# Which aspects of the farming lifestyle explain the inverse association with childhood allergy?

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**Background: Farmers' children have a reduced prevalence of allergic disorders. The specific protective environmental factors responsible are not yet identified.**
**Objective: We sought to determine whether farmers' children in the rural county of Shropshire, England, have a reduced risk of atopy and, if so, to identify the factors responsible.**
**Methods: The Study of Asthma and Allergy in Shropshire was a 2-stage cross-sectional study. In stage 1 a questionnaire to elicit allergic status, diet, and farming exposure was completed by the parents of 4767 children. In stage 2 a stratified subsample of 879 children underwent skin prick testing and measurement of domestic endotoxin.**
**Results: Compared with rural nonfarming children, farmers' children had significantly less current asthma symptoms (adjusted odds ratio (OR), 0.67; 95% CI, 0.49-0.91; $P = .01$) and current seasonal allergic rhinitis (adjusted OR, 0.50; 95% CI, 0.33-0.77; $P = .002$) but not current eczema symptoms (adjusted OR, 0.91; 95% CI, 0.68-1.21; $P = .53$) or atopy (adjusted OR, 0.68; 95% CI, 0.40-1.16; $P = .15$). In contrast, current unpasteurized milk consumption was associated with significantly less current eczema symptoms (adjusted OR, 0.59; 95% CI, 0.40-0.87; $P = .008$) and a greater reduction in atopy (adjusted OR, 0.24; 95% CI, 0.10-0.53; $P = .001$). The effect was seen in all children, independent of farming status. Unpasteurized milk consumption was associated with a 59% reduction in total IgE levels ($P < .001$) and higher production of whole blood stimulated IFN-$\gamma$ ($P = .02$).**
**Conclusion: Unpasteurized milk consumption was the exposure mediating the protective effect on skin prick test positivity. The effect was independent of farming status and present with consumption of infrequent amounts of unpasteurized milk.**
**Clinical implications: Unpasteurized milk might be a modifiable influence on allergic sensitization in children.**
**(J Allergy Clin Immunol 2006;117:1374-81.)**

***Key words:*** *Atopy, farm, unpasteurized milk, skin prick tests, children*

Environmental and occupational respiratory disorders

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Supported through a Wellcome Research Training Fellowship in Clinical Epidemiology (grant no. 056906/Z/99/Z) held by Dr Perkin.
Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.
Received for publication October 12, 2005; revised March 8, 2006; accepted for publication March 10, 2006.
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0091-6749/$32.00

doi:10.1016/j.jaci.2006.03.008

*Abbreviation used*
OR: Odds ratio

In 1996, Braun-Fahrländer et al[1,2] first reported that Swiss farmers' children have less allergy than other rural children. This observation has been replicated several times in Alpine farming communities[3-6] and in other countries, including Australia,[7] Finland,[8-10] and Canada.[11] Reduction in both parent- and child-reported symptoms and objective measures, such as skin prick positivity, have been observed. Some studies have found a stronger protective effect for those children in contact with livestock.[3,4,10] Other factors found to be protective have included barn exposure.[5] Period of exposure to the farm environment might also be important, with 2 studies suggesting that exposure at less than 1 year of age was particularly relevant,[5,12] although the authors of a study in Finland thought this might have been overemphasized.[10] Another significant factor appeared to be consumption of farm milk[5] or unpasteurized milk,[13] but a more recent study failed to confirm this.[10] None of these factors definitively explains the farming effect.

We have undertaken the first study of farmers' children in the United Kingdom. We were interested to know whether the more industrialized style of farming might still be associated with a protective effect and to look in more detail at what might be mediating the effect.

## METHODS

### Study participants

The Study of Asthma and Allergy in Shropshire took place in 2 stages. Shropshire was chosen because it was believed to have a mix of farming types. An initial questionnaire was sent to all the children in rural primary schools with significant numbers of farming children attending. The aim was to identify parent-reported symptoms of asthma, eczema, and allergic rhinitis by using questions from the International Study of Asthma and Allergy in Childhood.[14] A food-frequency questionnaire that asked about several foods, including fresh fruit and unpasteurized milk consumption, was included. In total, 7226 questionnaires were distributed to all the children in 73 schools (with an estimate of 821 farmers' children, 11.4%).

After the identification of the farmers' children from the primary survey, a stratified subsample of parents who replied from the 46 schools with the highest numbers of farmers' children were sent invitations to participate in the second stage of the study. This had several components: a detailed environmental questionnaire; allergy tests, including skin prick testing, a visible eczema examination, weight and height measurements, and venipuncture; and dust sample collection from the child's home to measure endotoxin and domestic allergen levels.

A stratified sampling technique was used to ensure a balance of animal exposure among the participating farming and nonfarming children. The subsample consisted of 4 strata: all the farmers' children who had replied to the initial questionnaire; children with current horse exposure, pony exposure, or both; children with current farm animal exposure (despite not having parents working on a farm); and children with no significant current animal contact outside the home (ignoring cats and dogs). The sampling ensured that the study population consisted of the 4 strata in the following ratio: 50%:12.5%:12.5%:25%, respectively.

## Skin prick testing

Skin prick testing was undertaken on the volar surface of one forearm with the following allergens (ALK-Abelló, Hørsholm, Denmark): dog hair, cat hair, horse hair, cow hair, 6-grass mix, house dust mite *(Dermatophagoides pteronyssinus)*, *Acarus siro*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, and positive and negative controls. The mean of the maximum diameter of the wheal and the midmaximum perpendicular diameter were measured after 15 minutes. For the primary outcome, a positive response was a 3-mm or larger mean wheal diameter (as per the European Academy of Allergology and Clinical Immunology [EAACI] recommendations).[15] As a secondary outcome, we investigated using any sized response.

## Endotoxin measurement

The homes of the examined children were visited to collect a dust sample from the living room for measurement of endotoxin and domestic allergens. Samples were kept refrigerated before being posted to the North West Lung Research Centre (Manchester, United Kingdom), where both allergen and endotoxin were analyzed from the same filter. Endotoxin content of the dust samples was determined by using the Endosafe Limulus Amebocyte Lysate assay (Charles River Laboratories, Wilmington, Mass).[16,17] Results are expressed as endotoxin units per milligram of fine dust.

## Blood sampling

Ten milliliters of venous blood was drawn after achievement of local anesthesia (amethocaine 4% gel; Smith & Nephew Healthcare Limited, Hull, United Kingdom). The blood taken was analyzed by the Protein Reference and Immunopathology Unit at St George's Hospital Medical School. Total IgE was measured with a fluorescence enzyme immunoassay (Pharmacia AutoCap; Pharmacia, Uppsala, Sweden). Whole-blood cytokine assays were undertaken to measure the secretion of IFN-γ in picograms per milliliter after stimulation with 5 μg/mL PHA (PHA-L; Sigma-Aldrich Company Limited, Gillingham, United Kingdom). IFN-γ was measured with a commercial Quantikine kit (R&D Systems Europe Limited, Abingdon, United Kingdom).

## Statistical analysis

The analysis was done with STATA 8.0 (Statacorp, College Station, Tex).[18] Logistic regression (*logistic* command) was used to adjust for confounding in the primary survey. A weighted analysis (*svyset* command) was used for the second stage of the study, with the individual weights assigned to the children being the inverse of their probability of being sampled and the 4 strata being those already defined above.

For the second-stage analysis, the *svylogit* command was used to perform logistic regression, and the *svyregress* command was used to fit linear regression models for complex survey data. IgE was not normally distributed and was therefore incorporated into the linear regression models log transformed. Approximately one third of the children had IFN-γ results at the upper end of the reference range. Log transformation did not normalize the distribution of the residuals in the linear regression analysis, and therefore the IFN-γ results were grouped (<300, 300-499, 500-999 and ≥1000 pg/mL) and analyzed with the *svytab* command in Stata. For the logistic and linear regression analyses, adjustment was made for variables known to potentially confound the relationship with atopy (age, sex, breast-feeding, family history of atopy, and number of older and younger siblings).

A meta-analysis was undertaken of the existing published farming studies to derive pooled estimates of effect for current asthma, eczema, allergic rhinitis, and atopy. Eligible studies were those identified in a systematic review of MEDLINE (1966-December 2004) and EMBASE (1980-December 2004) databases examining the influence of farm exposure in childhood on allergic status, supplemented with manual searches and articles known to the authors. Adjusted effect estimates were used where these were given in preference to crude effect estimates. Fixed-effects analysis was used unless there was a statistically significant test for heterogeneity, in which case a random-effects model was used.

## Ethical approval

Ethical approval to undertake the study was obtained from the Shropshire Research Ethics Committee. Permission to visit the schools was obtained from the Senior Primary Advisor for Shropshire County Council.

## Role of the funding source

The study was funded through a Wellcome Research Training Fellowship in Clinical Epidemiology (grant no. 056906/Z/99/Z) held by Dr Perkin. The Wellcome Trust had no direct role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the article for publication.

# RESULTS

A response rate of 66.0% (4767/7226) was achieved from the primary survey. This was less than had been anticipated; however, distribution of the questionnaires coincided with the worst flooding in Shropshire since 1947. Invitations to participate in the second stage of the study were sent to 1458 children, of whom 1073 (73.6%) replied and 944 (64.7%) consented to participate in one or more parts of the second stage. The actual number participating in the allergy tests was 879 (60.3%), with the difference of 65 children being accounted for by children on holiday or on sick leave (n = 40), refusing to participate on the day (n = 4), with insufficient time to test (n = 9), who left the school (n = 4), who mislaid the consent form (n = 1), and who consented dust sample collection only (n = 7). Children participating in the clinical allergy tests were similar in allergy prevalence to those not invited (current eczema: participated, 13.4%; not invited, 14.0%).

## Demographic differences

Respondents to the questionnaires were classified into one of 3 groups: farming children whose parents live and work on a farm (n = 535), laborer's children whose parents work on a farm but do not live on a farm (n = 281), and control children (n = 3951). Significant differences

**TABLE I.** Demographic profile of respondents to the initial questionnaire

| | Control subjects' prevalence, % (n) | Laborers' children's prevalence, % (n) | Farm children's prevalence, % (n) | $\chi^2$ Test for heterogeneity between farming groups |
|---|---|---|---|---|
| Pets inside the house | | | | |
| Currently | | | | |
| Any household pets | 70.4 (2748) | 72.6 (199) | 63.2 (330) | *P* = .002 |
| Dog | 39.4 (1539) | 46.0 (126) | 46.2 (241) | *P* = .002 |
| Cat | 37.2 (1451) | 40.5 (111) | 32.4 (169) | *P* = .04 |
| First year of life | | | | |
| Any household pets | 59.4 (2117) | 68.2 (165) | 56.2 (264) | *P* = .008 |
| Dog | 35.6 (1268) | 41.7 (101) | 40.8 (192) | *P* = .02 |
| Cat | 33.8 (1205) | 38.8 (94) | 28.5 (134) | *P* = .01 |
| Contact with animals outside the house | | | | |
| Currently | | | | |
| Any animal contact outside the house | 71.8 (2831) | 89.7 (252) | 96.8 (518) | *P* < .001 |
| Dog | 51.1 (2017) | 69.0 (194) | 85.4 (457) | *P* < .001 |
| Cat | 37.3 (1471) | 50.5 (142) | 62.1 (332) | *P* < .001 |
| Horse or pony | 17.0 (670) | 28.5 (80) | 35.3 (189) | *P* < .001 |
| Farm animals | 12.8 (505) | 50.9 (143) | 89.5 (479) | *P* < .001 |
| First year of life | | | | |
| Any animal contact outside the house | 58.6 (2030) | 80.9 (203) | 87.9 (442) | *P* < .001 |
| Dog | 44.3 (1535) | 64.9 (163) | 74.2 (373) | *P* < .001 |
| Cat | 31.3 (1085) | 44.6 (112) | 49.7 (250) | *P* < .001 |
| Horse or pony | 9.3 (323) | 19.5 (49) | 24.1 (121) | *P* < .001 |
| Farm animals | 11.8 (408) | 41.8 (105) | 67.3 (339) | *P* < .001 |
| Frequency with which child plays in a barn or stable | | | | |
| More than once per day | 1.0 (39) | 3.6 (10) | 7.7 (41) | *P* < .001 |
| Once per day | 1.6 (61) | 5.4 (15) | 11.1 (59) | |
| 1-6 times per week | 6.5 (252) | 18.0 (50) | 38.9 (207) | |
| Less than once per week | 33.4 (1302) | 44.6 (124) | 33.8 (180) | |
| Never | 57.6 (2244) | 28.4 (79) | 8.5 (45) | |
| Environmental | | | | |
| Breast-feeding | | | | |
| Ever | 68.9 (2698) | 67.5 (189) | 77.7 (410) | *P* < .001 |
| Duration (mo)† | 4.71 | 4.13 | 5.26* | *P* < .05* |
| Exclusive duration† | 2.75 | 2.69 | 2.85 | |
| Parental history of allergy | 57.7 (2277) | 45.9 (129) | 47.3 (253) | *P* < .001 |
| Family size, no. of children‡ | 2.51 | 2.58 | 2.65 | |
| Unpasteurized milk consumption | | | | |
| Never | 90.7 (3384) | 69.6 (185) | 58.2 (304) | *P* < .001 |
| Less than once per week | 3.7 (137) | 6.0 (16) | 5.6 (29) | |
| 1-2 times per week | 1.2 (43) | 1.9 (5) | 2.7 (14) | |
| 3-6 times per week | 0.8 (29) | 1.9 (5) | 3.3 (17) | |
| Once per day or more | 3.7 (137) | 20.7 (55) | 30.3 (158) | |

*ANOVA.
†Geometric mean.
‡Arithmetic mean.

were found in a number of environmental factors, particularly animal contact (Table I). Farmers' children were least likely to have pets inside the house, this being accounted for by having fewer cats in the house. They were most likely to have contact with all types of animals outside the house. However, 13% of control children were having regular contact with farm animals. Exposure to barns and stables was highly correlated with farming status, but 9% of control children were playing in barns or stables once a week or more.

There were marked differences in the family history of allergic disorders, with farm children least likely to have a parental history of allergies.

As expected, unpasteurized milk consumption increased from control subjects to farm children; however, approximately 10% of the control children were drinking unpasteurized milk, including 4% (137 children) who were drinking it daily.

## Farming status and allergy disease prevalence

Farmers' children had significantly less current asthma and current seasonal allergic rhinitis (Table II) both before and after adjustment for known confounding variables. The odds ratio (OR) for skin prick positivity was consistent with that for asthma symptoms, but with the smaller

**TABLE II.** Association of farming with allergic disease

| | Prevalence, % (n/N)* | Crude OR (95% CI)* | *P* value | Adjusted OR (95% CI)† | *P* value |
|---|---|---|---|---|---|
| Questionnaire | | | | | |
| Current asthma symptoms | | | | | |
| Control subjects | 15.7 (592/3777) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Laborers' children | 15.8 (42/266) | 1.01 (0.72-1.42) | .96 | 1.10 (0.78-1.56) | .59 |
| Farm children | 10.3 (52/503) | 0.62 (0.46-0.84) | .002 | 0.67 (0.49-0.91) | .01 |
| Current seasonal rhinitis | | | | | |
| Control subjects | 9.6 (365/3806) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Laborers' children | 6.7 (18/268) | 0.68 (0.42-1.11) | .12 | 0.76 (0.46-1.25) | .28 |
| Farm children | 4.7 (24/510) | 0.47 (0.30-0.71) | <.001 | 0.50 (0.33-0.77) | .002 |
| Current eczema symptoms | | | | | |
| Control subjects | 13.5 (512/3794) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Laborers' children | 12.7 (34/267) | 0.94 (0.65-1.36) | .73 | 0.99 (0.68-1.44) | .96 |
| Farm children | 12.0 (61/509) | 0.87 (0.66-1.16) | .11 | 0.91 (0.68-1.21) | .53 |
| Examination‡ | | | | | |
| Positive skin prick test result (any response) | | | | | |
| Control subjects | 26.2 (121/422) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Laborers' children | 29.6 (35/118) | 1.18 (0.72-1.95) | .51 | 1.24 (0.75-2.05) | .41 |
| Farm children | 19.4 (48/246) | 0.68 (0.44-1.05) | .08 | 0.68 (0.43-1.07) | .10 |
| Positive skin prick test result (≥3-mm mean response) | | | | | |
| Control subjects | 17.9 (81/422) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Laborers' children | 19.5 (23/118) | 1.12 (0.63-1.97) | .71 | 1.16 (0.65-2.06) | .62 |
| Farm children | 13.0 (32/246) | 0.69 (0.41-1.14) | .14 | 0.68 (0.40-1.16) | .15 |

*For subjects with complete covariate data included in the adjusted logistic regression model.
†Adjusted by using multiple logistic regression for age, sex, number of younger siblings, number of older siblings, breast-feeding duration, and parental history of allergy.
‡Prevalence percentages are weighted results for the skin prick test data.

numbers, it was not statistically significant. There was no significant reduction in current eczema symptoms.

The prevalence of sensitization to each allergen tested is presented in Table E1 in the Online Repository at www.jacionline.org for the 809 children who underwent skin prick testing. In examining the responses to individual allergens (using a 3-mm or greater mean response), farming children, compared with control children, had the lowest rates of sensitization to domestic pets (dog, 1.6% vs 2.4%; cat, 2.0% vs 6.3%) and house dust (3.6% vs 6.3%). Horse sensitization was reduced (1.6% vs 2.6%). They did not have a statistically significant increase in sensitization to environmental allergens prevalent on farms (cow, 1.2% vs 0.3%) and storage mites (4.0% vs 2.9%) and grass mix (6.3% vs 6.6%). In comparison, the laborers' children had the highest sensitization rates for all the allergens except *L destructor*.

## Protective effect on skin prick test positivity

We used weighted logistic regression to explore which factors in the children's environment might be affecting skin prick test positivity (Table III). The crude OR for the farming children in Table III is different from that in Table II because Table III only includes 683 children with complete covariate data for all the variables in the table. However, it is clear that farming status per se is not associated with a protective effect on atopy, with any effect being completely removed in the fully adjusted model.

We had insufficient pure arable farmers to assess their children as a separate group. Exposure to farm animals was strongly associated with farming status. However, neither early nor current farm animal exposure was associated with a protective effect on atopy, either in the crude analysis or after adjustment for other confounding variables.

Similarly, exposure to playing in a barn or stable was not associated with a significant protective effect on atopy, and the OR became closer to 1.0 after adjustment for other confounding variables.

Endotoxin exposure was also strongly related to farming status, with geometric mean levels in farm children of 48.9 IU/L ($P < .001$ vs control subjects), in farm laborers' children of 38.9 IU/L ($P = .01$ vs control subjects), and in control children of 33.2 IU/L. In the crude regression analysis the relationship with skin prick test positivity for endotoxin, although having an OR of less than 1, was not statistically significant, and the effect again diminished after adjustment for confounding variables.

## Unpasteurized milk

In contrast to the other factors above, unpasteurized milk consumption was associated with a significant 70% reduction in prevalence of skin prick test positivity, and this effect was little changed after adjustment for the other factors (Table III). Fig 1 indicates that the protective effect was apparent in all 3 groups of children defined by farming status. This consistent protective effect was not apparent

**TABLE III.** Environmental factors and their association with skin prick positivity (≥3-mm wheal)

| | Crude OR (95% CI)† | *P* value | Model 1 OR (95% CI)‡ | *P* value | Model 2 OR (95% CI)§ | *P* value |
|---|---|---|---|---|---|---|
| Farming status | | | | | | |
| Control subjects | 1.0 (Baseline) | | 1.0 (Baseline) | | 1.0 (Baseline) | |
| Laborers' children | 0.89 (0.44-1.78) | .73 | 0.93 (0.47-1.86) | .84 | 1.32 (0.66-2.69) | .42 |
| Farm children | 0.68 (0.37-1.24) | .21 | 0.65 (0.35-1.22) | .18 | 1.00 (0.49-2.05) | 1.0 |
| Early farm animal exposure | 0.58 (0.32-1.05) | .07 | 0.53 (0.29-0.99) | .05 | 0.71 (0.37-1.35) | .29 |
| Current farm animal exposure | 0.82 (0.47-1.45) | .49 | 0.85 (0.45-1.59) | .61 | 1.27 (0.65-2.46) | .50 |
| Barn or stable exposure* | 0.96 (0.86-1.06) | .40 | 0.97 (0.87-1.08) | .55 | 1.02 (0.93-1.13) | .65 |
| Endotoxin exposure* | 0.94 (0.59-1.49) | .79 | 0.98 (0.64-1.48) | .91 | 0.99 (0.65-1.51) | .96 |
| Organic food consumption* | 0.94 (0.48-1.85) | .86 | 0.93 (0.44-1.97) | .86 | 1.10 (0.56-2.16) | .78 |
| Farm/garden fruit consumption* | 0.56 (0.28-1.12) | .10 | 0.53 (0.26-1.10) | .09 | 0.60 (0.28-1.32) | .21 |
| Farm/garden vegetable consumption* | 0.66 (0.31-1.40) | .28 | 0.61 (0.28-1.34) | .22 | 1.19 (0.51-2.76) | .68 |
| Farm/garden egg consumption* | 0.78 (0.38-1.59) | .50 | 0.65 (0.32-1.36) | .25 | 1.03 (0.47-2.26) | .94 |
| Farm/garden meat consumption* | 0.44 (0.24-0.83) | .01 | 0.43 (0.23-0.80) | .007 | 0.60 (0.31-1.16) | .13 |
| Unpasteurized milk consumption* | 0.19 (0.08-0.44) | <.001 | 0.20 (0.09-0.44) | <.001 | 0.27 (0.12-0.60) | .001 |

*Change in OR per unit increase in variable: barn or stable exposure (frequency played in per week), endotoxin (natural log unit of international units per milligram of dust for endotoxin), and diet (yes or no).
†For subjects with complete covariate data included in the logistic regression.
‡Adjusted by using logistic regression for farming status, age, sex, number of younger siblings, number of older siblings, breast-feeding duration, and parental history of allergy.
§Adjusted by using logistic regression for farming status, age, sex, number of younger siblings, number of older siblings, breast-feeding duration, and parental history of allergy and other variables in the table.



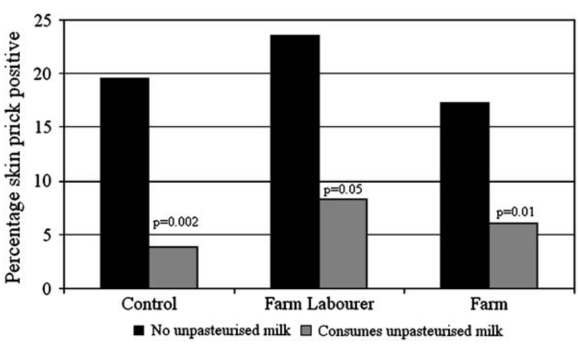


**FIG 1.** Protective effect of current unpasteurized milk consumption on skin prick test positivity.

for any other food assessed in the food-frequency questionnaire.

In Table IV we investigated further the effect of unpasteurized milk consumption on other allergic conditions, including whether there was any evidence for a dose-response relationship. There was no obvious effect on current asthma. Current seasonal allergic rhinitis was significantly reduced in the crude analysis, but the effect weakened when adjusted for confounding. However, if unpasteurized milk was included in a logistic model as a continuous variable (number of times consumed per week), there was a strong protective association with current seasonal allergic rhinitis (adjusted OR, 0.90; 95% CI, 0.83-0.97; $P = .004$). When both unpasteurized milk (as a continuous variable) and farming status were included in the logistic model together, both remained statistically significant (unpasteurized milk: adjusted OR of 0.92, 95% CI of 0.85-0.998, $P = .045$; farm child: adjusted OR of 0.59, 95% CI of 0.38-0.92, $P = .02$).

Current eczema symptom prevalence was significantly reduced in both the crude and adjusted analysis, regardless of the frequency of consumption.

The significant reduction in atopy was robust to the definition of a positive skin prick test response and occurred regardless of the frequency of consumption. The reduction was present for both indoor (house dust mite) and outdoor (grass pollen) allergens. This protective effect was also seen in the measurement of the children's total IgE levels. Children consuming any unpasteurized milk had a 59% reduction in geometric mean total IgE levels (68.6 kU/L vs 28.1 kU/L, $P < .001$ adjusted for the usual confounding variables). Similarly, children drinking unpasteurized milk were producing higher levels of IFN-γ (<300, 300/499, 500/999, and ≥1000 pg/mL: unpasteurized milk consumed: 16%, 19%, 14%, and 50%, respectively; unpasteurized milk not consumed: 32%, 13%, 24%, and 31%, respectively; $P = .02$, Pearson $\chi^2$ test).

## DISCUSSION

Our study found a significantly lower prevalence among farmers' children of current asthma and seasonal allergic rhinitis symptoms but not current eczema symptoms. A nonsignificant reduced rate of atopy among farming children was also observed. However, the effect estimate for atopy was consistent with a meta-analysis of the published farming studies to date (our effect, 0.68; fixed effects pooled estimate, 0.59; 95% CI, 0.52-0.68; $P < .001$).[2,4,5,7,10-13] Similar consistency was also shown for current asthma (our effect, 0.67; fixed effects pooled estimate, 0.71; 95% CI, 0.64-0.80;

**TABLE IV.** Association of frequency of unpasteurized milk consumption and current allergic symptoms and atopy

| | Prevalence, % (n/N)* | Crude OR (95% CI)* | *P* value | Adjusted OR (95% CI)† | *P* value |
|---|---|---|---|---|---|
| Questionnaire | | | | | |
| Current asthma symptoms | | | | | |
| None | 15.6 (579/3717) | 1.00 (Baseline) | | 1.99 (Baseline) | |
| Infrequent§ | 14.4 (33/230) | 0.91 (0.62-1.33) | .62 | 1.02 (0.69-1.50) | .93 |
| Frequent‖ | 11.9 (45/377) | 0.73 (0.53-1.02) | .06 | 0.90 (0.64-1.27) | .55 |
| Current seasonal allergic rhinitis | | | | | |
| None | 9.4 (351/3745) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Infrequent§ | 8.6 (20/233) | 0.91 (0.57-1.45) | .69 | 1.06 (0.66-1.72) | .80 |
| Frequent‖ | 4.5 (17/379) | 0.45 (0.28-0.75) | .002 | 0.61 (0.36-1.02) | .06 |
| Current eczema symptoms | | | | | |
| None | 14.2 (531/3731) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Infrequent§ | 8.2 (19/233) | 0.54 (0.33-0.86) | .01 | 0.54 (0.33-0.88) | .01 |
| Frequent‖ | 9.0 (34/379) | 0.59 (0.41-0.85) | .005 | 0.59 (0.40-0.87) | .008 |
| Examination‡ | | | | | |
| Positive skin prick test result (any response) | | | | | |
| None | 29.2 (177/590) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Infrequent§ | 4.1 (5/62) | 0.10 (0.04-0.29) | <.001 | 0.10 (0.03-0.28) | <.001 |
| Frequent‖ | 12.8 (19/111) | 0.35 (0.18-0.70) | .003 | 0.34 (0.17-0.69) | .003 |
| Positive skin prick test result (≥3-mm mean response) | | | | | |
| None | 20.0 (121/590) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Infrequent§ | 2.6 (3/62) | 0.11 (0.03-0.38) | .001 | 0.10 (0.03-0.37) | .001 |
| Frequent‖ | 5.6 (9/111) | 0.24 (0.11-0.54) | .001 | 0.24 (0.10-0.53) | .001 |
| Positive house dust mite result (≥3-mm mean response) | | | | | |
| None | 7.4 (45/590) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Infrequent§ | 2.6 (3/62) | 0.34 (0.09-1.24) | .10 | 0.32 (0.08-1.24) | .10 |
| Frequent‖ | 1.9 (3/111) | 0.24 (0.07-0.84) | .03 | 0.23 (0.06-0.85) | .03 |
| Positive grass pollen result (≥3-mm mean response) | | | | | |
| None | 7.8 (61/590) | 1.00 (Baseline) | | 1.00 (Baseline) | |
| Infrequent§ | 1.1 (1/62) | 0.13 (0.02-0.99) | .05 | 0.13 (0.01-1.09) | .06 |
| Frequent‖ | 3.1 (5/111) | 0.37 (0.14-1.03) | .06 | 0.30 (0.10-0.86) | .02 |

*For subjects with complete covariate data included in the adjusted logistic regression model.
†Adjusted by using multiple logistic regression for farming status, age, sex, number of younger siblings, number of older siblings, breast-feeding duration, and parental history of allergy.
‡Prevalence percentages are weighted results for the skin prick test data.
§Consumed 2 times a week or less.
‖Consumed 3 times a week or more.



$P < .001$).[2-5,7,9,11-13,19] and current eczema (our effect, 0.91; fixed effects pooled estimate, 0.97; 95% CI, 0.83-1.12).[3,9,12] Our effect for seasonal allergic rhinitis was at the lower end of the reference range of the pooled meta-analysis (our effect, 0.50; random effects pooled estimate for current hay fever symptoms, 0.64; 95% CI, 0.49-0.85; $P = .002$).[2-5,7,9,12,13]

Our findings suggest that multiple factors are underlying these protective effects among farming children on the basis of the different patterns seen for farming status and unpasteurized milk consumption. Unpasteurized milk was inversely associated with current eczema symptoms and atopy but not with current asthma symptoms, and the effect on seasonal rhinitis was of borderline statistical significance and dependent on how the unpasteurized milk consumption was classified. This contrasts with the protective effect of farming status on asthma, rhinitis, and atopy but not eczema. For current seasonal allergic rhinitis, confirmation that multiple factors were operating in the farm environment was indicated by the separate protective effects seen for farming status and unpasteurized milk when they were incorporated together in the same model.

The association of unpasteurized milk with objective measures, including skin prick tests, serum total IgE levels, and IFN-γ production in the stimulated whole-blood assay, suggests that the protective effect is a genuine phenomenon and not simply reflecting a diagnostic bias among the farming children.

In our logistic model incorporating all the variables of interest for atopy, it was notable that farming status per se, early and current farm animal exposure, barn or stable exposure,[5] and endotoxin exposure[6] all proved to be non-significant. In contrast, the protective effect of unpasteurized milk consumption was remarkably robust to extensive adjustment. It does, however, remain possible that there are other as-yet-unidentified confounding factors in the farming environment that might be responsible for the observed association between unpasteurized milk consumption and atopy.

Von Ehrenstein et al[3] observed a protective effect of whole milk consumption on asthma and hay fever but did not have data on unpasteurized milk consumption. Riedler et al[5] assessed the exposure of farm milk at different stages of a child's life (first year of life, 1-4 years of age, and older life). Early farm milk exposure was associated with a reduced prevalence of atopy (0.43; 95% CI, 0.24-0.77). No effect was seen for farm milk consumption beyond the first year of life. No mention is made of the specific effect of farm milk on eczema. Our finding is consistent with that of Wickens et al,[13] who, despite the study being very small, found a strong protective effect of unpasteurized milk consumption in the first 2 years of life on ever having had eczema (OR, 0.2; 95% CI, 0.1-0.8).

We chose to only enquire about current unpasteurized milk consumption. This is because, like Remes et al,[10] we have reservations about how many mothers would be feeding their infants unpasteurized milk in the first year of life when it is specifically recommended to avoid cow's milk in infancy in the United Kingdom.

We were unable to show any clear evidence of a dose-response relationship for the relationship with atopy or eczema. For house dust mite sensitization, there was a weak dose-response relationship, but the number of children in the infrequent consumption group was relatively small, and the CIs were therefore broad. It might be that even relatively infrequent exposure to unpasteurized milk is sufficient to have a protective effect. Unpasteurized milk is known to be rich in a variety of gram-negative species and their lipopolysaccharides, and it is plausible that a persistent exposure to a diverse milieu of bacteria from an early age is likely to have an effect on the developing immune system.[20] Unpasteurized milk can also contain lactobacilli, and our finding of a protective effect for eczema is consistent with the evidence of a protective effect of lactobacilli- and *Bifidobacterium* species–containing probiotics on eczema.[21]

Historically, there has been a marked decrease in unpasteurized milk consumption in the developed world, particularly in the latter half of the 20th century and in urban areas. Unpasteurized milk consumption might explain the protective effect of farming on atopy seen in other studies. However, this is a cross-sectional study, as are all the studies that have reported associations with farm or unpasteurized milk published to date. These associations do not confirm a causal relationship, and further investigation to identify specific protective agents or mechanisms is required. In addition, cohort studies are necessary to clarify the temporal sequence of exposure and outcome. This would identify critical periods of childhood when exposure to these putative protective agents or mechanisms might operate. However, it is important to mention that unpasteurized milk consumption is not hazard free, and milk-related outbreaks of *Cryptosporidium* species,[22] *Campylobacter* sepcies,[23] and *Escherichia coli* O157[24] have all been described. It is thus premature to recommend unpasteurized milk as a putative protective agent for allergic diseases.

Environmental and occupational respiratory disorders

We thank all the mothers and children who took part and the schools for their cooperation and help in recruitment. The fieldwork was undertaken by the author with the assistance of Kathryn Dovaston (research nurse) and Sarah Amatt and Vicky Stephenson (research assistants). We thank Professors Robert Niven and Adnan Custovic and Gael Tavernier and Mark Craven of the Respiratory Unit, Wythenshawe Hospital, for the measurement of endotoxin and domestic allergens. We thank Andrew Wise of the Protein Reference Unit, St George's Hospital, for the measurement of total IgE and the cytokine assays.

## REFERENCES

1. Braun-Fahrländer Ch, Gassner M, Sennhauser FH, Wüthrich B. the SCARPOL Team. Lower risk of allergic sensitization and hay fever in farmers' children in Switzerland. Epidemiology 1996;7 (suppl):S47.
2. Braun-Fahrländer Ch, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS, et al. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. Clin Exp Allergy 1999;29:28-34.
3. von Ehrenstein OS, von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. Clin Exp Allergy 2000;30:187-93.
4. 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.
5. Riedler J, Braun-Fahrländer C, Eder W, Schreuer M, Waser M, Maisch S, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet 2001;358:1129-33.
6. Braun-Fahrländer C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. N Engl J Med 2002;347:869-77.
7. 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.
8. Kilpeläinen M, Terho EO, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. Clin Exp Allergy 2000;30:201-8.
9. Remes ST, Pekkanen J, Soininen L, Kajosaari M, Husman T, Koivikko A. Does heredity modify the association between farming and allergy in children? Acta Paediatr 2002;91:1163-9.
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. Ernst P, Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on a farm. Am J Respir Crit Care Med 2000;161:1563-6.
12. Klintberg B, Berglund N, Lilja G, Wickman M, Hage-Hamsten M. Fewer allergic respiratory disorders among farmers' children in a closed birth cohort from Sweden. Eur Respir J 2001;17:1151-7.
13. Wickens K, Lane JM, Fitzharris P, Siebers R, Riley G, Douwes J, et al. Farm residence and exposures and the risk of allergic diseases in New Zealand children. Allergy 2002;57:1171-9.
14. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995;8:483-91.
15. EAACI. Position paper: allergen standardization and skin tests. Allergy 1993;48:49-82.
16. Cooper JF, Weary ME, Jordan FT. The impact of non-endotoxin LAL-reactive materials on Limulus amebocyte lysate analyses. PDA J Pharm Sci Technol 1997;51:2-6.
17. Levin J, Bang FB. Clottable protein in Limulus; its localization and kinetics of its coagulation by endotoxin. Thromb Diath Haemorrh 1968;19:186-97.
18. StataCorp. Stata Statistical Software: Release 8.0. College Station (TX): Stata Corp; 2003.

19. Chrischilles E, Ahrens R, Kuehl A, Kelly K, Thorne P, Burmeister L, et al. Asthma prevalence and morbidity among rural Iowa schoolchildren. J Allergy Clin Immunol 2004;113:66-71.
20. Suhren G, Hesselbarth H, Heeschen W, Südi JI. Evaluation of the lipopolysaccharide (LPS) content as determined by the limulus test in milk and milk products II: raw milk and influences of technological procedures. Milchwissenschaft 1986;41:156-60.
21. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clin Exp Allergy 2000;30:1604-10.
22. Harper CM, Cowell NA, Adams BC, Langley AJ, Wohlsen TD. Outbreak of *Cryptosporidium* linked to drinking unpasteurised milk. Commun Dis Intell 2002;26:449-50.
23. Morgan D, Gunneberg C, Gunnell D, Healing TD, Lamerton S, Soltanpoor N, et al. An outbreak of *Campylobacter* infection associated with the consumption of unpasteurised milk at a large festival in England. Eur J Epidemiol 1994;10:581-5.
24. Allerberger F, Wagner M, Schweiger P, Rammer HP, Resch A, Dierich MP, et al. *Escherichia coli* O157 infections and unpasteurised milk. Euro Surveill 2001;6:147-51.