doi: 10.1111/j.1365-2222.2006.02640.x

Clinical and Experimental Allergy, **37**, 661–670

ORIGINAL PAPER

Inverse association of farm milk consumption with asthma and allergy in rural and suburban populations across Europe

M. Waser*, K. B. Michels†, C. Bieli*, H. Flöistrup§, G. Pershagen§, E. von Mutius¶, M. Ege¶, J. Riedler‖ , D. Schram-Bijkerk, B. Brunekreef**, M. van Hage††, R. Lauener‡‡, C. Braun-Fahrländer* and the PARSIFAL Study team**

**Institute of Social and Preventive Medicine, University of Basel, Switzerland,* †*Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA,* §*Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden,* ¶*Dr. von Hauner Children's Hospital, University of Munich, Germany,* ‖*Children's Hospital, Schwarzach, Austria,* ***Institute for Risk Assessment Sciences, Utrecht University, Utrecht, and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands,* ††*Clinical Immunology and Allergy Unit, Department of Medicine, Karolinska Institutet and University Hospital, Stockholm, Sweden and* ‡‡*Zurich University Children's Hospital, Zurich, Switzerland*

Clinical and Experimental Allergy

Summary

Background Dietary interventions as a means for atopy prevention attract great interest. Some studies in rural environments claimed an inverse association between consumption of farm-produced dairy products and the prevalence of allergic diseases, but current evidence is controversial.

Objective To investigate whether consumption of farm-produced products is associated with a lower prevalence of asthma and allergy when compared with shop-purchased products.

Methods Cross sectional multi-centre study (PARSIFAL) including 14 893 children aged 5–13 years from five European countries (2823 from farm families and 4606 attending Steiner Schools as well as 5440 farm reference and 2024 Steiner reference children). A detailed questionnaire including a dietary component was completed and allergen-specific IgE was measured in serum.

Results Farm milk consumption ever in life showed a statistically significant inverse association with asthma: covariate adjusted odds ratio (aOR) 0.74 [95% confidence interval (CI) 0.61–0.88], rhinoconjunctivitis: aOR 0.56 (0.43–0.73) and sensitization to pollen and the food mix fx5 (cut-off level of $\geqslant 3.5$ kU/L): aOR 0.67 (0.47–0.96) and aOR 0.42 (0.19–0.92), respectively, and sensitization to horse dander: aOR 0.50 (95% CI 0.28–0.87). The associations were observed in all four subpopulations and independent of farm-related co-exposures. Other farm-produced products were not independently related to any allergy-related health outcome.

Conclusion Our results indicate that consumption of farm milk may offer protection against asthma and allergy. A deepened understanding of the relevant protective components of farm milk and a better insight into the biological mechanisms underlying this association are warranted as a basis for the development of a safe product for prevention.

Keywords allergy, anthroposophy, asthma, children, diet, farming, gastrointestinal microflora, self-production, sensitization

Submitted 20 June 2006; revised 6 October 2006; accepted 30 October 2006

Correspondence:
Marco Waser, Institute of Social and Preventive Medicine, University of Basel, Steinengraben 49, CH-4051 Basel, Switzerland.
E-mail: Marco.Waser@unibas.ch

The PARSIFAL study group: Göran Pershagen, Tobias Alfvén, Johan Alm, Anna Bergström, Lars Engstrand, Helen Flöistrup, Marianne van Hage, Niclas Håkansson, Gunnar Lilja, Fredrik Nyberg, Annika Scheynius, Jackie Swartz, Magnus Wickman (Sweden); Charlotte Braun-Fahrländer, Marco Waser, Felix Sennhauser, Roger Lauener, Johannes Wildhaber, Alex Möller (Switzerland); Bert Brunekreef, Dieneke Schram-Bijkerk, Gert Doekes, Mirian Boeve, Jeroen Douwes, Machteld Huber, Mirjam Matze (The Netherlands); Erika von Mutius, Marcus R. Benz, Jörg Budde, Markus Ege (Germany); Josef Riedler, Waltraud Eder, Ellen Üblagger, Gertraud Weiss, Mynda Schreuer (Austria), Karin B. Michels (USA)

Introduction

The role of dietary factors in the development of asthma and atopy is still controversial. It has been postulated that the decrease in vegetable consumption and a shift from animal to vegetable fats has contributed to the increase in asthma and allergic diseases over the last decades [1, 2]. Several studies reported positive associations between elevated margarine consumption and childhood atopy risk [3, 4], while studies in rural environments reported an inverse association between consumption of farm-produced dairy products such as yogurt and farm milk and the prevalence of atopy [5–8], allergic rhinitis [5, 8, 9], asthma [5], and atopic dermatitis [8, 9]. However, in a Finnish study among farm and non-farm children, no effect of dairy product consumption and atopy was observed, but regular intake of fresh vegetables, predominantly when grown in the own garden, significantly reduced the risk of atopic sensitization [10]. Thus, current evidence of the relation between farm-produced products and the prevalence of allergic disease is controversial and mechanisms underlying the observed associations are unknown. Experiments demonstrating a beneficial effect of adding apathogenic bacteria (probiotics) to children's diet as a means of preventing atopic dermatitis have [11, 12], however, stimulated the interest in a possible role of microbes associated with the consumption of farm-produced foods.

The large European PARSIFAL study (Prevention of allergy risk factors for sensitization in children related to farming and anthroposophic lifestyle) offered the opportunity to examine specifically the relation between self- or farm-produced products and the prevalence of asthma and allergic diseases in more than 14 000 school-aged children [13]. The study included farm children, children from Rudolf Steiner schools (families with an anthroposophic lifestyle), and reference children from rural and sub-urban areas. The anthroposophic lifestyle includes factors like a restrictive use of antibiotics, antipyretics, and vaccinations, and often a biodynamic diet. An earlier study conducted in an anthroposophic community in Sweden showed a lower prevalence of childhood allergy [14].

The present analyses of the PARSIFAL study specifically addressed the question of whether, first, consumption of self- or farm-produced products, especially farm milk is associated with a lower prevalence of asthma, allergic diseases, and atopic sensitization when compared with shop-purchased products, and second, whether these associations are limited to children from rural environments or explained by other concurrent farm exposures.

Methods

Study population

Within the PARSIFAL study, children aged 5–13 years, from farm families or attending Rudolf Steiner schools, were compared with children from rural non-farming environments (reference for the farm children) and with children from (sub)urban environments attending State schools (reference for the Steiner school children) in Austria, Germany, the Netherlands, Sweden, and Switzerland. Children in Steiner schools often come from families with an anthroposophic lifestyle, which includes a holistic approach to life, education, and medicine. The details of the study design are described elsewhere [13]. In brief, a total of 15 137 (70% participation rate) parents' completed questionnaires were collected. Two hundred and forty-four questionnaires were excluded because children were outside the age limits or main information was missing, leaving 14 893 children for the analyses. In all, 8788 children gave consent for blood sampling and of these 4854 were invited for blood sampling [all children from Austria (806), the Netherlands (691), and Sweden (944) and a random sample of children from Germany (1548) and Switzerland (865) due to the comparatively large number of recruited children]. Four thousand and forty-nine (83.4%) children provided a blood sample and 3979 samples yielded a sufficient volume for allergen-specific IgE measurements. The study was approved by local research ethics committees in each country and informed consent was obtained from the parents of each child.

Parents' questionnaire

The dietary component of the PARSIFAL questionnaire included questions on the frequency of current average consumption of self-produced or directly purchased on a farm- and store-purchased foods. These foods included milk, butter, and other dairy products as well as margarine, eggs, meat, vegetables, and fruits. Response options were restricted to four categories: never, less than once per week, one to six times per week, or once a day or more.

Validity and reproducibility were assessed with 24-h recalls performed as telephone interviews of 493 randomly selected participants from all involved study groups and study areas. The validity for foods consumed with high frequency such as milk, vegetables, and fruits was the highest (positive predictive value above 60%, and negative predictive value above 80%). The reproducibility of reported consumption of milk during the first year of life was concordant among 71% of participants for store-purchased milk and 85% for farm-produced milk. No significant differences were found in the validity of responses between the five countries participating or between the four groups of children.

Besides the dietary component, the parental questionnaire included questions on socio-demographic background, parents' atopic diseases, food avoidance due to allergies in the family, breastfeeding, and the child's height and weight. In addition, information on the child's farm activities as well as the mother's farm exposures during

pregnancy was available. A child who lived on a farm and whose family ran the farm was coded as being a farm child.

The prevalence of diseases and symptoms were assessed by questions of the validated and translated International Study of Asthma and Allergies in Childhood (ISAAC) [15]. Children ever diagnosed with asthma, or obstructive bronchitis more than once, were considered to have a doctor's diagnosis of asthma. Current wheezing was defined as having wheezing at least once during the past 12 months. In a subsample of the PARSIFAL study questionnaire, responses on asthma and current wheeze have been validated against a bronchial challenge with hypertonic saline and no significant differences in validity were found between the four study groups [16].

Children diagnosed with hayfever and whoever had the symptoms of hayfever, were considered to have a doctor's diagnosis of rhinoconjunctivitis. Current rhinoconjunctivitis symptoms were defined as sneezing, runny nose, nasal block-up, and itchy eyes during the past 12 months, without having a cold at the same time.

Children with an intermittent itchy rash lasting at least 6 months and who had been diagnosed with atopic/allergic eczema were considered to have a doctor's diagnosis of atopic eczema. Current atopic eczema symptoms was considered present if the child had ever had an itchy rash intermittently for at least 6 months and, in addition, reported an itchy rash in defined locations (bend of the arm/knee, backside of thighs, neck, and around eyes/ears) at any time during the last 12 months.

Allergen-specific immunoglobulin E measurements

All samples were screened with a mix of common inhalant allergens (Phadiatop: birch, timothy, mugwort, *Dermatophagoides pteronyssinus* and *farinae*, cat, dog and hose epithelium and *Cladosporium herbarum*) and a mix of common food allergens (fx5: egg white, milk, fish, wheat, peanut, soya bean) (Pharmacia CAP System; Pharmacia Diagnostics AB, Uppsala, Sweden). Sera that were scored positive in Phadiatop were further analysed separately against *Dermatophagoides pteronyssinus* (house dust mite) and *Lepidoglyphus destructor (storage mite)*, a mix of grass pollen, a mix of tree pollen, cat, and horse epithelium. All analyses were performed centrally at the Department of Clinical Immunology (Karolinska University Hospital, Stockholm, Sweden). Atopic sensitization was defined as allergen-specific IgE$\geqslant$0.35 kU/L. In addition, a cut-off value of 3.5 kU/L was also considered for the analyses. Pollen sensitization was defined as positive grass pollen mix and/or positive tree pollen mix.

Statistics

χ^2 Statistics were used to evaluate differences in dietary habits between farm children and farm reference children as well as between Steiner school children and their reference group. Consumption of products from self-production or directly purchased on a farm was compared with shop-purchased products.

Logistic regression analyses were performed to calculate adjusted odds ratios (aOR) of the association between asthma or allergy outcomes and farm-produced foods. Multivariate models evaluating the effect of each food item on allergy outcomes were adjusted for predefined covariates including study group (farm children, Steiner school children, and the respective reference groups), country, sex, age, mother's and father's reported asthma and/or hayfever, parents' education, maternal smoking during pregnancy, current environmental smoking at home, older siblings, exclusive breastfeeding >4 months, BMI, and food avoidance due to familial asthma and/or allergy. In a second step, models were mutually adjusted for all food items.

We also calculated stratified estimates for the four study groups. The degree of heterogeneity of the stratum-specific ORs across study groups was evaluated using standard meta-analytic techniques [17]. In models examining the association between farm milk consumption and health outcomes, the timing of consumption (only in the first year of life, only at present, both in the first year of life, and at present), and relevant concomitant farm exposures such as frequency of the child's current visits to animal sheds (less or more than once a week) were additionally tested. In a sensitivity analysis, we also tested whether the effect of farm milk consumption varied across individual countries. Stability of effect estimates was examined by removing each country, one at a time.

To assess the possible influence of allergy-related changes in dietary habits, the respective question was included in all regression models. For the final analyses, we excluded the 469 non-milk-drinking children to avoid potential primary milk avoidance due to allergy-related symptoms at younger ages. Statistical analyses were performed using STATA (version 8.2, Stata Corp LP, College Station, TX, USA).

Results

Table 1 shows the distribution of children's consumption of selected farm-produced or shop-purchased foods across study groups. Although the consumption of farm milk and of self-produced products was most common among farm children, relevant proportions of all other study groups also ate and drank these products.

Table 2 gives the results of the multivariate analyses evaluating the effect of each individual farm-produced food on asthma and allergy adjusting for the predefined covariates (left side). A significant inverse association with a doctor's diagnosed asthma was observed for all

Table 1. Consumption of selected foods according to the study group

	Farm children (%) ($n = 2823$)	Farm reference (%) ($n = 5440$)	P-value*	RSS children (%) ($n = 4606$)	RSS reference (%) ($n = 2024$)	P-value*
Milk consumption						
Never	5.1	2.8		3.2	1.4	
Shop milk	28.1	77.3		65.7	90.5	
Farm milk (ever)	66.8	19.9	< 0.001	31.1	8.1	< 0.001
Only in the first year of life	6.1	8.3		16.8	3.7	
Only at present	8.9	5.2		6.1	2.8	
Both in the first year and at present	51.9	6.3	< 0.001	8.2	1.7	< 0.001
Butter consumption						
No margarine and no butter	3.0	4.5		3.6	5.4	
Shop-purchased butter only	52.6	75.4		80.4	78.8	
Margarine (exclusively)	5.0	6.2		4.0	7.4	
Butter from farm milk (any)	39.4	14.0	< 0.001	12.0	8.5	< 0.001
Yoghurt consumption						
No	4.6	5.6		4.0	5.5	
Shop purchased only	56.5	77.9		78.2	82.4	
Self-produced or directly purchased on a farm	38.9	16.5	< 0.001	17.8	12.1	< 0.001
Egg consumption						
No	3.7	5.7		4.0	6.1	
Shop purchased only	27.8	55.4		70.3	75.3	
Farm-produced or directly purchased on a farm	68.5	38.9	< 0.001	25.7	18.6	< 0.001
Vegetable or fruit consumption						
No vegetables and no fruits	0.6	1.1		0.7	1.0	
Shop purchased only	15.8	42.8		56.2	67.3	
Self-produced or directly purchased on a farm	83.5	56.1	< 0.001	43.1	31.7	< 0.001
Food avoidance due to allergies in the family	4.9	8.8	< 0.001	17.6	10.3	< 0.001

*P-values are given for the comparison of farm children and Rudolf Steiner School (RSS) children vs. their respective reference groups.

farm-produced products except vegetables and fruits. In addition, farm milk and egg consumption were inversely related to diagnosed rhinoconjunctivitis. When simultaneous adjustment was made for all farm-produced foods (right side), only consumption of farm milk remained significantly and inversely associated with the prevalence of diagnosed asthma, diagnosed rhinoconjunctivitis, and current rhinoconjunctivitis symptoms. None of the food items was significantly associated with atopic eczema and current eczema symptoms.

Table 3 shows the association between farm milk consumption and sensitization to aero and food allergens, adjusted for predefined covariates and all farm-produced foods. Using a cut-off level of 0.35 kU/L, a significant inverse association was found for a sensitization to horse allergen, and associations for sensitization to pollen, cat dander, and to the food mix fx5 tended to be negative, whereas the association with house dust and storage mites tended to be positive. When the more clinically relevant cut-off level of $\geqslant 3.5$ kU/L was chosen, the negative association with farm milk consumption became stronger and statistically significant for pollen sensitization and the food mix fx5.

The inverse relation between farm milk consumption and the prevalence of diagnosed asthma, rhinoconjunctivitis, and pollen sensitization was observed in all four study groups without significant heterogeneity (Fig. 1). Similarly, no significant heterogeneity of the effects across study groups was observed for fx5 (p-heterogeneity 0.610) and horse dander (p-heterogeneity 0.465).

When the use of shop-purchased butter and the consumption of butter made out of farm milk was contrasted to margarine consumption, an inverse association was seen between butter consumption and asthma and wheeze even when simultaneously adjusted for farm milk consumption. For asthma: aOR 0.80 (95% CI: 0.65–1.00), 0.62 (0.46–0.84) for shop-purchased and farm-produced butter, respectively. For wheeze aOR 0.84 (0.65–1.06), 0.79 (0.57–1.08) for shop-purchased and farm-produced butter, respectively. No significant associations were observed for other allergy-related health outcomes.

A strong and consistent inverse association was observed for the prevalence of asthma, wheeze, rhinoconjunctivitis (diagnosed and symptoms), pollen sensitization, and fx5 in children who consumed farm milk since their first year of life (Table 4). The inclusion of other relevant concomitant farm activities in the multivariate regression model somewhat attenuated the effects and widened the confidence intervals (CIs) (Table 4), but the estimated protective effect

Table 2. Associations between asthma, rhinoconjunctivitis, and atopic eczema and production type of consumed foods

	Prevalence of health outcomes†, n (%) (N = 14 424)	Adjusted‡ OR (95% CI) for individual farm-produced foods (consumed ever in life†) Reference category: shop purchased products					Models simultaneously adjusted for all farm-produced foods				
		Farm milk	Butter from farm milk	Yoghurt from self-production§	Eggs from farm-production§	Vegetables or fruits from self-production§	Farm milk	Butter from farm milk	Yoghurt from self-production§	Eggs from farm-production§	Vegetables or fruits from self-production§
Dr's diagnosis of asthma	1250 (8.9)	0.74* (0.61–0.88)	0.72* (0.58–0.90)	0.81* (0.67–0.98)	0.81* (0.69–0.95)	0.90 (0.78–1.04)	0.79* (0.65–0.95)	0.79 (0.59–1.06)	1.03 (0.80–1.33)	0.90 (0.74–1.09)	1.02 (0.86–1.20)
Current wheezing	1073 (7.6)	0.86 (0.72–1.04)	0.89 (0.71–1.12)	0.92 (0.75–1.12)	0.84* (0.71–0.99)	0.92 (0.79–1.07)	0.90 (0.74–1.10)	0.97 (0.71–1.30)	1.05 (0.80–1.37)	0.86 (0.70–1.06)	1.00 (0.84–1.20)
Dr's diagnosis of rhinoconjunctivitis	591 (4.2)	0.56* (0.43–0.73)	0.73 (0.52–1.02)	0.87 (0.66–1.15)	0.79* (0.63–0.99)	0.87 (0.71–1.06)	0.58* (0.44–0.76)	0.81 (0.53–1.25)	1.20 (0.83–1.73)	0.89 (0.67–1.19)	0.98 (0.78–1.25)
Current rhinoconjunctivitis symptoms	1037 (7.3)	0.70* (0.57–0.85)	0.98 (0.77–1.24)	0.95 (0.77–1.17)	0.86 (0.72–1.03)	0.94 (0.80–1.10)	0.70* (0.57–0.86)	1.14 (0.83–1.56)	1.04 (0.78–1.38)	0.87 (0.70–1.09)	1.02 (0.85–1.22)
Dr's diagnosis of atopic eczema	1436 (10.1)	0.89 (0.75–1.06)	0.89 (0.73–1.09)	0.98 (0.82–1.18)	0.92 (0.79–1.06)	0.98 (0.86–1.13)	0.91 (0.76–1.08)	0.87 (0.66–1.14)	1.12 (0.89–1.43)	0.92 (0.77–1.10)	1.04 (0.88–1.22)
Current atopic eczema symptoms	1517 (10.7)	0.89 (0.76–1.05)	0.94 (0.77–1.14)	0.91 (0.76–1.08)	0.98 (0.85–1.13)	0.91 (0.80–1.04)	0.91 (0.77–1.07)	1.02 (0.79–1.32)	0.92 (0.73–1.16)	1.08 (0.90–1.29)	0.91 (0.78–1.06)

*P-value < 0.05.

†Four hundred and sixty-nine never-milk-drinking children excluded. Models were limited to 89.2% children without missing values in any of the exposure or outcome variable.

‡Adjusted for study group, country, sex, age, mother's and father's reported asthma and/or hayfever, parent's education, maternal smoking during pregnancy, current environmental smoking at home, older siblings, exclusive breastfeeding > 4 months, BMI, food avoidance due to familial asthma and/or allergy.

§Or directly purchased on a farm.

OR, odds ratio; CI, confidence interval.

Table 3. Adjusted† odds ratios (95% CI) for farm milk consumption ever in life and sensitization against aero and food allergens

	Sensitization cut-off (kU/L)	Prevalence of health outcomes‡, *n* (%) (*N* = 3818)	Farm milk consumption Reference category: shop milk consumption only
Phadiatop	⩾0.35	1,056 (28.1)	1.07 (0.86–1.32)
	⩾3.5	595 (16.0)	0.93 (0.71–1.22)
Food mix fx5	⩾0.35	430 (11.4)	0.80 (0.59–1.07)
	⩾3.5	33 (0.9)	0.42* (0.19–0.92)
Pollen	⩾0.35	702 (18.7)	0.80 (0.62–1.02)
	⩾3.5	348 (9.3)	0.67* (0.47–0.96)
House dust mite	⩾0.35	574 (15.3)	1.24 (0.94–1.62)
	⩾3.5	368 (9.8)	1.35 (0.98–1.87)
Storage mite§	⩾0.35	168 (4.5)	1.22 (0.78–1.92)
Cat dander§	⩾0.35	267 (7.1)	0.86 (0.59–1.25)
Horse dander§	⩾0.35	130 (3.5)	0.50* (0.28–0.87)

*P-value < 0.05.

†Adjusted for study group, country, sex, age, mother's and father's reported asthma and/or hayfever, parent's education, maternal smoking during pregnancy, current environmental smoking at home, older siblings, exclusive breastfeeding > 4 months, BMI, food avoidance due to familial asthma and/or allergy, and all other farm-produced foods in the table.

‡One hundred and sixty-one never milk drinkers were excluded from the analyses.

§Due to small numbers of sensitized children, only models with cut-off level 0.35 kU/L were performed.

CI, confidence interval.

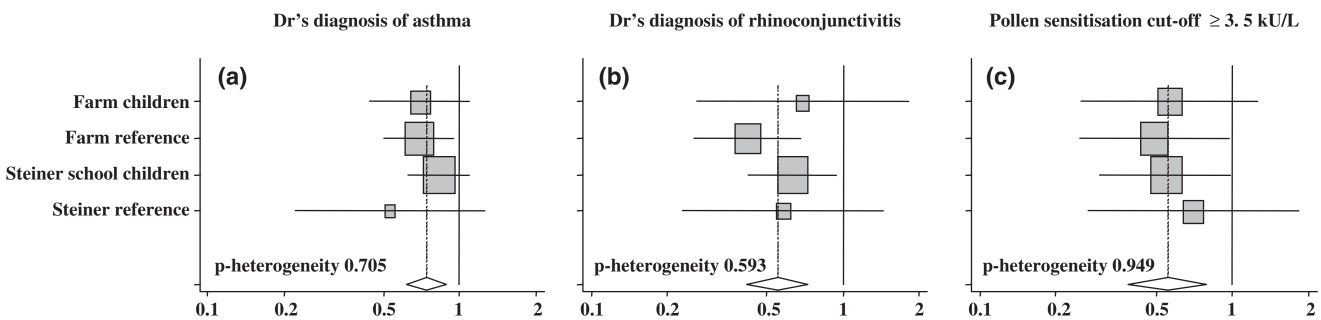

Fig. 1. (a–c) Forest plots of the association between asthma and allergy and consumption of farm milk ever for study groups using meta-analysis. The horizontal lines correspond with the 95% confidence intervals for each study group, with the corresponding box area drawn proportional to the weight for that group in the meta-analysis. The diamond represents the summary estimate. The *P*-value is given for the test of heterogeneity. Adjusted for country, sex, age, mother's and father's reported asthma and/or hayfever, parent's education, maternal smoking during pregnancy, current environmental smoking at home, older siblings, exclusive breastfeeding > 4 months, BMI, food avoidance due to familial asthma and/or allergy.

of farm milk consumption on asthma, rhinoconjunctivitis, and fx5 remained statistically significant.

The effect of being a farm child on asthma [aOR 0.73 (0.59–0.91)], rhinoconjunctivitis [0.42 (0.28–0.62)], and pollen sensitization [0.28 (0.19–0.40)] was only partially explained by farm milk consumption: farm milk adjusted effect of being a farm child on asthma [aOR 0.84 (0.67–1.06)], on rhinoconjunctivitis [aOR 0.55 (0.37–0.83)], and on pollen sensitization [aOR 0.36 (0.24–0.54)].

We also examined whether the observed effect of farm milk consumption was sensitive to the exclusion of specific countries by rerunning the analyses with each country being removed one at a time, but no relevant changes were observed.

Discussion

The analyses of the large cross-sectional study PARSIFAL give evidence of a significant inverse association between farm milk consumption and childhood asthma, rhinoconjunctivitis, sensitization to pollen, a mix of food allergens, and horse dander. Other farm-produced foods were not independently related to asthma and allergy prevalence. Of particular importance is the consistency of the findings across children from farming, rural non-farming, anthroposophic, and (sub)urban environments indicating that farm milk consumption represents a route of exposure that is independent of concomitant exposures to microbial compounds present in animal sheds and farm homes. The

Table 4. Sensitivity analyses for the association between asthma and allergy and farm milk consumption; adjusted OR (95% CI)

	n	Dr's diagnosis of asthma	Current wheezing	Dr's diagnosis of rhinoconjunctivitis	Current rhinoconjunctivitis symptoms	Pollen sensitization cut-off $\geqslant$ 3.5 kU/L	fx5 cut-off $\geqslant$ 3.5 kU/L
Timing of farm milk exposure							
Shop milk only (reference category)	9805	1	1	1	1	1	1
Farm milk only in the first year of life	1467	0.79 (0.61–1.01)	0.95 (0.74–1.22)	0.52* (0.35–0.75)	0.69* (0.52–0.90)	0.61* (0.37–1.00)	0.98 (0.69–1.44)
Farm milk only at present	869	0.74 (0.54–1.02)	0.85 (0.61–1.17)	0.58* (0.36–0.94)	0.85 (0.61–1.18)	0.73 (0.42–1.27)	0.86 (0.56–1.33)
Farm milk in the first year and at present	2204	0.67* (0.51–0.88)	0.77 (0.58–1.03)	0.61* (0.40–0.94)	0.60* (0.43–0.83)	0.51* (0.31–0.86)	0.61* (0.42–0.89)
Additional adjustment for the child's current visits to animal sheds							
Shop milk consumption only (Reference category)	9805	1	1	1	1	1	1
Farm milk in the first year and at present	2204	0.74* (0.56–0.98)	0.82 (0.61–1.10)	0.70 (0.45–1.07)	0.68* (0.48–0.94)	0.62 (0.37–1.04)	0.62* (0.42–0.91)

**P*-value < 0.05.

†Adjusted for study group, country, sex, age, mother's and father's reported asthma and/or hayfever, parent's education, maternal smoking during pregnancy, current environmental smoking at home, older siblings, exclusive breastfeeding > 4 months, BMI, food avoidance due to familial asthma and/or allergy.

OR, odds ratio; CI, confidence interval.

inverse association was not explained by concurrent farm activities of the child or farm exposures during pregnancy and was most pronounced in children drinking farm milk since their first year of life.

The results of the PARSIFAL study thus confirm an inverse association between farm milk consumption and allergic health outcomes reported previously [5–9]. However, the specific allergic health outcomes associated with farm milk consumption differ between studies. The strong effect on asthma was only reported by the ALEX study, which has been conducted in the same three alpine countries as the PARSIFAL study, but in geographically different and independent study populations [5]. Inverse associations between farm milk consumption and allergic rhinoconjunctivitis have been reported by the ALEX study [5], a study in New Zealand [9], and a recent study in the United Kingdom [8]. The ALEX study and surveys conducted in Crete [7], Northern Germany [6], New Zealand [9], and the United Kingdom [8] reported an inverse association between farm milk consumption and atopy whereas the PARSIFAL study observed an inverse association with most tested allergens, but not mites. No association between farm milk consumption and atopic sensitization was reported by a study conducted among rural children from Finland [10].

Allergen-specific differences in response to environmental exposures have already been reported by a series of farm studies that suggested a stronger association between farm residency and pollen sensitization and no or weak relations with mite sensitization [18–21]. However, other farm studies did not confirm these findings [8, 22, 23]. To evaluate whether the allergen-specific effects associated with farm milk consumption in the PARSIFAL study represent so far unappreciated peculiarities in the biology of allergen/immune system interactions deserves replication of these findings and further investigations of potential mechanisms.

The studies conducted in the United Kingdom and New Zealand reported strong and statistically significant inverse relations between farm or raw milk consumption and atopic eczema that was not observed in the present study. These contrasting findings may in part be explained by the amount of control for food avoidance that differed between the studies. Food avoidance due to a pre-existing allergy may bias the results in cross-sectional analyses. Eleven percent of the PARSIFAL population reported avoiding certain foods due to an existing allergy in one of the family members. Adjusting all regression models for this variable only slightly attenuated the effect estimates of farm milk consumption on asthma or rhinoconjunctivitis. However, the association between farm milk consumption and diagnosed eczema became non-significant when adjustment was made for food avoidance [diagnosed eczema without adjustment for food avoidance (aOR 0.80, 95% CI 0.68–0.95), and current eczema

symptoms (aOR 0.84, 95% CI 0.71–0.98), respectively]. When the study population was restricted to those without food avoidance, no significant association between farm milk consumption and diagnosed atopic eczema (aOR 0.90, 95% CI: 0.73–1.10) or current eczema symptoms (aOR: 0.94, 95% CI 0.79–1.13) was observed. We also excluded all non-milk-drinking children because this group may have changed dietary habits due to allergy-related skin or gastrointestinal problems early in life and not report it as deliberate food avoidance. However, this restriction had no strong impact on reported atopic dermatitis or any other allergic health outcome.

At present, we can only speculate about the components of farm milk responsible for the observed protective effect. Farm milk possibly contains different levels or a different composition of pathogenic and nonpathogenic microbes compared with milk purchased in a shop. The health effects of pathogens in raw milk such as salmonella or enterohaemorrhagic *Escherichia coli* (EHEC) are well recognized, and transmission of EHEC through unpasteurized cow's milk continues to cause serious health effects [24]. It is conceivable that the microbial burden of farm milk influences the gut microflora and thus the development of oral tolerance [25, 26]. Recent animal experiments have shown that colonization of germ-free mice with polysaccharide-A-producing *Bacteroides fragilis*, a ubiquitous gut microorganism and an important Gram-negative anaerobe that colonizes the mammalian lower gastrointestinal tract, restored normal cytokine production and established a proper T-helper type 1 (Th1)/Th2 balance for the host [27]. Gut microflora may also regulate immune responses outside the gut as has been evidenced in recent animal experiments. Mice were treated with antibiotics in drinking water, followed by a single oral lavage of yeast (*C. albicans*) [28]. They developed alterations of gastrointestinal bacterial populations and increased yeast numbers in the gastrointestinal microbiota. Subsequent intranasal exposure to mould spores led to an allergic response in the airways that was not observed when exposure occurred without prior alteration of the gut microflora. These results indicate that events in distal mucosal sites may play an important role in regulating immune response in the airways. Commensal microorganisms present in farm milk might therefore be responsible for the decreased risk for respiratory allergies such as asthma and hayfever.

The present study does not allow evaluating the effect of pasteurized vs. raw milk consumption because no objective confirmation of the raw milk status of the farm milk samples was available. Parental answers to a question on consumption of boiled vs. raw farm milk are likely to be biased due to the social desirability of responses because raw milk consumption is not recommended especially for young children. About half of the parents indicated that they usually did not boil the milk before consumption but no differential effects were observed between those boiling and those not boiling the milk. This might be a result of biased parental answers or may indicate that pasteurization is not of key importance because compounds other than microbes may play a role. This interpretation is supported by an analysis of Swiss alpine farm milk from exclusively grass-fed cows showing a higher content of omega-3 fatty acids than milk from cows fed conserved grass such as silage [29]. The relative concentrations of linolenic acid (18 : 3) and eicosapentaenoic acid (20 : 5) and the ratio of eicosapentaenoic acid to arachidonic acid (20 : 4) that is critical for the formation of omega-3-derived eicosanoids were significantly higher in milk from grass-fed cows and in cheese made from this milk [29, 30]. Research into fatty acid effects on allergic diseases has focused on the intake of omega-3 fatty acids that is potentially beneficial, and of omega-6 and trans-fatty acids which might be detrimental to asthma [31]. Elevated margarine consumption, which contributes to the intake of omega-6 fatty acid and of trans-fatty acids has been reported to increase childhood atopy risk in several epidemiological studies [3, 32]. Other studies indicated that full-fat milk and butter was associated with a reduced risk of asthma in young children [33–35]. In the present study, butter compared with margarine consumption was associated with a lower risk for asthma supporting a possible role of fatty acid intake. Future analyses of the farm milk compounds responsible for the beneficial effect therefore have to include fatty acid profiles in addition to microbial compounds.

Several limitations of the study have to be taken into account. First, dietary assessment is based on a limited set of variables that do not provide a complete representation of the child's diet. However, the primary aim of the present analyses was to compare farm-produced vs. shop-purchased products and their effect on allergic diseases and not to evaluate the effect of diet per se. The validity and reproducibility of the present dietary assessment has been shown to be good especially for farm milk consumption. Second, as no measurements of biological compounds of farm milk or other farm-produced products are available, the study reports associations and cannot provide an insight into the mechanism underlying the observed association between farm milk consumption and allergic diseases. Third, as the underlying mechanism of the farm milk effect is not known, the study does not allow to elucidate why consumption of farm milk is associated with different allergic health outcomes in different study populations.

In conclusion, the results of the present study indicate that consumption of farm milk is associated with a lower risk of childhood asthma and rhinoconjunctivitis. These results might be transferred to non-farming populations as they were observed in all subpopulations of the PARSIFAL study. Dietary interventions are an attractive

means for primary prevention. However, raw milk may contain pathogens such as salmonella or EHEC, and its consumption may therefore imply serious health risks [24]. A deepened understanding of the relevant 'protective' components of farm milk and a better insight into the biological mechanisms underlying the reported epidemiological observation are warranted as a basis for the development of a safe product for prevention. At this stage, consumption of raw farm milk cannot be recommended as a preventive measure.

Acknowledgements

The authors thank all fieldworkers and other PARSIFAL team members, especially Stina Gustafsson, Eva Hallner, André Lauber, Wiveka Lundberg, Helena Svensson, Anki Wigh, Annika Zettergren, Anne-Charlotte Öhman-Johansson (Sweden); Susanne Löhliger, Remo Frey (University Children's Hospital Zurich), Marianne Rutschi, Stefan Worminghaus (study center support), Michaela Glöckler (head of the medical section of the Goetheanum in Dornach) (Switzerland); Anja Strengers, Marieke Siekmans, Patricia Jansen-van Vliet, Janneke Bastiaanssen, Marieke Dijkema, Siegfried de Wind, Jack Spithoven, Griet Terpstra, Gert Buurman (the Netherlands); and Helmut Egger, Martina Burger, Bernadette Burger, Elisabeth Buchner (Austria). We would also like to thank all the school doctors and teachers, and all the children and parents who contributed to this study.

This study was supported by a research grant from the European Union QLRT 1999-01391, by a research grant of the Swiss State Secretariat for Education and Research (BBW-01.0592), of the Swiss National Research Foundation (NF-32-100324), and of the Kuehne-Foundation, Switzerland, and by funding from the Swedish Foundation for Health Care Science and Allergy Research.

References

1 Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997; **10**:6–12.
2 Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? *Thorax* 1994; **49**:171–4.
3 Bolte G, Frye C, Hoelscher B, Meyer I, Wjst M, Heinrich J. Margarine consumption and allergy in children. *Am J Respir Crit Care Med* 2001; **163**:277–9.
4 Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005; **115**:1109–17; quiz 1118.
5 Riedler J, Braun-Fahrländer C, Eder W *et al.* Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001; **358**:1129–33.
6 Radon K, Windstetter D, Eckart J *et al.* Farming exposure in childhood, exposure to markers of infections and the development of atopy in rural subjects. *Clin Exp Allergy* 2004; **34**:1178–83.
7 Barnes M, Cullinan P, Athanasaki P *et al.* Crete: does farming explain urban and rural differences in atopy? *Clin Exp Allergy* 2001; **31**:1822–8.
8 Perkin MR, Strachan DP. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? *J Allergy Clin Immunol* 2006; **117**:1374–81.
9 Wickens K, Lane JM, Fitzharris P *et al.* Farm residence and exposures and the risk of allergic diseases in New Zealand children. *Allergy* 2002; **57**:1171–9.
10 Remes ST, Iivanainen K, Koskela H, Pekkanen J. Which factors explain the lower prevalence of atopy amongst farmers' children? *Clin Exp Allergy* 2003; **33**:427–34.
11 Isolauri E. The use of probiotics in paediatrics. *Hosp Med* 2000; **61**:6–7.
12 Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001; **357**:1076–9.
13 Alfven T, Braun-Fahrlander C, Brunekreef B *et al.* Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle – the PARSIFAL study. *Allergy* 2006; **61**:414–21.
14 Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999; **353**:1485–8.
15 Asher MI, Keil U, Anderson HR *et al.* International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; **8**:483–91.
16 Ublagger E, Schreuer M, Eder W *et al.* Validation of questions on asthma and wheeze in farming and anthroposophic children. *Clin Exp Allergy* 2005; **35**:1033–9.
17 Sharp SJ. Meta-analysis regression. In: Stata-technical-bulletin ed. College Station, TX: StataCorp LP, 1998; 16–22.
18 Filipiak B, Heinrich J, Schafer T, Ring J, Wichmann HE. Farming, rural lifestyle and atopy in adults from southern Germany – results from the MONICA/KORA study Augsburg. *Clin Exp Allergy* 2001; **31**:1829–38.
19 Gassner-Bachmann M, Wüthrich B. Bauernkinder leiden selten an Heuschnupfen und Asthma. *Dtsch Med Wschr* 2000; **125**:924–31.
20 Klintberg B, Berglund N, Lilja G, Wickman M, van Hage-Hamsten M. Fewer allergic respiratory disorders among farmers' children in a closed birth cohort from Sweden. *Eur Respir J* 2001; **17**:1151–7.
21 Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy* 2000; **30**:194–200.
22 Downs SH, Marks GB, Mitakakis TZ, Leuppi JD, Car NG, Peat JK. Having lived on a farm and protection against allergic diseases in Australia. *Clin Exp Allergy* 2001; **31**:570–5.
23 Portengen L, Sigsgaard T, Omland O, Hjort C, Heederik D, Doekes G. Low prevalence of atopy in young Danish farmers and farming students born and raised on a farm. *Clin Exp Allergy* 2002; **32**:247–53.
24 Allerberger F, Friedrich AW, Grif K *et al.* Hemolytic-uremic syndrome associated with enterohemorrhagic *Escherichia coli* O26:H infection and consumption of unpasteurized cow's milk. *Int J Infect Dis* 2003; **7**:42–5.
25 Noverr MC, Falkowski NR, McDonald RA, McKenzie AN, Huffnagle GB. Development of allergic airway disease in mice

following antibiotic therapy and fungal microbiota increase: role of host genetics, antigen, and interleukin-13. *Infect Immun* 2005; **73**:30–8.

26 Hooper LV, Gordon JI. Commensal host–bacterial relationships in the gut. *Science* 2001; **292**:1115–8.

27 Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 2005; **122**: 107–18.

28 Noverr MC, Noggle RM, Toews GB, Huffnagle GB. Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. *Infect Immun* 2004; **72**:4996–5003.

29 Hebeisen DF, Hoeflin F, Reusch HP, Junker E, Lauterburg BH. Increased concentrations of omega-3 fatty acids in milk and platelet rich plasma of grass-fed cows. *Int J Vitam Nutr Res* 1993; **63**:229–33.

30 Hauswirth CB, Scheeder MR, Beer JH. High omega-3 fatty acid content in alpine cheese: the basis for an alpine paradox. *Circulation* 2004; **109**:103–7.

31 McKeever TM, Britton J. Diet and asthma. *Am J Respir Crit Care Med* 2004; **170**:725–9.

32 von Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998; **351**:862–6.

33 Wijga AH, Smit HA, Kerkhof M *et al*. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: the PIAMA birth cohort study. *Thorax* 2003; **58**:567–72.

34 Woods RK, Walters EH, Raven JM *et al*. Food and nutrient intakes and asthma risk in young adults. *Am J Clin Nutr* 2003; **78**:414–21.

35 Dunder T, Kuikka L, Turtinen J, Rasanen L, Uhari M. Diet, serum fatty acids, and atopic diseases in childhood. *Allergy* 2001; **56**:425–8.