	Control	Farm	Control
Braun-Fahrlander et al. 1999 ⁵	Switzerland 6 to 15 year olds	307	1313	7.8%	9.6%	5.2%	9.1% ^a					7.2%	13.3% ^a	15.6%	19.6%
Ormland et al. 1999 ⁶	Denmark young adults	1901	407	8.0%	8.4%			1.9%	3.2%						
Ernst and Cormier 2000 ⁷	Canada 12 to 19 year olds	1034	5981	5.8%	8.3% ^a	20.9%	25.8% ^a	12.9%	17.4% ^a	40.8%	53.4% ^a	30.2%	35.0% ^a	11.3%	12.1%
Masley et al. 2000 ⁸	Canada 0 to 17 year olds	316	74	10.1%	10.8%										
Riedler et al. 2000 ⁹	Austria 8 to 11 year olds	282	1710	1.1%	3.9% ^a	4.7%	7.5%			18.8%	32.7% ^a	3.1%	10.3% ^a	11.4%	10.9%
Von Ehrenstein et al. 2000 ¹⁰	Germany 5 to 7 year olds	1181	8466	3.4%	6.4% ^a	5.6%	8.1% ^a					1.8%	4.9% ^a	13.8%	15.5%
Downs et al. 2001 ¹²	Australia 7 to 12 year olds	142 crop	341	43.4%	40.6%	40.6%	41.5%			46.0%	41.0%	36.2%	29.7%		
		157 mixed	860	30.1%	40.0% ^a	33.6%	43.8% ^a			29.7%	49.0% ^a	27.2%	36.7% ^a		
Klintberg et al. 2001 ¹³	Sweden 7 to 8 year olds	136	571	2.2%	8.6% ^a	8.1%	13.0%			30.7%	32.7%	3.8%	9.7% ^a	28.7%	33.0%
Riedler et al. 2001 ¹⁴	W. Europe 6 to 13 year olds	593 ^b	170	5.4%	11.8% ^a	5.6%	15% ^a					7.6%	20.0% ^a		
Horak et al. 2002 ¹⁵	Austria 7 to 8 year olds	107	603							8.4%	25.5% ^a				
Remes et al. 2002 ¹⁶	Finland 13 to 14 year olds	924	6998	5.0%	5.6%	4.2%	4.3%					22.8%	26.9% ^a	23.5%	24.3%
Wickens et al. 2002 ³⁴	New Zealand 7 to 10 year olds	94 ^{**}	199	34%	33%	20%	23%			32%	32%	31%	33%	38%	36%
		95 ^c	198	39%	31%	25%	21%			37%	30%	39%	29%	41%	34%
Remes et al. 2003 ¹⁷	Finland 6 to 13 year olds	102	136							27.9%	39.5% ^a				

* assessed with skin prick testing or serum IgE.

^a statistically significant prevalence difference: farm vs. non-farm.^b farm exposures (stables or unpasteurized milk) in early childhood.^{**} farm residence in first year of life.^c farm residence at time of survey.

Barnes et al. noted a reduced prevalence of atopic sensitization among children in Crete who had early life contact with livestock (OR=0.67; 95% CI: 0.46-0.99).¹¹ This effect was even observed among urban children who did not live on a farm but reported regular contact with livestock. A similar association was reported for the consumption of unpasteurized milk and decreased prevalence of atopy (OR=0.65; 95% CI: 0.41-1.00). Riedler et al. also noted a protective effect of livestock exposure and consumption of unpasteurized milk in their cross-sectional survey of school children in Austria, Germany, and Switzerland.¹⁴ Exposure to stables and farm milk in the first year of life was associated with decreased prevalence of asthma (OR=0.14; 95% CI: 0.04-0.48), hay fever (OR=0.20; 95% CI: 0.08-0.50), and atopic sensitization (OR=0.32; 95% CI: 0.17-0.62).

Many of these studies also suggest that the frequency of exposure to a farm environment and/or to livestock is related to decreasing prevalence of atopy or asthma. In the Von Ehrenstein et al. study, children of full-time farmers had lower risk of atopic disease than children of part-time farmers, and increasing exposure to livestock was associated with decreasing prevalence of atopic disease (OR=0.41; 95% CI: 0.23-0.74).¹⁰ In the study conducted by Braun-Fahrlander et al., children of full-time farmers had lower serum IgE levels than children of part-time farmers suggesting a dose-response effect between farm exposures and atopic sensitization.⁵

In a cross-sectional study of children 6 to 13 years of age in Finland, Remes et al. report a decreased prevalence of atopy among farmers' children (OR=0.56; 95% CI: 0.40-0.78).¹⁷ Exposure to livestock was inversely associated with atopy in a dose-dependent manner (OR=0.46; 95% CI: 0.22-0.97 for daily contact with livestock compared to no contact with livestock). Pet ownership was also associated with a decreased risk of atopy (OR=0.60; 95% CI: 0.42-0.85).

Two recent studies conducted in farming populations outside of Europe seem to suggest that farm residence without livestock exposure may not affect prevalence rates. Downs and colleagues investigated asthma and atopy among children 7 to 12 years of age from two farming regions in Australia.¹² No protective effect of farming was observed among children living in a primarily crop farming region. However, the prevalence of asthma and atopy was reduced among farm children living in a region with both livestock and crop farming compared to their non-farm peers from the same region.

In a cross-sectional survey of 293 children from a large-scale livestock and crop farming region in New Zealand, current farm residence was generally associated with increased prevalence of asthma and atopy.³⁴ Farm residence during the first year of life also did not appear to protect against asthma and atopy among children 7 to 10 years of age. Early life contact with pigs, and consumption

of unpasteurized dairy products, did appear to marginally decrease the prevalence of atopic conditions among both the farm and non-farm children studied.

LIVESTOCK EXPOSURE AND THE "HYGIENE HYPOTHESIS"

If livestock exposure is indeed associated with a decreased prevalence of asthma and atopy, then additional research is needed to explore the underlying mechanisms of this association. Contact with livestock may increase allergen, dust, and microbial exposures.^{5,12,14,16,19,35} Researchers have proposed a hypothesis that may help explain how microbial exposures relate to the development of asthma and atopy.

The basic premise of the "hygiene hypothesis" is that early life exposures to microbes influence the development of the immune system in a manner that reduces a child's likelihood of developing asthma and atopy.³ Specifically, microbial exposures may influence the balance of type 1 (Th1) and type 2 (Th2) helper T cells by promoting Th1 responses and down-regulating Th2 responses. Th1 cells are associated with responses to infection and the production of interferon- γ . Th2 derived cytokines induce the production of IgE and the maturation of mast cells, basophils, and eosinophils. Th2 cells are therefore generally associated with "atopic" immune responses.

Children exposed to livestock may be exposed to more bacteria and viruses than are children without livestock exposure.^{5,9,12-14,16,35} In particular, contact with livestock may increase a child's exposure to endotoxin, a component of the outer membrane of gram negative bacteria and a strong promoter of interleukin-12 and the maturation of naïve T cells into Th1 cells.^{5,14,34,36-38} Early childhood exposure to endotoxin may protect against asthma and atopy by promoting Th1 cells and inhibiting Th2 cells. Additionally, several researchers have suggested that children exposed to high levels of endotoxin may develop an immune tolerance to it.^{5,13,14,39} Paradoxically, high levels of endotoxin exposure have been shown to exacerbate respiratory symptoms in adult farmers.^{22,40,41} Therefore, the timing and dose of endotoxin exposure seem critical to its association with asthma and atopy.

Clearly, further study is needed to clarify the exact nature of the association between livestock exposure and atopic conditions. In addition to increased endotoxin exposure, children with livestock contact may also be exposed to zoonotic pathogens, dander, feed additives, and dust.^{5,12,42} Missing from all these studies of childhood exposures is a comprehensive longitudinal study that follows children exposed to both livestock and crop farming into their adult years. This type of study is particularly necessary, because studies have reported an increased risk of respiratory disease in adult farmers compared to non-farmers.^{8,18,19} It is currently not clear if the apparent protective effect of farm exposures in childhood persists into adulthood.

ADULT STUDIES

Three studies have retrospectively examined the association between early life farm exposure and adult asthma and atopy (table 3). Kilpeläinen et al. investigated the relationship between early childhood farm residence and asthma and atopy in 10,667 Finnish university students.³⁵ Farm residence in childhood was associated with a decreased prevalence of allergic rhinitis after adjusting for gender, day care attendance, tobacco smoke exposure, parental history of atopy, and number of older siblings (OR=0.63; 95% CI: 0.50-0.79). Early childhood farm residence was not significantly associated with asthma (OR=0.70; 95% CI: 0.46-1.06). Skin prick testing and methacholine challenge testing was performed in a subsample of these young adults.⁴³ No difference in airway hyperreactivity was noted, but students who lived on a farm during childhood were more likely to be sensitized to house dust mite (OR=5.43; 95% CI: 1.60-18.46). Sensitivity to pollens and cats were less common among adults who grew up on farms.

Leynaert et al. surveyed 6,251 adults participating in the European Community Respiratory Health Survey.⁴⁴ Living on a farm in childhood was not associated with asthma (OR=0.82; 95% CI: 0.53-1.27) or wheeze (OR=1.09; 95% CI: 0.82-1.46) but was significantly associated with a decreased risk of atopic sensitization (OR=0.68; 95% CI: 0.55-0.86). Adults who lived on farms during childhood were less likely to be sensitized to house dust mite and cat than were adults who did not live on a farm.

Atopic sensitization was less common among Danish college students who were raised on farms compared to controls (OR=0.55; 95% CI: 0.40-0.76).⁴⁵ Bronchial hyperreactivity (OR=0.61; 95% CI: 0.39-0.95), asthma (OR=0.79; 95% CI: 0.49-1.27), and rhinoconjunctivitis (OR=0.70; 95% CI: 0.49-0.99) were also less common among students raised on a farm, but the association with asthma did not reach statistical significance. The authors

also examined students who were working in agriculture at the time of the survey. Atopic sensitization was less common among these students, but no differences in the prevalence of bronchial hyperreactivity, asthma, or rhinoconjunctivitis compared to controls were observed.

DISCUSSION

The findings from recent studies of European, Canadian, and Australian farm children suggest that farm exposures may confer some protection against asthma and atopy in childhood, but several studies did not observe this relationship. The protective effect appears to be stronger for the development of atopic conditions than for the development of asthma, which is consistent with studies from the adult literature.^{35,43-45} The timing of exposures also appears to be important. Early life exposures tend to confer protection, while later life exposures either do not provide any protection or may exacerbate current symptoms.^{9,34,45}

Although, farm children in these studies frequently differed from non-farm children in regards to various exposures such as tobacco smoke, family size, and home heating, the associations between farming and atopic disease often persisted after adjusting for these exposures.^{5,7,9,10,12,13,16,17} Contact with animals was consistently associated with a reduced risk of atopic disease.

Several studies reported that farm children were more likely to own pets than non-farm children,^{5,7,13,17,34,43} and some found a protective effect of pet ownership.^{13,34,43} Although conventional medical advice has been to remove pets from the home to avoid asthma and atopy, it appears that some exposure to pets may actually help protect against these conditions. However, the timing of these exposures seems critical. Early life exposures may be protective, while later life exposures may actually worsen symptoms among children who already have asthma or other atopic conditions.^{34,46}

Table 3. Prevalence of asthma and other atopic conditions in adults with early childhood farm exposures.

Study	Population	Sample size		Asthma		Wheeze		Airway hyperreactivity		Atopic sensitization*		Hay fever/allergic rhinitis	
		Farm	Control	Farm	Control	Farm	Control	Farm	Control	Farm	Control	Farm	Control
Kilpeläinen et al. 2000 ³⁶	Finland	1095	1243	3.7%	5.3%							13.9%	20.8% ^a
Leynaert et al. 2001 ⁴⁵	Europe	548	5703	4.4%	4.9%	25.0%	23.2%			27.0%	35.4% ^a		
Portengen et al. 2002 ⁴⁶	Denmark	505**	402	5%	8%	5%	12% ^a	6%	8%	13%	27% ^a		
		494 ^c	402	9%	8%	11%	12% ^a	11%	8%	23%	27% ^a		

* assessed with skin prick testing or serum IgE.

^a statistically significant prevalence difference: farmers vs. controls.

** farm residence in early childhood.

^c current occupational farm exposures.

Several studies have reported a protective effect of early life livestock exposure.^{9-11,13,14,16,17} Children exposed to livestock may be exposed to animal danders, bacteria and viruses, pesticides, feed additives, and dust,^{5,9,16,36} but few studies have examined these more specific exposures in detail. Children exposed to livestock may also be exposed to higher levels of endotoxin as discussed above, and this may confer protection against asthma and atopy.^{14,34,36} Endotoxin exposure, however, may only be a surrogate marker of microbial exposures in the farming environment, and more detailed investigations into specific exposures are needed.^{16,38} Data from adult studies suggest that exposures to different types of livestock (cattle, hogs, poultry, etc.) may have different effects on asthma and atopy.^{6,19,23,25} Generally, poultry and hog farming are associated with increased risk of respiratory symptoms.^{23,25} Most of the livestock exposures in the European studies involved cattle.^{13,14,21}

Limitations of current studies

Studies of asthma and atopy in rural and farming populations have primarily been cross-sectional surveys. The prevalence rates from these studies are difficult to compare because varying methods were used to define asthma and atopy. These studies primarily rely on self-reported questionnaire responses about wheeze, allergy symptoms, and diagnosed asthma. Even the more “clinical” measures of atopic sensitization (skin prick testing and serum IgE) and bronchial hyperreactivity (methacholine challenge testing) are difficult to compare across studies because of varying methodologies.

It is also difficult to establish the timing of exposure and disease using cross-sectional studies. Several authors have suggested that the decreased prevalence of asthma and atopy observed in some studies may reflect a “healthy farmer effect”.^{5,12,23,44} Over time, persons with asthma or atopy symptoms may self-select out of farming into other occupations with less respiratory exposures. Thus, when a cross-sectional survey is performed, asthma and atopy appear less common in the farming population because only the “healthy farmers” have remained in agriculture.

Several studies of farm children have attempted to adjust for this “healthy farmer effect” by collecting information about parental history of asthma and atopy.^{5,10,13,16} Parental history of atopic conditions was more common among non-farm children in some studies,^{5,10,16,17,44} while in others it was not.^{12,13} Importantly, the protective effect of farming remained in many of these studies after adjusting for parental history in multivariable models.^{5,10,13,14,16,17,44}

The majority of studies of asthma and atopy in farm children have been conducted in Europe. Most of the farms in Europe are small-scale, family-owned operations, and 85% to 90% of farms in these studies reported livestock ownership.^{9,10,14,42} Farming practices differ around the world, thus, it is difficult to make inferences about the relationships between farming and atopic diseases without considering other types of farming. The Canadian study

conducted by Ernst and Cormier involved large-scale farming operations in Quebec and reported a protective effect⁷; however, the two published Australian studies investigated much larger crop and livestock farming operations and did not consistently report a protective effect.^{12,34}

Future directions

Current studies suggest that rural living and early childhood farm exposures may confer some protection against the development of asthma and atopy, but it is difficult to draw any firm conclusions about causality given the limitations described above. Prospective studies are needed to better examine the timing of farm exposures in relation to the onset of asthma and atopy. Standard definitions of asthma and atopy are needed to facilitate comparisons of data across studies. Studies need to be replicated in various populations with differing agricultural exposures, and specific farm exposures (endotoxin, grain dust, microbes, pesticides, etc.) need to be rigorously evaluated.

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