



Maternal farm exposure/ingestion of unpasteurized cow's milk and allergic disease

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Purpose of review

The prevalence of allergic diseases has reached a high prevalence in affluent countries. Yet, there are areas and living conditions associated with very low rates which are attributable to environmental exposures. One example is the low prevalence of childhood asthma and allergies amongst children raised on farms, particularly those exposed to farm animals and unprocessed cow's milk very early in life which are being reviewed in this article.

Recent findings

Several studies have shown that maternal exposure to various farm animals in pregnancy is related to a reduced risk of atopic dermatitis in the child and immune responses which have generally been regarded as protecting from the development of asthma and allergies. In addition, maternal and infant consumption of unprocessed cow's milk has repeatedly been associated with protection from childhood asthma and allergies. The precise nature of the protective factors remains to be elucidated. Maternal exposures to farm animals result in increased microbial exposures, the diversity of which has been associated with protection from childhood asthma. The beneficial milk constituents may, however, not be contained in the microbial contamination of milk samples but rather in the whey fraction of unprocessed cow's milk.

Summary

Better understanding of these protective exposures might in the future enable the development of new prevention strategies.

Keywords

allergies, asthma, cow's milk, farm exposure, protection

INTRODUCTION

Allergic diseases were rare before the 1950s, but since these conditions have developed into a major health concern [1]. As of the beginning of this century, about 50% of all children (in some areas even 70%) have a positive allergy test to 'normal' environmental exposures such as house dust, animal dander, pollen, and food. The new onset of allergic diseases is highest early in life. IgE antibodies directed against food allergens, in particular cow's milk and hen's egg, can already be detected shortly after birth. Not all children in whom specific IgE antibodies towards cow's milk allergens are detected will have a clinical reaction after ingestion of these foods. These asymptomatic sensitized children are, however, at increased risk of subsequent allergic manifestations. Findings from longitudinal population-based cohorts suggest that early sensitization to food allergens, particularly to hen's egg, are a predictor of subsequent sensitization to inhalant allergens and also childhood asthma [1].

In these individuals, the production of specific IgE antibodies towards cow's milk and egg white are likely to indicate an early beginning of an atopic predisposition which will become manifest in later childhood as either allergic rhinitis or allergic asthma.

FARM EXPOSURES

There are natural models of asthma and allergy prevention. Numerous population-based studies have shown that the risk of developing childhood

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KEY POINTS

- Maternal exposure to farm animals protects the child from developing asthma and allergies.
- Likewise, maternal consumption of unprocessed cow's milk protects the child from developing asthma and allergies.
- Environmental exposure to microbes may in part explain the maternal farm animal effect.
- The farm milk effect may not relate to microbial gut exposures but to heat labile components of the whey fraction in unprocessed cow's milk.

asthma, hay fever, and allergic sensitization to both food and inhalant allergens is significantly reduced in children growing up in farming environments [2]. The farm studies initially performed in Central Europe (Germany, Austria, and Switzerland) and thereafter also in other European countries, Canada, the USA, and New Zealand suggest that protection is mostly related to dairy farming as compared to other types of farming [2]. This notion was recently confirmed in the multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community (GABRIEL) Advanced Studies in over 9000 school-aged children living in rural environments in Germany, Austria, and Switzerland where cows on the farm were associated with protection [3[¶]]. This effect was even more pronounced when farming families additionally cultivated land to produce their own crops. In further, more detailed analyses of the children's individual activities on the farm, exposure to cows, straw, and their consumption of unprocessed cow's milk were the major protective exposures identified out of a large array of farming exposures assessed in minute detail by an exhaustive questionnaire which had a priori been developed with farming families. Children exposed to straw were very often also exposed to grass, hay, and manure. Therefore, their individual contribution could not be disentangled with certainty.

Maternal exposure to farm animals

The comprehensive GABRIEL questionnaire also assessed the timing of the various farm exposures. The effects of exposures early in life (i.e. from pregnancy up to age 3 years) showed much stronger effects than exposure only at school age [3[¶]], confirming previous findings [4]. In the GABRIEL population, about half the study population was already exposed *in utero* through their mothers

working on the farm. In the European Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Life Style (PARSIFAL) Study, another large cross-sectional survey amongst children living in rural environments, prenatal exposure to animal sheds had the strongest effect on atopic sensitization [adjusted odds ratio (aOR)=0.36, 95% confidence interval (CI) 0.25–0.51], whilst the effect somewhat decreased with later start of exposures: aOR=0.54 (95% CI 0.32–0.92) for first contact in the first year of life and aOR=0.77 (95% CI 0.49–1.22) for first exposure between the first year of life and school age [5]. Finally, in the Swiss PARSIFAL sample maternal and not school age exposure was found to play a significant role for the expression of receptors of the innate immune system [5]. Geometric means of the expression of the genes for TLR2, TLR4, and CD14 at school age were significantly higher amongst children whose mothers had been exposed to animal sheds during pregnancy. Interestingly, maternal exposure was not as important for the development of asthma and hay fever, suggesting that postnatal exposures may be as relevant for reducing the risk of upper and lower airway involvement, that is, asthma and allergic rhinitis.

These findings indicate a major role for prenatal and postnatal exposures, but may be biased by the retrospective exposure assessment and by recall bias occurring in cross-sectional surveys. Therefore, the prospective birth cohort PASTURE/EFRAIM was initiated. This birth cohort recruited 1133 women in the third trimester of pregnancy who were living in rural areas in Europe. Of these children, 47% were born to farming families. The significant protective influence of maternal exposures during pregnancy on a number of allergic outcomes in the newborn and infant was documented. Two major relevant environmental exposures of the mother were identified: consumption of unprocessed cow's milk and exposure to increasing numbers of farm animal species such as cows, pigs, poultry, horses, sheep, or goats. Maternal exposure to many farm animal species affected a number of relevant outcomes. The risk of atopic dermatitis developing in the first year of life was reduced by more than half amongst children whose mothers had contact with three or more farm animal species during pregnancy compared to children of mothers without contact [6[¶]]. Likewise, this maternal exposure was related to an increased production of interferon γ (INF γ) and TNF α from stimulated but unfractionated cord blood nuclear cells [7] (Fig. 1). Given the lack of fractionation, the cellular source (or sources) of the cytokines remained undefined. However, allergen-specific IgE antibodies detectable in these

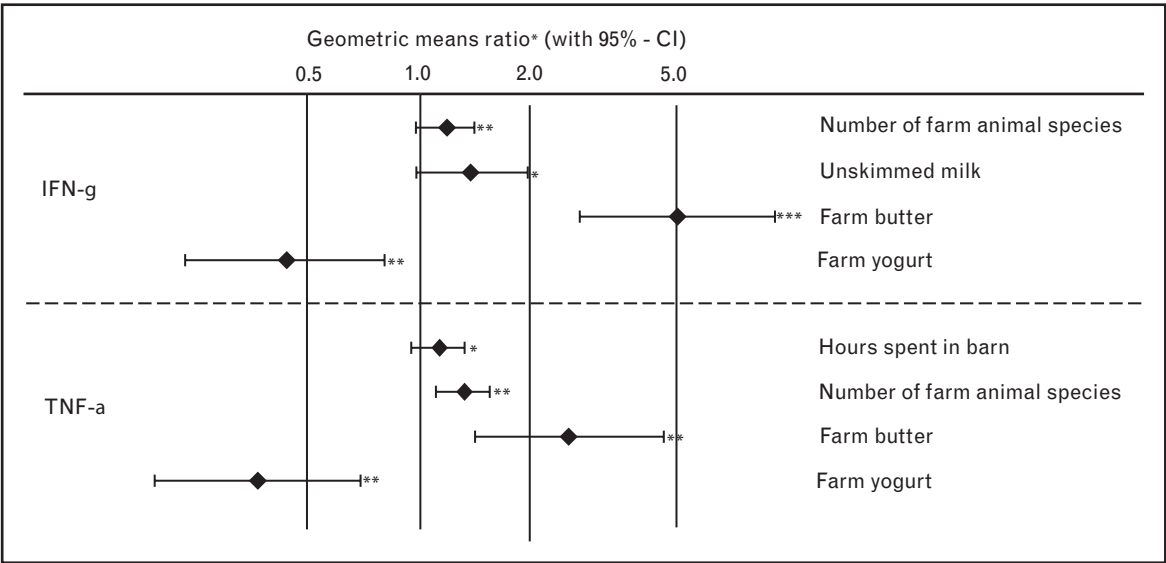


FIGURE 1. Effect of farming exposure and consumption of dairy products on cytokine levels. Number of farm species – per animal species. Unskimmed milk – yes versus no. Farm butter – consumption of butter made from farm milk (at least once a week). Farm yoghurt – consumption of yoghurt made from farm milk (at least once a week). Hours spent in barn – per 5 h. Data from [7].

cord blood samples were correlated with a decreased production of IFN γ in these same samples [8], adding biological plausibility to these findings.

A smaller birth cohort enrolling a total of 82 neonates born to farming and nonfarming mothers in southern Germany investigated neonatal immune responses in more detail [9]. Cord blood CD4⁺CD25^{hi} Treg cells from children born to stable-exposed mothers were both more numerous

and more efficient in suppressing T-cell proliferation (Fig. 2). Again, maternal exposure to increasing numbers of farm animal species substantially enhanced the expression of the Treg cell marker glucocorticoid-induced TNF receptor (GITr) and the secretion of IFN γ by cord blood cells in response to allergen and peptidoglycan [9]. Although the population sample size was rather small, these results again point towards the intriguing relationship

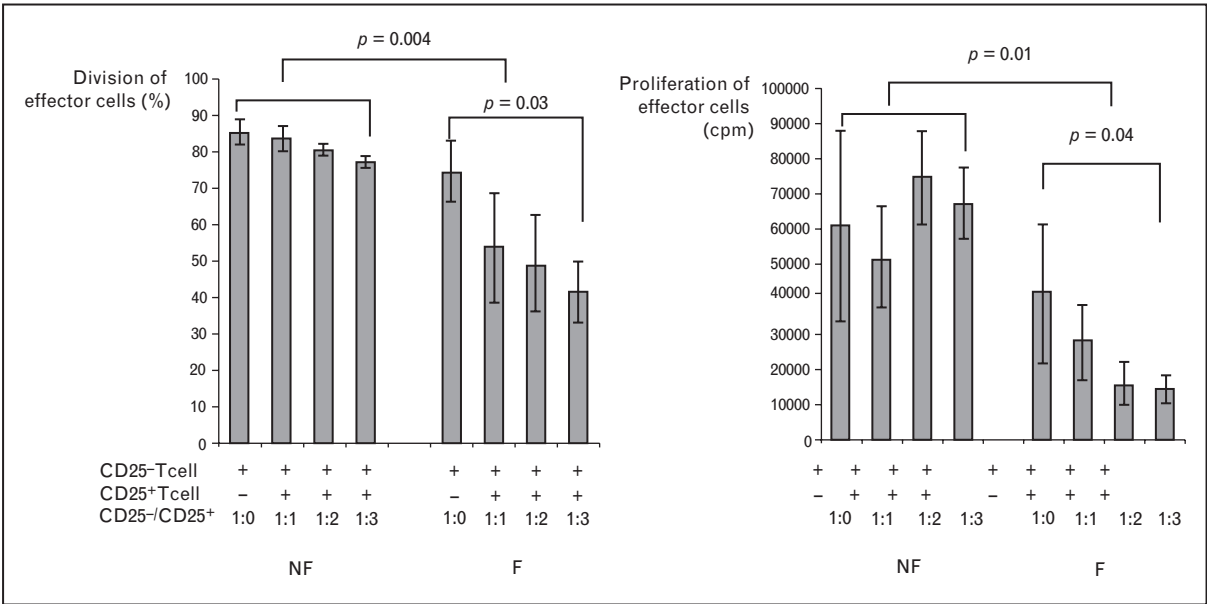


FIGURE 2. The suppressive capacity of CD4⁺CD25⁺ Treg cells on CD4⁺CD25⁻ T effector cells in cord blood mononuclear cells of offspring of nonfarming mothers (NF) and offspring of farming mothers (F). Data from [9].

between immune modulation and number of farm animal species to which mothers are exposed during pregnancy. Finally, in the retrospective analysis of the PARSIFAL data, maternal exposure to increasing farm animal species was also related to increased gene expression of TLR2, TLR4, and CD14 in the offspring at school age [5]. The interpretation of this powerful predictive variable remains to be elucidated. The presence of many different farm animal species may increase the dose and diversity of related microbial exposures. In school age children, the diversity of environmental microbial exposures has been shown to significantly decrease the risk of asthma, but not atopy [10²²]. Therefore, microbial exposures in the environment may be more important for the protection from developing upper and lower airway disease postnatally rather than shaping the systemic immune responses towards tolerance of ubiquitous allergens. Alternatively or additionally, xenogeneic signals conferred by many different animal species may also be relevant for protection from allergy development.

Consumption of unprocessed cow's milk

In addition to the strong protective exposures related to animal sheds for cows, other farm animals, and their fodder, the consumption of unprocessed cow's milk has been shown in numerous studies to be an additional and independent protective factor for the development of childhood asthma, hay fever, and atopic sensitization [11²²]. The Allergy and Endotoxin Study was the first to report that children living in rural areas had a significantly reduced risk to suffer from asthma, hay fever or allergic sensitization at school age when consuming unprocessed cow's milk during their first year of life [4]. This inverse association was independent of other farm exposures such as farm animals or animal fodder. The PARSIFAL study confirmed these inverse associations. This study furthermore showed consistent effects across different subgroups of children, also from nonfarming families [12]. In these nonfarm children, the consumption of unprocessed cow's milk was equally associated with strong protection from asthma and allergic illnesses, suggesting that other sections of the population, not just farm children, also benefit from the consumption of unprocessed cow's milk. The protective 'raw milk effect' was also confirmed in independent studies in the UK, Crete, and New Zealand [13–15]. The results of these studies have been reviewed previously in great detail in [11²²], demonstrating the consistency of effects between different populations.

In the most recent survey, the EU-funded GABRIEL Advanced Studies, the beneficial effect of unprocessed cow's milk was further studied to assess the precise nature of the 'raw milk effect' and its responsible milk constituents [16²²]. A total of 7606 school-aged children provided serum samples for the measurement of specific IgE antibodies towards inhalant and food allergens. Their parents furthermore reported the onset and persistence of asthma and other allergic illnesses. The consumption of unprocessed cow's milk significantly decreased by about half the risk of childhood asthma (aOR = 0.59, 95% CI 0.46–0.74, $P < 0.05$), allergic sensitization (aOR = 0.70, 95% CI 0.57–0.86, $P < 0.001$), and hay fever (aOR = 0.51, 95% CI 0.37–0.69, $P < 0.05$) independently of other farm exposures. The 'raw milk effect' was seen not only for inhalant allergens, but also for food allergens (aOR = 0.73, 95% CI 0.61–0.88, $P = 0.001$). This protective effect for food allergy by consumption of unprocessed cow's milk had also been found in the PARSIFAL survey (aOR = 0.42, 95% CI 0.19–0.92, $P < 0.05$). Again, exposure early in life had stronger effects than school age consumption [12]. This inverse relation was independent of a family history of allergic illnesses, as it was also seen amongst children with a positive family history. It is intriguing that no significant association was observed once the raw milk was boiled, suggesting that heat treatment destroys protective substances contained in raw cow's milk.

Most of these surveys had a cross-sectional design and less information originates from birth cohort studies. However, in the above-mentioned PASTURE/EFRAIM birth cohort maternal consumption of unprocessed cow's milk has also been assessed during an interview in the last trimester of pregnancy [17]. Specific IgE levels for food and common inhalant allergens were assessed in the newborn's serum. In multivariable analysis, maternal farm milk consumption during pregnancy was not related to IgE levels against seasonal allergens in cord blood. Yet, maternal consumption of boiled farm milk during pregnancy, but not unboiled farm milk, was positively associated with specific IgE to cow's milk in cord blood [18]. Furthermore, the consumption of unboiled but not boiled farm milk during the first year of life increased gene expression of the TLRs in the infant [19²³] (Fig. 3), again indicating that boiling raw cow's milk might affect mechanisms of tolerance towards cow's milk allergens.

In this birth cohort, maternal consumption of farm-produced butter during pregnancy enhanced the production of $\text{INF}\gamma$ and $\text{TNF}\alpha$ from unfractionated cord blood mononuclear cells [7] (Fig. 1).

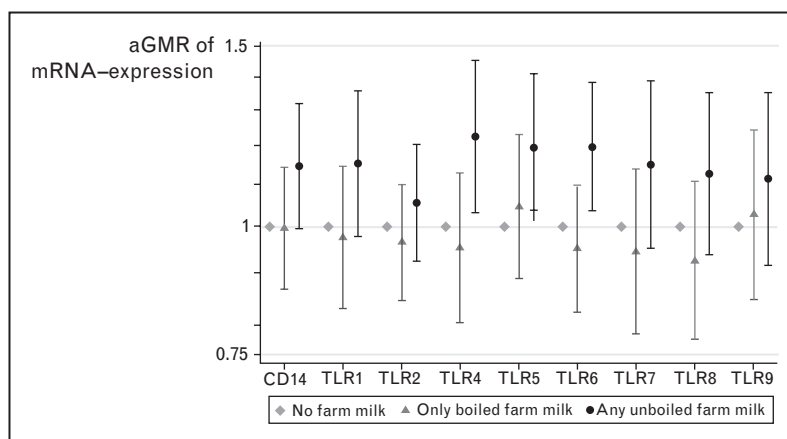


FIGURE 3. Adjusted association of child's farm milk consumption during the first year of life and mRNA expression at year 1 expressed as geometric mean ratios and 95% confidence intervals adjusted for confounding factors. Data from [19].

Furthermore, an additive effect was observed for the combined consumption of butter and unskimmed farm milk on IFN γ and TNF α production, suggesting that consumption of dairy products originating from unprocessed cow's milk during pregnancy modulates cytokine production patterns in newborn babies. In the more elaborate birth cohort of Schaub *et al.* [9], maternal intake of unprocessed farm milk was related to epigenetic changes in the cord blood. The relevance of maternal exposures on the demethylation of an evolutionarily conserved element within the FOXP3 locus (TSDR) was explored in 59 individuals. The amount of demethylated TSDR was higher in newborns of mothers consuming unprocessed cow's milk during pregnancy. Because of the low sample size and the strong correlation between different farm exposures, these data must however be interpreted with caution.

The first study to assess the constituents in milk consumed by children with asthma and atopy, respectively, and nonaffected controls was performed in the GABRIEL Advanced Studies [16²²]. In a nested case-control sample of 900 study participants, cow's milk samples from farming and nonfarming families were collected as consumed by the children at their homes, and viable bacterial counts, whey protein levels, and total fat content were analysed. Unboiled farm milk samples had high numbers of detectable micrococci and staphylococci (85.2%), lactobacilli (94.1%), bacilli and bacterial endospores (63.4%), and psychrotrophic bacteria (58.4%). Also, pathogenic *Listeria innocua* and *Listeria ivanovii* were found in three unboiled farm milk samples. However, neither the total viable bacterial count nor the bacterial subgroups were related to childhood asthma or atopy [16²²]. These findings are in agreement with the previous observations showing no relation between levels of

endotoxin, a cell surface marker for Gram-negative bacteria, in processed and unprocessed bovine milk and the development of childhood asthma and allergies [20]. Total fat content was furthermore not related to asthma or allergy, but individual fatty acids had not been measured.

In turn, increased levels of whey proteins were inversely associated with asthma, but not allergic sensitization [16²²]. Significant inverse associations indicative of a dose-response relation for asthma were observed for lactoferrin ($P=0.02$), TGF- $\beta 2$ ($P=0.02$), α -lactalbumin ($P=0.02$), and β -lactoglobulin ($P=0.04$). There was also an inverse, though not dose-dependent relation between the level of immunoglobulin G in milk samples and asthma in the child. The lack of association between allergic sensitization and whey proteins despite the protective effect of unboiled and unprocessed cow's milk on allergic sensitization described above suggests that other fractions and compounds confer the protective effect for allergic sensitization and hay fever.

A number of candidates come to mind when attempting to explain the asthma-protective and allergy-protective effect of consumption of unprocessed cow's milk. Two recent reviews have discussed in detail the potential protective mechanisms [11²², 21²²]. Although the current evidence is weak to suggest a major role for microbial constituents of raw cow's milk, we cannot exclude the possibility that specific probiotics might in the future be detected when using next-generation pyrosequencing methods.

Unprocessed cow's milk contains the natural amount of milk fat and polyunsaturated as well as conjugated fatty acids (CLA) [7]. Dietary supplementation with CLA-rich alpine butter can also influence human breast milk composition of fatty

acids and CLA isomer profiles [22]. A study of CLA supplementation in a randomized controlled trial in young healthy volunteers found decreased plasma IgE levels and increased levels of IL-10 after CLA supplementation, suggesting an anti-allergic potential of CLA [23]. Thus, the fatty acid composition of unprocessed cow's milk may have a role in explaining the protective 'raw farm milk' effect.

There is increasing evidence from mouse studies that breast milk can induce immune tolerance at very low doses of allergen transfer through breast milk and thereby prevent asthma development [24–30]. This induction of tolerance upon allergen transfer through breast milk required the presence of TGF- β in maternal milk [24]. In addition, the in-vitro data suggested that milk-borne immune complexes have intrinsic tolerogenic properties, as they were able to induce the differentiation of allergen-specific FoxP3⁺ Treg. The high ratio of IgG/allergen of milk-borne immune complexes [25] as well as milk antibodies glycosylation might be responsible for these tolerogenic properties [31–33]. Both immunoglobulins and TGF- β are contained in unprocessed cow's milk.

CONCLUSION

The increasing evidence of protection through maternal exposures to farm animals, their fodder, and intake of unprocessed cow's milk suggests that novel strategies for the prevention of these diseases could be developed. Consumption of cow's milk as a means of primary prevention is an attractive vision. Undoubtedly, the consumption of raw milk as it can still be purchased in some countries harbours too many risks, amongst these the development of severe and life-threatening diseases such as listeriosis and the haemolytic uremic syndrome elicited by enteropathogenic *Escherichia coli*. The relevant milk constituents must be identified first, and innovative mild processing of bovine milk samples must be developed by the dairy industry to preserve the protective factors and master the microbiological risks. Likewise, the application of microbes on airway mucosa is an attractive vision. Experiments in mice have been very encouraging, but the move to application in humans is challenging and necessitates a microbiologically safe product.

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Conflicts of interest

E.v.M. is a consultant to GlaxoSmithKline, Protectimmun and Novartis. In the past, she also received lecture fees from InfectoPharm and Nestlé Research.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 637).

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