Consumption of unprocessed cow's milk protects infants from common respiratory infections

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Background: Breast-feeding is protective against respiratory infections in early life. Given the co-evolutionary adaptations of humans and cattle, bovine milk might exert similar anti-infective effects in human infants.
Objective: To study effects of consumption of raw and processed cow's milk on common infections in infants.
Methods: The PASTURE birth cohort followed 983 infants from rural areas in Austria, Finland, France, Germany, and Switzerland, for the first year of life, covering 37,306 person-weeks. Consumption of different types of cow's milk and occurrence of rhinitis, respiratory tract infections, otitis, and fever were assessed by weekly health diaries. C-reactive protein levels were assessed using blood samples taken at 12 months.
Results: When contrasted with ultra-heat treated milk, raw milk consumption was inversely associated with occurrence of rhinitis (adjusted odds ratio from longitudinal models [95% CI]: 0.71 [0.54-0.94]), respiratory tract infections (0.77 [0.59-0.99]), otitis (0.14 [0.05-0.42]), and fever (0.69 [0.47-1.01]). Boiled farm milk showed similar but weaker associations. Industrially processed pasteurized milk was inversely associated with fever. Raw farm milk consumption was inversely associated with C-reactive protein levels at 12 months (geometric means ratio [95% CI]: 0.66 [0.45-0.98]).
Conclusions: Early life consumption of raw cow's milk reduced the risk of manifest respiratory infections and fever by about 30%. If the health hazards of raw milk could be overcome, the public health impact of minimally processed but pathogen-free milk might be enormous, given the high prevalence of respiratory infections in the first year of life and the associated direct and indirect costs. (J Allergy Clin Immunol 2015;135:56-62.)

Key words: *Respiratory infections, rhinitis, otitis, fever, inflammation, C-reactive protein, infancy, milk, prevention, epidemiology*

Cow's milk has been a readily available source of protein and energy for humans ever since the Neolithic period. Mutations in the human lactase gene prevented downregulation of lactase

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Abbreviations used
GEE: General estimation equation
hsCRP: High-sensitivity C-reactive protein
aOR: Adjusted odds ratio
PASTURE: Protection against Allergy—Study in Rural Environments
RTI: Respiratory tract infection
UHT: Ultra-heat treatment

levels, thereby rendering native cow's milk digestible also to adolescents and adults. The enormous pace—in genetic terms—by which the mutations spread across the populated world emphasizes the evolutionary advantage of cow's milk consumption and its impact on population fertility.[1]

This indicates that consumption of bovine milk matches human needs remarkably well despite varying proportions of fat, protein, and carbohydrate contents. Reasons for this relatively fast mutual adaptation might be found in successful breeding of animals, effectively a form of co-evolution. In turn, additional genetic and epigenetic changes in humans might have occurred in analogy to the lactase mutations. Beyond using nutrients and energy, the human organism might also profit from functional properties of cow's milk, such as host-defense proteins.[2,3] In a way, cow's milk might provide passive immunity to humans, in analogy to human breast milk, and might also prevent or attenuate infections in humans. Indeed, numerous agents with beneficial anti-microbial or immune-modulatory effects are shared in bovine and human milk, such as immunoglobulins, cytokines, growth factors, lactoferrin, oligosaccharides, and milk fat globule membranes.[4]

The price humankind had to pay for the advantages of cow's milk was the risk of serious infections that can be transmitted by raw milk, such as tuberculosis, brucellosis, listeriosis, or enterohemorrhagic *Escherichia coli* causing hemolytic-uremic syndrome.[5-7] By the introduction of pasteurization and other industrial processing techniques, the critical issue of milk-borne infections has effectively been solved. In contrast to the mutual adaptation between humans and cattle, which evolved over several millennia, the replacement of fresh raw milk by processed milk was a rather recent change, which in itself might bear unknown disadvantages. For instance, heat-susceptible milk ingredients such as proteins or even microbial components might be altered by industrial processing,[8,9] possibly losing some of their properties that are beneficial for human health. Despite maintained nutritional value, functional proteins are denatured by ultra-heat treatment (UHT).[10,11]

The question remains whether industrial processing could abolish the postulated anti-infective effects, because these might be tightly linked to heat-sensitive molecules, such as whey proteins.[11] In other words, the rationale for the present analysis was the assumption that children consuming raw cow's milk were less affected by common infections as compared with children fed with processed milk. Though in most European countries, consumption of raw milk is vigorously discouraged, it is still practiced by many farming families. Infants are particularly susceptible to infective agents, because their immune system is immature. For the same reason, however, this age group might profit most from the beneficial immunomodulatory qualities of unprocessed cow's milk.

The aim of this study was to assess the effects of consumption of raw, boiled, and industrially processed milk types on common infections in the first year of life in a prospective multi-center birth cohort in 5 European countries.

METHODS

For the prospective birth cohort Protection against Allergy—Study in Rural Environments (PASTURE), pregnant women were recruited during the third trimester of pregnancy in rural areas of Austria, Finland, France, Germany, and Switzerland; half of the women lived and worked on livestock farms.[12] Questionnaire information on lifestyle and parental background was obtained within the third trimester of pregnancy and at 2 and 12 months of the child's age. In addition, parents reported information on feeding practices, farm-related exposures, and the occurrence of infection outcomes using weekly diaries kept between 8 and 53 weeks of life. The study was approved by the local research ethics committees in each country, and written informed consent was obtained from all parents.

Presence of infections was registered by the diaries, in particular occurrence during the last 7 days of a cold or runny nose (rhinitis), fever (at least 38.5°C), otitis, cough, or diarrhea for at least 2 days. These outcomes were defined as occurrence or absence in a given week between week 8 and 53 of life. Respiratory tract infections (RTI) were any occurrence of rhinitis or cough in the absence of other respiratory symptoms such as wheeze.[13] Cough was defined as cough without concomitant wheeze, in order to minimize confounding by allergy.

Explanatory variables based on diaries were defined as occurrence or absence in a given week and included exclusive or any breast-feeding, infant formula, contact with cow, pig, or horse stables, and quarterly seasons of milk sampling. Consumption of cow's milk, which was either bought at a shop (industrially processed milk, ie, UHT or pasteurized milk) or obtained directly from a farm (farm milk), was coded for weekly intervals in the following categories: (1) UHT milk and no farm milk, (2) pasteurized milk and no UHT and no farm milk, (3) boiled farm milk irrespective of any shop milk, (4) raw farm milk irrespective of any shop milk. Weekly diaries provided data on the quantity of milk (in units of 200 mL) and whether farm milk was consumed. Every 4 weeks, parents were asked whether they had boiled the milk and whether they had fed the infant shop milk. The type of shop milk was asked at 12 months of age by the following question: Did your child consume i) pasteurized cow's milk or ii) UHT milk after 8 weeks of life?

Covariables were selected *a priori* and included farming (living on a farm vs not), siblings, maternal education, parental history of atopic disease (asthma, hay fever, or atopic dermatitis) (derived from pregnancy questionnaires), and sex, mode of delivery, birth weight, and use of hypoallergenic infant formula (derived from 2-month questionnaires). To avoid collinearity, farming was replaced by contact to stables where applicable. Variables based on 1-year questionnaires were contact with dogs or cats and exposure to environmental tobacco smoking. Introduction of complementary foods during the first year of life was described by a food diversity score.[14] Age or follow-up time was entered as a continuous variable in weeks.

Statistical analyses considered a follow-up time from week of life 8 to 53 with non-missing information on variables used in present analyses in more than half of the average follow-up time (40 weeks). The median follow-up time was 42 weeks, with an interquartile range of 4 weeks. In total 983 individuals, ie, 87% of the originally included 1,133 children,[15] contributed to this analysis, with 37,306 person-weeks of observation. Weekly period prevalences refer to children with information available for the respective week. In a subsample of 602 children, high-sensitivity C-reactive protein (hsCRP) was measured at age 1 year.[16]

Longitudinal associations of individual outcomes and exposures were derived from general estimation equations (GEE) and expressed as adjusted odds ratios (aOR) with 95% CI. Due to the given data structure with unequal spacing and gaps, an exchangeable correlation structure was used; sensitivity analyses assuming unstructured and autoregressive matrices yielded similar effect estimates. When data on exposures or outcomes were missing from a

TABLE I. Study population characteristics

	No.	%
Sex		
Female	482	49.0
Male	501	51.0
Older siblings		
0	360	36.6
1	295	30.0
2 or more	328	33.4
Maternal age		
<25	94	9.6
≥25 and <30	336	34.2
≥30 and <35	361	36.7
≥35	192	19.5
Maternal education		
Low	159	16.2
Medium	436	44.4
High	388	39.5
Parental history of atopic disease		
No	587	59.7
Yes	396	40.3
Birth mode		
Vaginal	810	82.4
Cesarean	173	17.6
Birth weight (kg)		
≥4.0	128	13.0
≥3.5 and <4.0	352	35.8
≥3.0 and <3.5	391	39.8
≥2.5 and <3.0	98	10.0
<2.5	14	1.4
Smoke exposure		
No	825	83.9
Maternal smoking	123	12.5
Locations other than home	35	3.6
Farmer		
No	509	51.8
Yes	474	48.2
Total	983	100.0

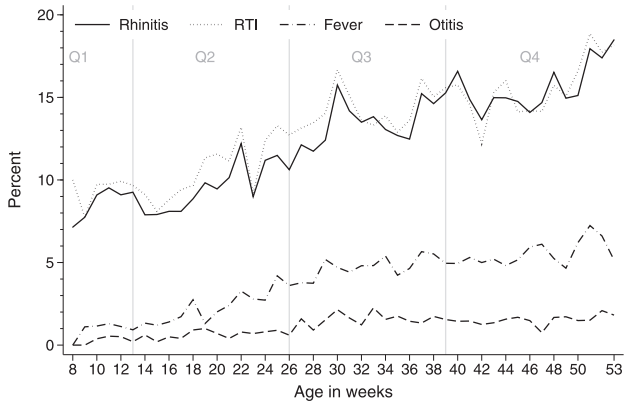

FIG 1. Point prevalences of infections during the first year of life. Quartiles are marked by Q1 through Q4.

diary, the week in question was excluded from the analysis. As a sensitivity analysis, relative risk ratios were calculated by GEE using Poisson instead of logistic models, which led to the same conclusions. Associations of hsCRP levels at age 1 and milk consumption during the first year of life were computed by log-linear models and expressed as geometric means ratios and 95% CI. All statistical analyses were performed using STATA/SE 12.1 (STATACorp, College Station, Tex).

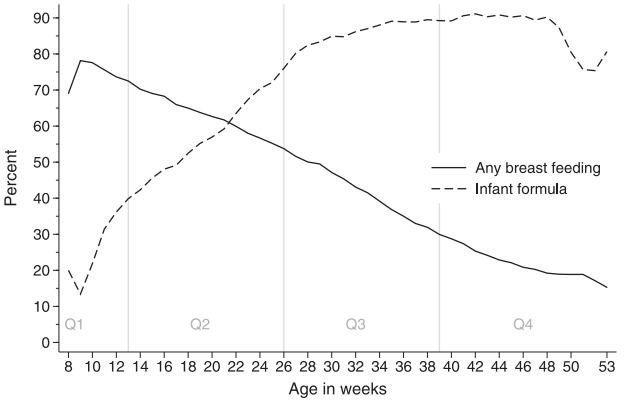

FIG 2. Frequency of breast-feeding and infant formula during the first year of life. Quartiles are marked by Q1 through Q4.

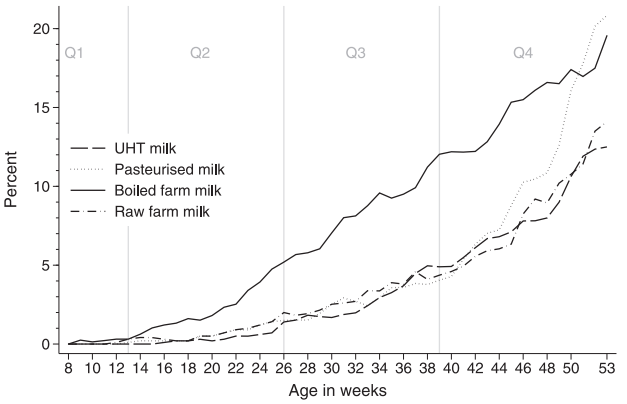

FIG 3. Frequency of consumption of raw and processed cow's milk during the first year of life. Quartiles are marked by Q1 through Q4.

RESULTS

Population characteristics are given in Table I. The subsample of children whose serum hsCRP values were measured (n = 602) was comparable to the entire study population with respect to outcomes and exposures (Table E1, available in this article's Online Repository at www.jacionline.org). Rhinitis and cough occurred in the majority of study participants (Table E1) and increased continuously in prevalence during the first year of life (Fig 1). Other infections such as diarrhea or otitis were less common (Table E1) and showed more or less stable prevalences over time. All outcomes were most prevalent during winter (data not shown). Fever was reported to accompany episodes of otitis (35%), diarrhea (29%), cough (18%), rhinitis (16%), and RTI events (14%) at the given percentages of weekly occurrences. Children with older siblings had significantly more infections (eg, aOR for rhinitis and 2 or more siblings vs none: 1.46 [1.26-1.69]; $P < .001$).

About 80% of children were initially breast-fed, with a linear decline to about 20% over the first year of life (Fig 2). Conversely, infant formula feeding increased from about 20% by 2 months to more than 90% by 8 to 9 months (Fig 2). At about 3 months, feeding of cow's milk started, with the steepest increase for boiled farm milk, followed by pasteurized, UHT, and raw milk (Fig 3). At 12 months, about 20% of children consumed regularly boiled farm milk and pasteurized milk, respectively, and about 12%

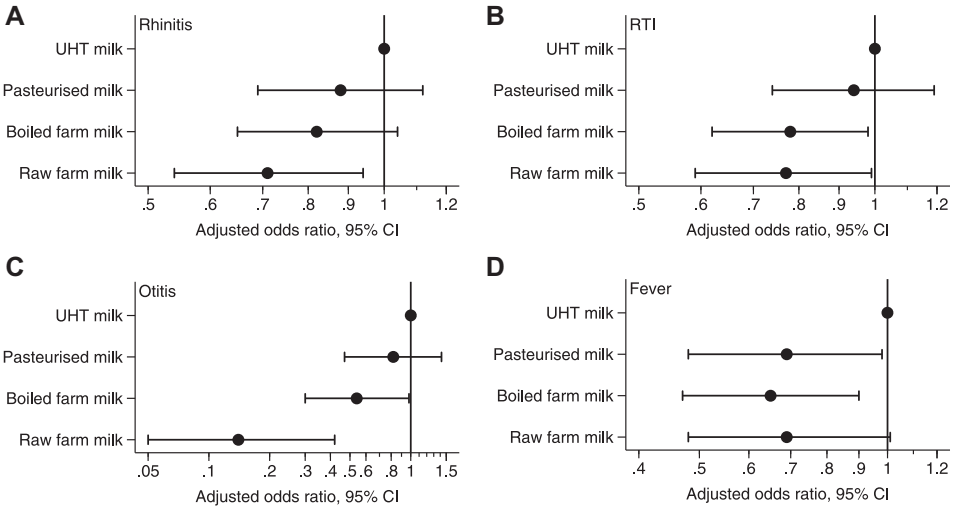

FIG 4. A-D, Adjusted associations of milk consumption and infections. Odds ratios *(black circles)* and 95% CI *(bars)* are given for associations of milk consumption with infection outcomes between week 8 and 53 weeks of life. General estimation equations adjusted for center, stable visits, breast-feeding, sex, siblings, maternal education, season of sampling, parental history of allergies, solid food score, birth mode, birth weight, contact with dogs, contact with cats, exposure to smoking, and age (squared) plus interaction terms of age with center. Rhinitis adjusted for concomitant occurrence of wheeze, otitis adjusted for concomitant occurrence of wheeze and rhinitis.

consumed UHT and raw milk, respectively. Irrespective of farming, raw milk consumption was more common in children with more siblings; eg, the aOR for raw milk versus no raw milk and 2 or more siblings versus none was 2.22 [1.73-2.84]; $P < .001$. More siblings and birth weight >4 kg increased the risk of all investigated outcomes (see Table E2 in this article's Online Repository at www.jacionline.org). Rhinitis and RTI occurred less often in farmers but more often with a positive parental history of atopy. Higher maternal education was positively associated with rhinitis, RTI, and otitis.

Exclusive breast-feeding was inversely related to fever (aOR = 0.64 [0.49-0.83]; $P = .001$); any breast-feeding was related to otitis (0.61 [0.46-0.81]) and diarrhea (0.55 [0.43-0.70]). The associations of any breast-feeding with rhinitis and RTI were modified by farming; ie, only among children not living on farms was breast-feeding inversely related to rhinitis (0.84 [0.75-0.94]) and RTI (0.82 [0.73-0.91]).

When assessing the relationship of regular milk consumption to disease outcomes, UHT milk was used as a reference category, because UHT impacts most strongly on heat-sensitive milk properties. All subsequent models were adjusted for breast-feeding (Fig 4). Among all fresh milk types, raw farm milk exerted the strongest protective effects on rhinitis (aOR = 0.71 [0.54-0.94]; $P = .015$), RTI (0.77 [0.59-0.99]; $P = .045$), otitis (0.14 [0.05-0.42]; $P < .001$), and fever (0.69 [0.48-1.01]; $P = .058$). Similar effects were seen for boiled farm milk on RTI and fever (0.78 [0.62-0.98]; $P = .030$ and 0.65 [0.47-0.90]; $P = .009$, respectively). For rhinitis and otitis, weaker effects were seen (0.82 [0.65-1.04]; $P = .096$ and 0.54 [0.30-0.98]; $P = .043$, respectively). For pasteurized shop milk, the associations were not significant except for with fever (0.69 [0.48-0.98]; $P = .038$). Crude estimates are shown in Table II. There were no clear associations of milk consumption with diarrhea (data not shown). Infant formula (vs no infant formula) did not protect from infections such as rhinitis (0.97 [0.87-1.08]) and otitis (0.95 [0.67-1.35]), nor from fever (1.19 [0.98-1.45]); it did not confound or modify the protective effects of raw and boiled milk. A quantitative analysis of amount of milk consumed per week did not reveal any threshold phenomenon on any type of infection (data not shown). The association of raw milk consumption with rhinitis was fairly homogeneous across study regions ($I^2 = 39.8\%$; $P = .156$).

All assessed children had hsCRP values within the reference range, ie, below 5 mg/L. However, within this range, children who consumed raw milk had lower hsCRP values (geometric means ratio [95% CI], P value: 0.66 [0.45-0.98], .039) irrespectively of disease symptoms or fever (Fig 5). hsCRP levels were not related to duration of breast-feeding (data not shown).

DISCUSSION

The main finding of this analysis was an inverse association between consumption of unprocessed cow's milk and rhinitis, RTI, and otitis (Fig 4). This effect was strongest when cow's milk was consumed raw; boiled farm milk exhibited an attenuated effect. Irrespective of heat treatment, all milk types except UHT exerted an independent protective effect on fever. Raw milk consumption was also associated with reduced hsCRP levels at age 1 year.

In this study, data on infections and milk consumption were collected prospectively using a weekly diary. The immediate capturing of outcome and exposure is a major strength, as it renders recall bias unlikely. Reverse causation may play a role in the inverse associations of raw milk consumption and diarrhea, as children with diarrhea may not have consumed raw milk. For outcomes not related to digestion, reverse causation is implausible.

That the infections were reported by the parents but not confirmed by a physician might be seen as a potential shortcoming. However, we consider this to be of limited relevance for several reasons. First, most infectious episodes are usually not presented to a physician; hence, parental observations might be more sensitive though less specific. The significant association of

TABLE II. Crude associations between milk consumption and infections

Milk consumption	Rhinitis	RTI	Otitis	Fever
UHT milk	1.00	1.00	1.00	1.00
Pasteurized milk	0.93 [0.73-1.17]; .528	0.97 [0.77-1.23]; .820	0.88 [0.50-1.54]; .648	0.71 [0.50-1.01]; .056
Boiled farm milk	0.80 [0.64-0.99]; .039	0.74 [0.60-0.92]; .007	0.50 [0.29-0.87]; .015	0.61 [0.45-0.83]; .002
Raw farm milk	0.72 [0.56-0.93]; .011	0.75 [0.59-0.97]; .028	0.13 [0.04-0.41]; <.001	0.66 [0.46-0.95]; .026

Crude odds ratios by GEE models are given with 95% CI and *P* values.

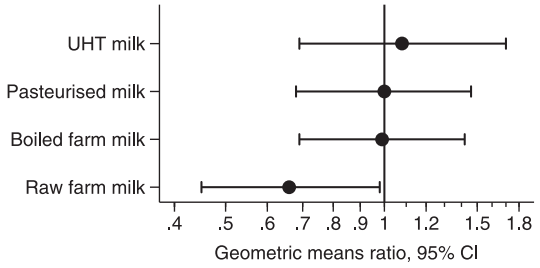

FIG 5. Mutually adjusted effect of milk consumption during week 8 to 53 on hsCRP levels at age 1. Geometric means ratios *(black circles)* and 95% CI *(bars)* adjusted for center, sex, older siblings, and contact with stable during first year of life.

infections with older siblings suggests that parents do not overlook infections in their younger children; otherwise, the association estimates were close to unity. Second, parents usually measure fever in this age group with an ear or clinical thermometer, rendering it a more objective outcome variable than just reported symptoms. Third, the diaries were filled out with very few missing values, and the correlation patterns of the diary variables over time did not show any evidence of retrospective completion of the diaries. Fourth, the pronounced increase in respiratory infections coincides with tapering-off of passive immunity starting at 3 to 6 months of age. Fifth, incidence patterns match those of similar studies with respect to seasonal variations and their steady increase during the first year of life.[17-19] Nevertheless, we acknowledge that knowing the causal agents might have added another dimension to our analyses, because respiratory infections can be caused by 200 different types of viruses, though only a few common viruses are relevant, above all human rhinovirus and respiratory syncytial virus.[20]

As expected, breast-feeding showed protective effects on diarrhea, fever, otitis, and, in reference children, on rhinitis and RTI. This is in line with a recent report on breast-feeding and a lower risk of hospitalization for diarrhea or lower respiratory tract infections as compared with formula feeding.[21] In our population, the association of breast-feeding with rhinitis and RTI was restricted to nonfarm children, though breast-feeding was equally common in farm families. This might be explained by additional farming exposures.[22]

The protective effects of raw cow's milk on infections were comparable to those of breast-feeding, suggesting similar anti-infective properties of bovine and human milk, although their ingredients differ in many aspects[2]: The variations in the milk proteomes reflect the differences in immune development between human infant and calf; eg, bovine milk, except colostrum, contains much fewer immunoglobulins than human milk. This also explains why the risk of diarrhea is only reduced by human breast milk and not by cow's milk. In contrast to respiratory infections, immunoglobulins may exert a local effect, thereby directly protecting the intestinal mucosa.

As suggested by Fig 4, cow's milk might exert 2 distinct effects on infections: (1) the occurrence of symptoms such as rhinitis, RTI, and otitis is mostly influenced by raw milk and partially by boiled unprocessed milk, whereas (2) all types of milk except UHT reduced the risk of fever to the same extent. These differential phenomena might point toward various procedures in industrial milk treatment, which discriminate processed milk from raw milk. They include centrifugation; fat separation; homogenisation; and heat treatment, which comprises primarily pasteurization and UHT. Pasteurization is the traditional method of heat processing at temperatures of 72°C to 75°C for 15 to 30 seconds. UHT achieves very high temperatures, ie, more than 135°C for 5 seconds,[8] and usually involves previous heating to more than 90°C for 20 to 30 seconds. The protective effect of pasteurized but not UHT milk against fever points toward relatively heat-tolerant proteins and oligosaccharides. These components are not modified by pasteurization but might be inactivated or destroyed by UHT. As recognizable by an altered taste, UHT treatment causes material chemical changes in milk.[23,24] Furthermore, UHT milk can be stored more than 3 months at room temperature without relevant microbial growth; the long storage time, however, implies degradation of other bioactive substances.

Despite heat treatment, boiled raw milk maintained some protective properties of raw milk. One explanation might be found in viable (probiotic) or nonviable microorganisms, which are present in raw milk, whereas in industrially processed milk they are essentially removed by centrifugation. Viable and even nonviable microorganisms may trigger pattern-recognition receptors of the innate immunity, such as the toll-like receptors or soluble CD14. The latter forms a complex with TLR4 and is present in unprocessed but not in processed bovine milk.[2] Lactoferrin has been demonstrated to interfere with both bacterial and viral infections by binding to viral particles or by adsorption to receptors on the host cell surface, thus blocking viral activities.[25] Bovine lactoferrin supplementation protected pre-term infants from bacterial sepsis.[26] As milk glycans harboring virus receptors have been detected by functional glycomic analyses, it is conceivable that these molecules block viruses also *in vivo*.[27] In the case of raw milk, all possible ingredients affected by industrial milk processing are candidates for the anti-infective effect; the underlying mechanisms, however, remain elusive.

The inverse association of raw milk consumption with hsCRP values implies a sustained anti-inflammatory effect. Low-grade inflammation as determined by slightly elevated normal-range CRP values has been suspected to contribute to chronic disease risk in later life.[28,29] In children, increased hsCRP levels have been related to obesity, respiratory impairment, asthma severity, and atherogenic lipid profiles.[16,30]

The effect of raw milk versus UHT milk was present in all study centers, with the exception of Austria, where hardly any UHT milk was consumed (7.4% of children) and thus the reference

category was insufficiently represented. Since raw milk is also being increasingly replaced by industrially processed milk in developing countries, the detected associations are likely to be applicable to many parts of the world. The protective effect of raw cow's milk on common respiratory infections and fever adds a public health dimension to this basic food. Respiratory infections have a huge impact on health and society, being a major cause of morbidity and mortality worldwide, especially among children.[20] Based on World Health Organization estimates, the disease burden of acute respiratory illness is 94 million disability-adjusted life years and 3.9 million deaths worldwide.[31] Broken down to a single episode, total costs of €123 for outpatient treatment, nonmedical costs, and indirect costs due to caregivers' loss of work days have been estimated for German children age 0 to 3 years; hospitalization costs amounted to €2579 per episode, with infants being the most cost-intensive age group.[32] Moreover, respiratory infections in early life have been implied in the development of chronic diseases such as asthma.[33] However, it remains unclear whether viral infections, in particular by respiratory syncytial virus and human rhinovirus, trigger asthma development or whether they unveil an underlying predisposition for epithelial barrier dysfunction of the bronchial mucosa. In our study population, children consuming raw milk were twice as likely to have older siblings and consequently to be exposed to viruses. Nevertheless, they were less likely to respond with symptomatic disease. Hence, they might cope with such infections more easily; and airway cell damage might be limited. Preventing such infections could thus promote respiratory health in general and prevent the onset of asthma[11] or at least exacerbations. If the detected association of raw milk consumption and lower hsCRP values can be substantiated, raw milk might also play a role for noncommunicable diseases characterised by an inflammatory state.

Taken together, we have found protective effects of raw (vs UHT) milk consumption on respiratory infections and fever. Protection against fever was also observed with consumption of pasteurized milk in contrast to UHT milk. Once more, raw milk can confer life-threatening infectious diseases. Hence, there is a need for minimally processed but microbiologically safe milk. If efforts were taken by dairy farmers, milk industries, microbiologists, and health protection agencies to create such a minimally processed and safe cow's milk, a novel basic food might emerge with an enormous public health value. A prevention strategy based on a well-accepted food of everyday nutrition might succeed without profound changes in lifestyle.

Key messages

- **The inverse association of consumption of unprocessed cow's milk with respiratory infections in infants indicates presence of anti-infective or immunomodulatory molecules relevant to such infections in humans.**
- **Preventing respiratory infections in early life could not only promote respiratory health in general but may beneficially influence subsequent development of severe airway diseases such as asthma. Microbiologically safe yet minimally processed milk might be of major public health relevance for common respiratory infections.**

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TABLE E1. Study population characteristics

	Person-weeks (%)	Children with at least 1 occurrence in first year (%)	Children with at least 1 occurrence in first year and hsCRP values (%)
	37306 (100.0)	983 (100.0)	602 (100.0)
Rhinitis	4610 (12.4)	890 (90.5)	551 (91.5)
RTI	4876 (13.1)	911 (92.7)	560 (93.0)
Cough	3293 (8.8)	780 (79.4)	475 (78.9)
Otitis	428 (1.2)	194 (19.7)	123 (20.4)
Fever	1404 (3.8)	658 (66.9)	404 (67.1)
Diarrhea	547 (1.5)	319 (32.5)	195 (32.4)
Any breast-feeding			
No	19952 (53.5)	817 (83.1)	486 (80.7)
Not exclusive	10468 (28.1)	725 (73.8)	475 (78.9)†
Exclusive	6886 (18.5)	614 (62.5)	397 (66.0)
Milk consumption			
No milk	30632 (82.1)	979 (99.6)	602 (100.0)
UHT milk	1186 (3.2)	113 (11.5)	64 (10.6)
Pasteurized milk	1380 (3.7)	166 (16.9)	119 (19.8)
Boiled farm milk	2829 (7.6)	218 (22.2)	122 (20.3)
Raw farm milk	1279 (3.4)	131 (13.3)	90 (14.9)
Infant formula	25109 (71.8)*	922 (93.8)	557 (92.5)
hsCRP [mg/L] (median, total range)			0.06 (n.d.-3.53)

The left column describes exposures and outcomes using the questionnaire weeks as observational units. The second column reflects the same information but on an aggregated level using the individual children as observational units. Both columns differ because children can change exposure and outcome categories over time.
n.d., Not detected (ie, below detection limit).
*Referring to 34,987 weeks of 983 participants, due to missing values for infant formula; all other variables did not have missing values by definition.
†Difference between all children and children with hsCRP measurements, based on 2-sample tests of proportions; $P = .02$.

TABLE E2. Crude associations of covariables and infections

	Rhinitis			RTI			Fever			Otitis		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Farmer												
No	1.00			1.00			1.00			1.00		
Yes	0.81	(0.72-0.91)	<.001	0.82	(0.73-0.91)	<.001	0.89	(0.78-1.02)	.107	0.75	(0.52-1.06)	.106
Older siblings												
0	1.00			1.00			1.00			1.00		
1	1.52	(1.32-1.75)	<.001	1.50	(1.31-1.73)	<.001	1.39	(1.17-1.64)	<.001	2.72	(1.71-4.34)	<.001
2 or more	1.31	(1.14-1.51)	<.001	1.40	(1.22-1.60)	<.001	1.49	(1.26-1.75)	<.001	2.21	(1.37-3.55)	.001
Maternal education												
Low	1.00			1.00			1.00			1.00		
Medium	1.28	(1.07-1.54)	.007	1.18	(0.99-1.41)	.057	0.93	(0.77-1.14)	.494	1.62	(0.86-3.06)	.137
High	1.51	(1.26-1.82)	<.001	1.37	(1.15-1.63)	<.001	0.97	(0.80-1.19)	.802	2.51	(1.35-4.66)	.004
Parental history of atopic disease												
No	1.00			1.00			1.00			1.00		
Yes	1.21	(1.08-1.36)	.001	1.12	(1.00-1.26)	.050	0.96	(0.84-1.11)	.605	0.92	(0.64-1.32)	.663
Sex												
Female	1.00			1.00			1.00			1.00		
Male	1.00	(0.89-1.12)	.951	1.01	(0.90-1.13)	.928	1.07	(0.94-1.23)	.312	1.31	(0.92-1.87)	.130
Birth mode												
Vaginal	1.00			1.00			1.00			1.00		
Cesarean	0.95	(0.81-1.10)	.481	1.01	(0.87-1.17)	.894	0.86	(0.71-1.03)	.100	0.78	(0.47-1.28)	.329
Birth weight (kg)												
≥4.0	1.00			1.00			1.00			1.00		
≥3.5 and <4.0	0.84	(0.70-1.00)	.053	0.81	(0.68-0.96)	.017	0.88	(0.72-1.09)	.253	0.55	(0.34-0.89)	.016
≥3.0 and <3.5	0.82	(0.69-0.98)	.032	0.86	(0.73-1.02)	.089	0.89	(0.73-1.10)	.285	0.59	(0.37-0.95)	.028
≥2.5 and <3.0	0.81	(0.64-1.03)	.089	0.74	(0.58-0.94)	.013	0.74	(0.55-0.99)	.041	0.59	(0.30-1.16)	.125
<2.5	0.67	(0.39-1.18)	.164	0.75	(0.45-1.26)	.275	1.11	(0.65-1.92)	.696	1.40	(0.49-4.00)	.526
Smoke exposure												
No	1.00			1.00			1.00			1.00		
Maternal smoking	0.91	(0.76-1.09)	.325	0.84	(0.70-1.00)	.050	0.98	(0.79-1.20)	.819	1.33	(0.82-2.15)	.245
Locations other than home	0.81	(0.58-1.14)	.220	0.72	(0.51-1.01)	.060	0.88	(0.59-1.30)	.509	0.73	(0.24-2.24)	.581

Crude odds ratios by GEE models are given with 95% CI and *P* values.