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OPINIONS IN ALLERGY

Can farm milk consumption prevent allergic diseases?

C. Braun-Fahrländer[1,2] and E. von Mutius[3]
[1]Swiss Tropical and Public Health Institute, Basel, Switzerland, [2]Faculty of Medicine, University of Basel, Basel, Switzerland and [3]Dr. von Haunersche Children's Hospital of Ludwig Maximilian University, Munich, Germany

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Summary
Cow's milk is an important part of human diet and a source of food allergy for some individuals. Medical guidance strongly discourages consumption of raw milk because of the known health risk associated with pathogenic bacteria present in unpasteurized milk. Despite these risks there is a growing body of epidemiological evidence suggesting that consumption of unprocessed cow's milk does not increase but rather decreases the risk of asthma, hay fever and atopic sensitisation. The article reviews the epidemiological literature and discusses components of unprocessed milk potentially responsible for this protection. It focuses on the role of bacteria in raw milk, the fatty acid profile, whey proteins and finally the role of allergens in milk. Although the epidemiological evidence consistently suggest a protective role of unprocessed cow's milk consumption on the development of asthma, hay fever and atopic sensitization the underlying mechanisms are not yet understood and the consumption of raw milk cannot be recommended as a preventive measure for allergic diseases.

Keywords allergy, asthma, epidemiology, farm milk, milk components
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Correspondence:
Charlotte Braun-Fahrländer, Swiss Tropical and Public Health Institute, Basel, Switzerland, PO Box 4002 Basel, Switzerland.
E-mail: c.braun@unibas.ch
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Introduction

Since thousands of years cow's milk has been part of the human diet. In the Western world today, cow's milk is produced on an industrial scale and undergoes pasteurization and homogenization necessary for preservation along the supply chain. Current medical guidance is strongly prohibitive of consumption of raw milk, based on the reports of outbreaks of disease from exposure to pathogenic bacteria in unpasteurized milk [1]. Pathogens such as *Salmonella enteritidis* and *Salmonella typhimurium* as well as *Listeria monocytogenes*, which can induce severe diarrhoea and listeriosis, particularly in young infants and pregnant women may be found in raw milk [2]. The allergological literature mostly deals with cow's milk consumption in infancy as a risk factor for the development of allergic diseases such as cow's milk allergy and several allergenic epitopes such as α-lactalbumin, β-lactoglubulin and casein have been characterized in milk [3,4].

Despite the notion of early milk consumption being a risk factor, there is an increasing body of evidence that unprocessed cow's milk does not increase, but may rather decrease the risk of asthma, hay fever and atopic sensitization. In this article, we review the epidemiological evidence and discuss potential sources of protection.

Over the last decade a growing body of literature has emerged identifying consumption of unprocessed farm milk to be associated with a reduced risk of developing childhood asthma and allergy [5–13]. These studies were possible because consumption of unprocessed milk is still rather common among dairy farming families and to some extent among rural non-farming families in Europe.

Epidemiological evidence

Several of these epidemiological studies have been conducted in alpine countries such as Austria, Germany (Bavaria), and Switzerland [5–7, 12, 13], others are based on populations from England, Crete [9], Northern Germany [10], and New Zealand [11]. Table 1 summarizes the main findings of these observational studies.

The ALEX study was the first to report that children living in rural areas of Bavaria (Germany), Austria and Switzerland had a reduced risk to suffer from asthma, hay fever or atopic sensitisation at school age when they consumed farm milk during their first year of life [5]. This inverse association was independent of being a farm child and an additive effect was seen from the combination of early milk consumption and early stable exposure. The

Table 1. Overview of epidemiological studies assessing the effect of farm milk consumption on asthma and allergic diseases

Authors	Study population	Countries	Exposure	Main results
Cross-sectional studies				
Riedler et al. [5]	Rural farm and non-farm children ($n = 812$) aged 6–12 years, (ALEX Study)	Austria, Germany, Switzerland	Milk directly produced or purchased on a farm	Consumption of farm milk during first year of life significantly inversely associated with asthma, hay fever, and atopy, independent of other farm exposures
Waser et al. [6]	Rural farm and non-farm, Steiner Schools', and peri-urban children ($n = 14\,893$) aged 5–13 years, (PARSIFAL-Study)	Sweden, the Netherlands, Austria, Germany, Switzerland	Milk directly produced or purchased on a farm	Adj. OR and (95% CI) of farm milk consumption ever in life and asthma: 0.47 (0.61–0.88), rhinoconjunctivitis: 0.56 (0.43–0.73), sensitization to pollen: 0.67 (0.47–0.96), and food mix: 0.42 (0.19–0.92). Association observed in all subgroups, independent of farm-related co-exposures
Bieli et al. [7]	ALEX ($n = 576$) and PARSIFAL ($n = 1478$) children with available DNA samples	Sweden, the Netherlands, Austria, Germany, Switzerland	Milk directly produced or purchased on a farm	Association between farm milk and asthma varied between genotypes of CD14/-1721. Adj. OR (95%CI) AA: 0.81 (0.07–0.47); AG: 0.47 (0.26–0.86); and GG: 0.98(0.46–2.08). Similar patterns for symptoms of hay fever and pollen sensitization. CD14/-1721 also modified association between farm milk and CD14 gene expression
Perkin and Strachan [8]	Rural farm and non-farm children ($n = 4767$), subsample ($n = 879$) with skin prick test	England	Unpasteurized milk (based on food-frequency questionnaire)	Current unpasteurized milk consumption associated with less eczema adj. OR and (95% CI): 0.59 (0.40–0.87) and atopy: 0.42 (0.10–0.53), and higher production of whole blood stimulated IFN-γ. Effect independent of farming status. No effect on asthma
Barnes et al. [9]	Rural farm and non-farm and urban children aged 11–19 years ($n = 929$)	Crete (Greece)	Unpasteurized milk products	Adj. OR and (95% CI) of atopy and unpasteurized farm milk consumption with and without simultaneous farm animal contact: 0.32 (0.13–0.78) and 0.58 (0.34–0.98), respectively
Radon et al. [10]	Rural farm and non-farm young adults aged 18-44 years ($n = 321$)	Northern Germany	Raw, unboiled farm milk	Raw milk consumption and atopy adj. OR and (95% CI): 0.65 (0.36–1.18). In those visiting animal houses before age 7 years raw milk consumption and atopy: 0.35 (0.17–0.74)
Wickens et al. [11]	Children living on farms or in small towns, aged 7–10 years ($n = 293$)	New Zealand	Unpasteurized milk ever, yogurt at least weekly before age 2 years	Adj. OR and (95% CI) for early yogurt consumption and hay fever 0.30 (0.1–0.7); any unpasteurized milk and atopic eczema: 0.2 (0.1–0.8). No significant association between unpasteurized milk consumption and asthma or atopy
Remes et al. [14]	Rural farm and non-farm children aged 6–15 years ($n = 710$)	Finland	Farm milk in infancy	Farm milk consumption not associated with atopy. No other allergic health outcomes reported
Cohort Study				
Ege et al. [12]	922 farm and non-farm children, followed since pregnancy (PASTURE study)	Finland, France Austria, Germany, Switzerland	Maternal consumption of boiled and unboiled farm milk during pregnancy	Maternal consumption of farm milk during pregnancy not related to IgE to seasonal allergens in cord blood of neonates. Boiled farm milk consumption during pregnancy positively associated with specific IgE to cow's milk: adj. OR and (95% CI): 1.78 (1.08–2.93)
Pfefferle et al. [13]	PASTURE study	Finland, France Austria, Germany, Switzerland	Skimmed and unskimmed farm milk, farm produced butter and yogurt during pregnancy	Maternal consumption of farm produced butter during pregnancy associated with increased IFN-γ and TNF-α production in cord blood, farm produced yogurt inversely associated with these cytokines

PARSIFAL study confirmed these inverse associations and showed consistent effects across different subgroups of children from non-farming families. [6]. Combining the data of the ALEX [5] and the PARSIFAL [6] study a significant interaction between genetic variation in CD14 and farm milk consumption was shown [7] suggesting that innate immunity mechanisms might mediate the effect of farm milk consumption on allergic diseases. Perkin and Strachan [8] studied children living in rural areas of Shropshire, England, and found children currently consuming unpasteurized milk to have significantly less current eczema symptoms and less atopic sensitization and an increased IFN-γ production in stimulated whole-blood assay. Again, this effect was independent of being a farm child. Barnes' et al. [9] study in Crete included urban and rural children and found the consumption of unpasteurized farm milk to have a protective effect on atopy independent of farm animal contact and being a rural child. Radon et al. [10] examined young adults in Northern Germany and did not find an independent protective effect of unpasteurized milk consumption on atopy. It was only the combination of unpasteurized milk consumption and regular visits to animal houses before the age of 7 years that was protective. In a small study in New Zealand, early life consumption of yogurt was found to be associated with less hay fever, and unpasteurized milk consumption to be associated with a reduced risk of atopic eczema [11]. Remes et al. [14], on the other hand evaluating factors that might explain the lower prevalence of atopy among farmer's children in Finland found no effect of farm milk consumption on atopy.

Studies discussed so far were all cross-sectional in design limiting inference about the temporal sequence of exposure and health effect. More recently, first results of the ongoing prospective birth cohort study Protection against Allergy Study in Rural Environments (PASTURE) involving more than 900 children from rural areas in five European countries have been published [12, 13]. Information on maternal farm-related exposures and nutrition during pregnancy was obtained by means of an interview during the last trimester of pregnancy. Specific IgE levels for food and common inhalant allergens were assessed in cord blood of the children and in peripheral blood samples of their mothers. 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, indicating that boiling the milk might alter the yet unknown protective factors of unprocessed farm milk. Examining the association between maternal farm exposures and cytokine production in cord blood in the same birth cohort, Pfefferle et al. [13] reported that consumption of farm-produced butter during pregnancy enhanced the production of cord blood INF-γ and TNF-α, whereas maternal consumption of farm-produced yogurt resulted in significantly lower levels of these cytokines. Furthermore, an additive effect was observed for the combined consumption of butter and unskimmed 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 of offsprings at birth.

Taken together, the available epidemiological literature suggests that the consumption of unprocessed cow's milk has indeed a protective effect on the development of asthma and allergies but there is considerable heterogeneity between studies with respect to the health outcomes that are inversely associated with farm milk consumption and also with respect to the type of farm milk products that seem to confer protection. The studies, however, consistently show that the protective effect of farm milk consumption is independent of other farm-related exposures and might thus be mediated by other mechanisms. Consumption of a safe and protective cow's milk as a means of primary prevention remains an attractive vision. Yet, it requires answering the question of what is it about 'farm milk' that confers this protection and what is it about pasteurized and homogenized milk that confers risk.

Processing of cow's milk

Cow's milk produced or bought directly on a farm and consumed by rural families differs in many aspects from commercial milk, even if the families skim or heat the raw milk before consumption. Milk purchased directly from a farm does not undergo the processing steps necessary for preservation of commercial milk. Commercial milk is commonly homogenized and heat treated.

Homogenization

Homogenization is a treatment which prevents a cream layer from separating out of the milk and allows standardization of the fat content. It involves the milk being pumped at high pressures through very narrow pipes, breaking up the fat globules. The process results in profound changes in the physical structure of milk fat by reducing the fat globule size and including caseins and some whey proteins such as the cow's milk allergens β-lactoglobulin and α-lactalbumin at the droplet interface [15]. Thus, the context of presentation of potentially allergenic structures may be changed. Allergy-related health effects associated with homogenization have been discussed in the context of milk allergy (reviewed in [15]). In animal models there is some evidence that homogenization favours milk allergy [16], but these findings have not been confirmed in clinical studies [15]. No studies exist so far examining a potential effect of homogenization on the development of asthma or allergic diseases other than milk allergy.

Pasteurization

While homogenized milk emulsion is more stable and shelf-life increases, intensive heat treatments [pasteurization or ultra-high temperature process (UHT)] are necessary to preserve product microbiological quality. Pasteurization typically uses temperatures below the boiling point. High-temperature short-term pasteurized milk is heated to 72 °C for 15–20 s, while UHT processing holds the milk at a temperature of 135 °C for a fraction of a second. Pasteurization aims at slowing microbial growth in the milk but may also affect heat-sensitive milk components such as proteins.

Bacterial composition

If the epidemiologically observed protective farm milk effect is indeed related to the heat treatment of milk one might speculate that under the hygiene hypothesis a higher microbial load of unprocessed farm milk might be responsible for this protective effect. Milk is an excellent growth medium allowing rapid proliferation of microbes including pathogens and there is ample evidence that the microbial composition of raw and pasteurized milk differs greatly [17, 18]. The analysis of the microbial composition of raw milk is usually based on samples taken from the milk tank on a farm. Bulk milk samples have been reported to yield higher levels of lipopolysaccarides (LPS) before than after pasteurization [19]. However, little information exists on the microbial composition of milk as it is consumed in every day life by rural families. Home stored milk might undergo re-contamination during storage. Within the PASTURE cohort study, endotoxin (LPS), the cell wall component of the outer membrane of Gram-negative bacteria, has been measured in milk samples collected from the homes of rural farm and non-farm families [20]. Endotoxin levels of farm milk samples compared with commercial milk samples did not differ significantly when storage conditions and temperature during transportation to the laboratory were taken into account, challenging the idea of enteral exposure to endotoxin being responsible for the protective 'farm milk effect'. Yet, the results do not exclude that the levels of certain viable bacteria measured in different milk samples might be associated with protection from allergic diseases.

Fat and fatty acids

Epidemiological studies provide some evidence that consumption of milk fat-containing products such as full cream milk and butter are associated with a reduced risk of asthma [6, 21]. The PASTURE cohort study has shown that consumption of unprocessed farm milk and farm-produced butter by the pregnant mother increased levels of cord-blood INF-γ and TNF-α. These products contain the natural amount of milk fat and polyunsaturated fatty acids (PUFA) [13]. Black and Sharpe [22] have hypothesized that the declining ratio of n-3/n-6 PUFA in modern diets may have contributed to the rise in asthma over the past decades. They argued that n-3 fatty acids reduce prostaglandin formation by competitive inhibition with n-6 fatty acids (linoleic acid) and by inhibiting the action of cyclo-oxygenase. More recent research indicates that the mechanisms are undoubtedly more complex [23, 24]. Yet, in the context of mechanisms underlying the protective role of farm milk it is interesting to note that cheese from cows fed on alpine pastures contains significantly more n-3 fatty acids and a significantly lower n-6 : n-3 ratio compared with conventionally produced cheese [25], and that elevated n-3 fatty acids in cow's milk results from feeding grass-only diets compared with a silage-concentrated diet [26]. Pasture-feeding also increases the proportion of conjugated linoleic acids (CLA) when compared with milk from cows kept indoors and fed with silage and concentrates [27]. A higher proportion of feed grasses and a lower amount of concentrates fed to cows of organic farmers also explained the higher CLA levels in milks from organic farms as compared with conventional production [28]. Dietary supplementation with CLA-rich Alpine butter can also influence human breast milk composition of fatty acids and CLA isomers profiles [29].

Evidence from *in vivo* studies is available, demonstrating the ability of CLA to modify soluble factors or mediators of immunity such as eicosanoids, prostaglandins, cytokines, and immunoglobulin production (reviewed in [30, 31]). In mice experiments, feeding of a diet enriched with c9,t11-CLA resulted in significantly reduced IgE production and allergen-induced airway hyperresponsiveness [32]. 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 [33]. Most recently, a prospective birth cohort study in the Netherlands (KOALA) showed that higher concentrations of the main n-3 long chain polyunsaturated fatty acids (LCP) in human breast milk were associated with a lower risk of eczema at 2 years of age and a lower risk of allergic sensitization at 1 year of age. In addition, an independent inverse association was observed between the breast milk concentrations of ruminant fatty acids the most abundant isomeric form of CLA in breast milk and atopic outcomes [34].

Thus, the fatty acid composition of unprocessed farm milk may indeed have a role in explaining the protective effect of farm milk consumption. As the type of farming [35], feeding practice and altitude [27] influence the fatty acid profiles of cow's milk these factors might partly explain the heterogeneity between studies with respect to the observed health effects of farm milk consumption.

Milk proteins

Milk contains 3.3% total protein, approximately 82% is casein and the remaining 18% is serum or whey protein. The whey protein family consists of approximately 50% β-lactoglobulin, 20% α-lactalbumin, serum albumin, immunoglobulins, lactoferrin, and many minor proteins and enzymes [36]. β-lactoglobulin is the major allergen in cow's milk, responsible for triggering milk allergy. Milk processing such as heating does not affect caseins which are heat-stable but causes denaturation, aggregation and insolubilization of whey proteins. Commercial milk processing also includes homogenization a process which induces fat globule disruption thus creating a greater droplet surface area to which casein micelles adsorbe [37].

Whey proteins

There is increasing interest in whey as a potentially rich natural source of bioactive compounds to reduce disease risk and to prevent disease development [38]. Dietary supplementation with bovine whey proteins has been shown to enhance innate immunity by priming normal human blood neutrophils [39]. To our knowledge, no study has so far documented effects of whey protein supplementation on allergic diseases such as asthma or hay fever. But in experimental studies in rats whey proteins have been found to protect the animals against gut inflammation by reducing inflammation markers (IL-β, calprotectin) and clinical symptoms such as diarrhoea and fecal blood loss [40]. Whey proteins have also been reported to exert beneficial effects on inflammation in patients with cystic fibrosis [41].

Lactoferrin is a natural defence protein present in most secretions commonly exposed to normal flora including milk. It is a multifunctional protein playing an important role in host defence against infections and excessive inflammation. Lactoferrin has marked effects on immune cells in culture, being an immunostimulator and immunoregulator [42]. It inhibits the proliferative response and cytokine production of Th1, but not Th2 cell lines [43].

Whey also contains cytokines such as TGF-β a multifunctional cytokine which is found in cow's and human milk. A systematic review of TGF-β in breast milk on immunological outcomes in infancy and early childhood found two-third of the studies to demonstrate a protective effect of breast milk TGF-β on allergy-related outcomes [44]. In a recent animal model orally administered TGF-β1 was shown to retain biological activity in the intestinal mucosa and to enhance the induction of oral tolerance to high-dose antigen [45]. To our knowledge there are no data on TGF-β and lactoferrin in bovine milk as a potential protective factor for the development of allergic diseases. However, Verhasselt et al. [46] have recently demonstrated in an animal model that TGF-β in breast milk can confer allergy protection in the progeny.

Allergen exposure

It is puzzling that early consumption of unprocessed cow's milk decreases the risk of developing asthma and allergies later in life because cow's milk contains well-known food allergens. One might speculate that milk processing such as homogenization and pasteurization might alter the context in which potentially allergenic structures are presented to the immune system. Homogenisation may alter allergen presentation by changing the milk fat structure as discussed above. Pasteurization might not only destroy pathogens but also other heat-sensitive milk components such as the whey proteins discussed above. Presentation of allergenic epitopes may also be influenced by complexing the allergen with immunoglobulins as recently proposed in an animal model of allergen tolerance. In the BALBc mouse the ovalbumin (OVA) allergen is efficiently transferred from the mother to the neonate through breast milk. Breast milk from antigen-exposed sensitized mother mice containing OVA-IgG immune complexes that were transferred to the newborn induced oral tolerance in the offspring [47] Whether modern milk processing may alter the context of allergen presentation of bovine milk and thus influence its allergenic potential obviously remains to be elucidated.

Conclusions

Raw milk consumption is discussed with passion. A lobby attributing numerous health benefits to its consumption (http://www.realmilk.com) is contrasted by medical experts and legislation in many countries prohibiting or strongly discouraging raw milk consumption. The epidemiological evidence of a protective effect of unpasteurized milk for the development of asthma and allergic diseases adds new arguments to the discussion of the Janus face of raw milk. Most importantly we need to understand which components and mechanisms are underlying the observed protective effect and risks to ultimately be able to utilize safe and protective milk as a means of primary prevention. Until then, the consumption of raw milk can in no ways be recommended as a preventive measure for allergic diseases. Raw milk may be contaminated by a variety of pathogens, some of which are associated with human illness and disease [2]. We must therefore put all our scientific efforts into the deciphering of the protective and risk contexts of cow's milk exposures to develop better ways of processing a preserved and safe product in the future.

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