

Environmental influences on childhood allergies and asthma – The Farm effect

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Abstract

Asthma and allergies are major health problems and exert an enormous socio-economic burden. Besides genetic predisposition, environmental factors play a crucial role in the development of these diseases in childhood. Multiple worldwide epidemiological studies have shown that children growing up on farms are immune to allergic diseases and asthma. Farm-related exposures shape children's immune homeostasis, via mediators such as N-glycolylneuraminic acid or arabinogalactan, or by diverse environmental microbes. Moreover, nutritional factors, such as breastfeeding or farm milk and food diversity, inducing short-chain fatty acids-producing bacteria in the intestine, contribute to farm-related effects. All farm-related exposures induce an anti-inflammatory response of the innate immunity and increase the differentiation of regulatory T cells and T helper cell type 1. A better understanding of the components of the farm environment, that are protective to the development of allergy and asthma, and their underlying mechanisms, will help to develop new strategies for the prevention of allergy and asthma.

KEYWORDS

allergy, anti-inflammatory, asthma, diversity, farming, farm effect, innate immunity, microbiome, nutrition, regulatory T cells

1 | INTRODUCTION

Asthma and allergic diseases are major health problems with substantially high healthcare costs. Atopy typically first manifests as atopic dermatitis, and food allergies usually appear in the first two years of life.^{1,2} As children grow older, allergic airway diseases, such as allergic rhinitis or asthma, may develop, following the so-called atopic march. Approximately, 10 to 20% of the children suffer from asthma and 30 to 40% from allergic rhinitis in industrialized countries

in modern times.^{1,3} Furthermore, children with allergic rhinitis have an increased risk to develop asthma.

Several epidemiological studies worldwide have shown that children growing up on farms have a lower incidence of allergic diseases and asthma.⁴ Lifestyle at farms, like early exposure to the environmental factors and nutrition and the parallel development of the gut microbiome and metabolome, influence the immune homeostasis of children. More and more data show that the cross-talk between the intestinal microbiota and the lung, termed as gut–lung axis, might

Abbreviations: ALEX, Allergy and Endotoxin study; CARE, Childhood Allergy, Nutrition and Environment study; GABRIEL, Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community; LPS, Lipopolysaccharide; PARSIFAL, Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Life Style study; PASTURE, Protection Against Allergy Study in Rural Environments study; SCFA, Short-chain fatty acids; TLR, Toll-like receptor.

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play an important role in the development of asthma and respiratory allergies. Importantly, the intestinal microbiota composition seems to be influenced by elements present in the farm environment.⁵⁻⁷

This review first summarizes the current knowledge regarding the influence of farm environment and lifestyle on intrauterine and childhood immune homeostasis, with a focus on immune mechanisms induced either by microbial components or by environmental microbial diversity. Second, early-life nutrition and other important farm-associated factors, their influence on the gut microbiome and metabolome and how these factors shape the immune homeostasis are reviewed. A better understanding of factors from the farm environment, which are protective of the development of allergy and asthma, and their underlying mechanisms, will help to develop new strategies for allergy prevention.

2 | ALLERGIES, FARM ENVIRONMENT, MICROBES, AND THE IMMUNE SYSTEM

During Neolithic era 7700 years ago, when farmers got settled, they got exposed to and infected with assemblage of new pathogens that spread from animals, such as influenza or tuberculosis. Under the pressure of these new pathogens, the evolution of the human immune system favored genes that aid a hyperalert inflammatory response to these pathogens that can be deadlier than the pathogen itself.⁸

Nowadays, it is widely accepted that a symbiotic relationship with a diverse range of beneficial microbes in the environment, on the skin and in the gut or lung are responsible for a healthy immune homeostasis leading to adequate immune regulation and low incidence of allergic diseases in farmers.⁹⁻¹¹ By contrast, Western lifestyle, including indoor living environment, high sugar and fat diet, and reduced physical activity, leads to dysbiosis in the gut and skin microbiome, which is associated with a loss immune homeostasis.¹¹

It is known that atopic asthma is induced via a type 2 immune response including T helper cell type (T_H) 2 and IgE antibody-mediated mast cell degranulation. However, in nonatopic asthma, innate immune cells, such as basophils, group 2 innate lymphoid cells, and eosinophils, are also involved and cytokines such as IL-33, TSLP, IL-5, IL-13 play an important role.¹²

An enormous number of microbes colonize our skin and internal mucosal body surfaces. The microbiome is defined as the sum of these microbes including their genetic material occupying a well-defined habitat, have distinct physio-chemical properties, and specific interactions with each other and with the various cells present in the specific tissues. The establishment of a stable microbiome early in life is crucial for proper growth and development of the child including healthy immune homeostasis. One important mechanism how microbes influence the immune development is by regulation of the balance between inflammation and immune tolerance, which is critical in the development of inflammatory diseases, such as asthma or allergic rhinitis.¹³ Immune tolerance is mediated via presentation of antigens by CD103 and CD11b dendritic cells

Key Message

Living on a farm was shown to be protective on the development of asthma and allergic diseases. Especially, the diversity of its environment, including nutrition, play an important role on this protective effect. The underlying mechanism includes the regulation of the innate immunity and the induction of regulatory T cells and T helper cell type 1. Studies on farm environment could definitely help to develop new strategies for prevention of allergy and asthma. However, future research is needed, and it should involve dietary interventions based on these farm studies.

in the gastrointestinal and respiratory tract leading to induction of regulatory T cells in mesenteric or regional lymph nodes.¹⁴ Other cell types that are known to play a crucial role in immune tolerance induction are group 3 innate lymphoid cells present in peripheral blood or tonsils expressing CD40L upon IL-15 stimulation, that induces IL-10 secretion in regulatory B cells. Finally, regulatory innate lymphoid cells express surface markers such as CD25 and CTLA-4 and secrete IL-10.¹⁵

The innate immunity mediates the first immune response to evolutionary conserved foreign patterns such as lipopolysaccharide (LPS) upon their recognition by pattern recognition receptors such as Toll-like receptors (TLR). Besides of the initiation of a rapid antimicrobial response, TLR activation induces a strong inflammation by increase of cytokines and generation of co-stimulatory molecules. Regulation of the TLR signaling cascade is crucial not only for adequate inflammatory responses and innate host defense, but also for adaptive immune responses.¹⁶

3 | FARMING LIFESTYLE AND ALLERGY

3.1 | Intrauterine and early-life farm exposures

Children from rural farming environments were found to have a risk reduction of 32%–78% for developing asthma compared with children from nonfarming rural surroundings.^{17,18} The presence of livestock in proximity of the farming family and exposure to fodder (i.e., silage and hay) seem to be crucial factors for this observed protective effect.¹⁸⁻²¹

One suggested “window of opportunity” is the intrauterine milieu, but also the early-life environment appears to have a persistent impact on allergy and asthma risk. Prenatal exposure by maternal contact with farm animals (i.e., cattle, pigs, horses, and poultry) demonstrated a protective effect on the development of atopic dermatitis in the first 2 years of life.²² Significant reduction of asthma symptoms at pre-school-age and at school-age was reported after maternal exposure to livestock during pregnancy.^{18,23,24} Moreover, early-life exposure and ongoing

exposure were identified as relevant contributors. Furthermore, the Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Life Style (PARSIFAL) cross-sectional study undertaken in rural areas of Europe, reported a significant protective effect of animal exposure during pregnancy for atopic sensitization at school-age, whereas the effect of ongoing exposure was found to be protective for allergic rhinoconjunctivitis.²⁵ Finally, farm-milk consumption, especially in the first year of life, was inversely associated with respiratory allergies.²⁶ This will be discussed more extensively below.

Furthermore, maternal exposure during pregnancy is considered as one “window of opportunity” in the context of farm exposures to skew the T helper cell balance towards T_H1 cells away from allergy inducing T_H2 cells. Moreover, maternal exposure to farming activities and farm dairy products during pregnancy increased TNF-alpha and IFN-gamma levels in the offspring.²⁷ The presence of TNF-alpha upon sensitization in the presence of the bacterial cell wall component endotoxin dictates the ability of $CD11b^+$ myeloid dendritic cells to suppress allergic T_H2 -cell responses by production of IL-12. IL-12 leads to induction of transcription factor T-bet driving the phenotype of IFN-gamma producing T_H1 .²⁸ Additionally, farm exposure during pregnancy resulted in increased number and function of cord blood regulatory T cells and increase Foxp3 transcription factor expression due to Foxp3 promoter demethylation. In parallel, the level of T_H2 cytokine IL-5 was decreased.²⁹

3.2 | School-age farm exposures

In school-age, exposure to livestock was shown to reduce the risk of atopic diseases in children living on farms in a dose-dependent manner.^{22,23,29} In the cross-sectional European Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL) study, exposure to cows, stay in cow sheds, and contact with hay were inversely associated with asthma in preschool-age children.¹⁸ In the PARSIFAL study, different exposures, such as pig keeping, stay in animal sheds and use of silage were found protective for asthma at school-age, while the presence of hares and sheep keeping were identified as risk factors.²¹ Moreover, exposure to pigs was shown to be inversely associated with atopy at school-age in an independent study conducted in New Zealand.³⁰

In childhood, farming lifestyle was associated with an increased spontaneous production of T_H1 and regulatory cytokines from unstimulated peripheral blood monocytes. Peripheral blood monocytes of children living on a farm produced more IL-10, IL-12, and IFN-gamma, compared with the children not living on farms.³¹

Interestingly, proximity to animals and fodder storage might protect children from the development of asthma and allergies either by directly influencing the immune homeostasis or via increased exposure towards endotoxin and microbial diversity in the environment.³²

4 | FARMING LIFESTYLE AND THE IMMUNE SYSTEM

4.1 | N-glycolylneuraminic acid and arabinogalactan

Farming lifestyle comprises exposures to animals, pets, and plant-derived factors reducing the risk of atopy.^{22,23} Animal and pets-derived N-glycolylneuraminic acid induced a strong anti-N-glycolylneuraminic acid IgG response in children living on farms, which was associated with a lower incident of nonatopic wheeze and asthma and more expression of regulatory T cell transcription factor Foxp3. In fact, in mouse models, N-glycolylneuraminic acid application increased the levels of regulatory T cells.^{33,34} Moreover, plant-derived arabinogalactan application to mice protected against allergic airway inflammation.³⁵ Arabinogalactan binds to the immune modulatory receptors DC-specific ICAM-3: grabbing non integrin (DC-SIGN) and macrophage mannose receptor 1 (MMR-1). Stimulation of these receptors with arabinogalactan simultaneously with TLR4 stimulation with LPS increased the expression of the E3 ubiquitin-protein ligase tripartite motif containing protein 21 (TRIM21) and decreased the phosphorylation of NF- κ B p65 in human dendritic cells. This led to a reduced activation and to reduced costimulatory molecules and proinflammatory cytokine production.³⁶

4.2 | Environmental endotoxin and microbial diversity

In 2002, Braun-Fahrlander et al. published one of the first studies showing that the bacterial cell wall component LPS or endotoxin was present in high concentration in the farm environment of the children of the Allergy and Endotoxin (ALEX) study. In fact, the LPS levels in farmers' children's mattress were not only reversely associated with the incidence of hay fever, atopic asthma, and atopic sensitization, but also with the secretion of TNF-alpha, IFN-gamma, IL-10, and IL-12 in LPS-stimulated leukocytes.³⁷

Leukocytes of children living on farms expressed more TLR, such as TLR2 or TLR4.^{25,38} Enhanced TLR expression at birth was inversely associated with the development of atopic dermatitis.²² This might be based on parallelly up-regulated regulatory molecules of the TLR-signaling cascade, such as SOCS4 and IRAK-2 in leukocytes of children living on the farm and the enhanced expression of regulatory cytokines IL-10 and TGF-beta.³⁹ Furthermore, continuous LPS-exposure protected mice from the development of allergic-airway inflammation by reduction of epithelial-derived cytokine secretion what reduced the type 2 immunity. The effect was largely dependent on the ubiquitin-modifying enzyme A20 in lung epithelium. A20 attenuates NF- κ B activation by deubiquitinating key signaling intermediates downstream of TLR, IL-1 receptor, and TNF-family receptors.^{40,41}

The European cross-sectional studies PARSIFAL and GABRIEL showed that children, who lived on the farm, were exposed to a greater diversity of environmental microorganisms than their classmates not living on the farm. The increased diversity of microbial exposure was inversely related to the risk of asthma (odds ratio [OR] for PARSIFAL, 0.62; 95% confidence interval [CI], 0.44–0.89; OR for GABRIEL, 0.86; 95% CI, 0.75–0.99).⁴²

A study compared microbial composition of dust samples from Amish and Hutterite homes. Amish and Hutterites are US agricultural populations whose lifestyles and genetic ancestries are remarkably similar in many respects, but Amish follow traditional farming practices while the Hutterites use industrialized farming practices. The prevalence of asthma and allergic sensitization was, respectively, 4 and 6 times lower in the Amish population compared with the Hutterites. By contrast, median endotoxin level in Amish house dust was 6.8 times higher and the microbial composition was different. Interestingly, differences in the proportions, phenotypes, and functions of innate immune cells were found and intranasal application of dust extracts from Amish but not Hutterite homes significantly inhibited airway hyperreactivity and eosinophilia in mice in a MyD88 and Trif-dependent manner.⁴³

Finally, by mathematical modeling Kirjavainen et al. reported (a) differences in house dust microbiota composition between farm and nonfarm homes; (b) in nonfarm homes, asthma risk decreases as the similarity of their home bacterial microbiota composition to that of farm homes increases; (c) the protective microbiota had a low abundance of Streptococcaceae, was independent of richness and total bacterial load, and was associated with reduced proinflammatory cytokine responses against bacterial cell wall components *ex vivo*.⁴⁴

5 | NUTRITION, INTESTINAL MICROBIOME, AND METABOLITES

5.1 | Breastfeeding

The role of breastfeeding and farming environment in the development of atopic diseases in childhood remains unclear. The Protection against Allergy Study in Rural Environments (PASTURE) study showed that sIgA levels in breastmilk were associated with environmental factors related to farming lifestyle, such as contact to farm animals or cats during pregnancy, but not with raw milk consumption. Furthermore, sIgA levels in breastmilk were inversely associated with atopic dermatitis up to the age of 2 years, independent of duration of breastfeeding. The dose of sIgA ingested in the first year of life was associated with reduced risk of atopic dermatitis up to the age of 2 (aOR, 0.74; 95% CI, 0.55–0.99) and 4 years (aOR, 0.73; 95% CI, 0.55–0.96). By contrast, no associations between sIgA and atopy or asthma up to age 6 were observed.⁴⁵ Additionally, it was shown that breastmilk of mothers living on the farm contained significantly higher levels of regulatory cytokines TGF- β and IL-10 compared with breast milk of mothers living in urban areas.⁴⁶

5.2 | Food diversity, gut microbiome, and short-chain fatty acids

An increased food diversity within the first 2 years of life had a protective effect on allergic respiratory diseases, such as asthma and allergic rhinitis.^{47,48} For each additional food item introduced in the first year of life, a significant risk reduction of 26% was observed for the development of asthma in childhood. Food items with the strongest risk reducing effect on the development of asthma were butter, yogurt, and vegetables or fruits.⁴⁸ Parallely, a reduced gut microbiota diversity in the first month of life has been associated with asthma at school-age.⁴⁹ One underlying mechanism might be the interaction between the diet and the gut microbiota, resulting in the production of microbial metabolites. It has been shown that metabolites secreted by the intestinal microbiota, such as short-chain fatty acids (SCFA), tryptophan, or retinoic acid, induce immune tolerance in the lungs.^{7,50–52}

SCFA seem to play a crucial role in linking the intestinal microbiome with the lung. SCFA are produced by commensal bacteria in the distal colon by fermentation of fiber in large quantities. The major SCFA are acetate, propionate, and butyrate. Children, who are colonized with butyrate-producing bacteria in the first year of life, suffered less from asthma later in life. Nutritional factors such as cow's milk product consumption were associated with early-life colonization of these bacteria.⁵³ In the context of the Childhood Allergy, Nutrition and Environment (CARE) study, it was found that endospores are mainly butyrate-producers. Endospores are bacteria in a status that is resistant against heat, oxygen, or low pH. In this status, bacteria are often transferred to new environments, as it is the case in newborns.⁵⁴ Moreover, mouse models showed that SCFA, especially butyrate, have strong anti-inflammatory effects and protected animals from the development of allergic airway inflammation, by stimulating the expansion of regulatory T cells and increasing the production of IL-10.^{55,56} Additionally, high levels of butyrate and propionate measured in fecal samples of one-year-old children of the PASTURE-study were associated with a lower rate of asthma and allergic diseases later in life. High levels of butyrate were found in children that consume cow's milk products, fish, and vegetables or fruits in the first year of life.⁵⁵

5.3 | Farm-milk

Four large European studies showed that consumption of unprocessed cow's milk directly obtained from the farm, so-called "farm-milk," was associated with the protection of asthma, wheezing, allergic rhinitis, and atopic sensitization.

In the ALEX study, exposure of children younger than 1 year, compared with those aged 1–5 years, to stables and consumption of farm-milk was associated with lower frequencies of asthma (1% vs. 11%), hay fever (3% vs. 13%), and atopic sensitization (12% vs. 29%).²³ In the PARSIFAL study, farm-milk consumption ever in life showed a statistically significant inverse association with asthma:

TABLE 1 Influence of farm-related exposures on the host

Exposure	Host	Reference
Farming intrauterin	TNF-alpha, IFN-gamma	27
	T _H 1	28
	Regulatory T cells	29
Farming school-age	T _H 1	31
	IL10, IL12, IFN-gamma	
N-glycolylneuraminic acid	Regulatory T cells, IL-10	33
Arabinogalactan	Less co-stimulatory molecules	36
	Less proinflammatory cytokines	
LPS/endotoxin	Less TNF-alpha, INF-gamma, IL-10, IL-12	37
	TLR expression	22,25,38
	SOCS4, IRAK-2	39
	IL-10, TGF-beta	
	A20 mediated reduced cytokine secretion	40,41
Environmental microbes	MyD88 and Trif dependent inhibition of airway hyperreactivity and eosinophilia	43
	Less proinflammatory cytokines	44
Breast feeding	sIgA	45
	TGF-beta, IL-10	46
Food diversity	Colonization with butyrate-producing bacteria	53
	SCFA	55,56
	Regulatory T cells, IL-10	
Farm-milk	Bovine serum albumin (BSA), α -lactalbumin, β -lactoglobulin	58
	Anti- β -lactoglobulin IgA and IgG	61
	TGF-beta	62
	ω -3 polyunsaturated fatty acids	63
	Regulatory T cells	59
	TLR4, TLR5, TLR6	64
	Gene-environment CD14/-1721	65

aOR, 0.74 (CI 0.61–0.88), rhinoconjunctivitis: aOR 0.56 (CI 0.43–0.73) and sensitization to pollen and the food allergens (cut-off level of 3.5 kU/L): aOR 0.67 (CI 0.47–0.96) and aOR 0.42 (CI 0.19–0.92), respectively, and sensitization to horse dander: aOR 0.50 (CI 0.28–0.87). Remarkably, these associations were independent of farm-related co-exposures.⁵⁷ Furthermore, in the GABRIEL study, raw milk consumption was inversely associated with asthma (aOR, 0.59; CI 0.46–0.74), atopy (aOR, 0.74; CI 0.61–0.90), and hay fever (aOR, 0.51; CI 0.37–0.69), again independent of other farm exposures. Interestingly, however, boiled farm-milk did not show a protective effect.⁵⁸ Finally, significant protective effect of farm-milk consumption on diagnosis of asthma at age 4 years was present in the children of the PASTURE cohort (OR, 0.45; CI, 0.23–0.88; $p = .019$; $n = 988$). Furthermore, farm-milk consumption within the first year of life was inversely associated with occurrence of rhinitis (aOR, 0.71; CI 0.54–0.94), respiratory tract infections (aOR, 0.77; CI, 0.59–0.99), otitis media (aOR, 0.14; CI 0.05–0.42), and fever (aOR, 0.69; CI 0.47–1.01).^{26,59} Interestingly, cheese consumption (vs. no-consumption)

had a significant protective effect on atopic dermatitis (OR, 0.51; CI, 0.29–0.90) and food allergy (OR, 0.32; CI, 0.15–0.71), but no effect on atopic sensitization, allergic rhinitis, and asthma at 6 years among the PASTURE study children.⁶⁰

The protective effect of the farm milk on asthma was suggested to be associated with the level of whey proteins present in the farm milk. Increased levels of bovine serum albumin (BSA), α -lactalbumin, and β -lactoglobulin were inversely associated with the incidence of asthma (aOR for highest versus lowest level of BSA, 0.53; CI 0.30–0.97), (aOR for interquartile range of α -lactalbumin, 0.71; CI 0.52–0.97), (aOR for interquartile of β -lactoglobulin range, 0.62; CI 0.39–0.97). Interestingly, total viable bacterial counts and total fat content of milk were not significantly related to asthma.⁵⁸ Additionally, increased IgA or IgG antibodies against β -lactoglobulin at age 1 increased the risk of atopic sensitization at the age of 6 years.⁶¹ Furthermore, levels of the regulatory cytokine TGF-beta were increased in farm-milk.⁶² Higher levels of ω -3 polyunsaturated fatty acids of farm-milk were inversely associated with the incidence

of asthma (aOR, 0.29; CI 0.11–0.81).⁶³ Also, farm-milk exposure increased regulatory T cells in childhood, and this, was associated with less asthma (aOR, 0.26; CI 0.08–0.88) and perennial IgE (aOR, 0.21; CI 0.08–0.59).⁵⁹ Moreover, farm-milk consumption in the first year of life was associated with increased expression of TLR4, TLR5, and TLR6.⁶⁴ Finally, gene-environment interactions played a role in farm-milk mediated protection from the development of asthma. The protective effect of farm-milk consumption on asthma, allergic rhinoconjunctivitis, and pollen sensitization was stronger in children carrying the A allele in CD14/-1721 than in children homozygous for the G allele. This might be mediated through farm-milk-induced up-regulated CD14 gene expression, a co-receptor of TLR4.⁶⁵

6 | CONCLUSION

Living on a farm, including nutrition influence the immune homeostasis either by regulating the innate immune system or by induction of regulatory T cells or T_H1 (Table 1). One crucial “window of opportunity” for the beneficial effect of these exposures seems to be either intrauterine or early in childhood. Furthermore, the diversity plays an important role on the protective effect of farm environment on asthma and allergic diseases, (a) as the diversity of environmental microbes, (b) as the diversity of the gut microbiome, and (c) as the diversity of the nutrition.

However, the effect of these diversities on the development of asthma or allergies in childhood is still not fully understood. Also, little is known about timing, quantity, and content. Furthermore, only limited data are available about the influence of genetics, environmental factors, demographics, and location of the child. And finally, it is not even fully understood what a healthy environmental or gut microbiome composition is.⁶⁶

This review showed that diversity patterns provided by the farm environment could play an important role in protecting children from the development of allergic diseases and asthma. As nutritional habits are easy to transfer to children not growing up on a farm, one focus of future research should definitely involve dietary interventions.

AUTHOR CONTRIBUTIONS

Remo Frei, Kristina Heye and Caroline Roduit: writing—original draft.

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