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Farm exposure in utero may protect against asthma, hay fever and eczema

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ABSTRACT

Objectives: To assess which factors contribute to the lower prevalence of allergic diseases in farmers' children, and the importance of timing of exposure.

Methods: In a cross-sectional questionnaire survey we assessed asthma symptoms, hay fever and eczema as well as current, early and prenatal farm-related exposures in 1,333 farmers' children and 566 reference children aged 5-17 years.

Results: Farmers' children had less asthma symptoms and eczema. Current and maternal exposure during pregnancy to animals and/or grain and hay reduced the risk of asthma symptoms, hay fever and eczema. The exposure-response association for maternal exposure was non-linear for most outcomes. After mutual adjustment the effects of prenatal exposure remained unchanged whereas current exposure remained protective only for asthma medication, 'asthma ever' and hay fever. Exposure during the first two years was not associated with symptoms after controlling for prenatal exposure. A combination of prenatal and current exposure was most strongly associated with wheeze (OR=0.48, CL=0.28-0.80), asthma medication (OR=0.50, CL=0.30-0.82), asthma ever (OR=0.50, CL=0.33-0.76), hay fever (OR=0.47, CL=0.30-0.73), and eczema (OR=0.46, CL=0.30-0.70).

Conclusions: Prenatal exposure may contribute to the low prevalence of asthma, hay fever and eczema in farmers' children, but continued exposure may be required to maintain optimal protection.

INTRODUCTION

An increasing number of studies have reported a reduced risk of atopy, hay fever, asthma and eczema in farmer's children and adolescents,[1, 2] Recent studies among adult farmers have demonstrated that protection against atopy and atopic asthma may continue into adulthood [3-5], and that long-term continual exposure may be required to maintain optimal protection.[6-8] The specific protective factors were not conclusively determined, although it was indicated that contact with livestock as well as consumption of unpasteurised milk were particularly protective.[2, 9]

The underlying immunological mechanisms involved in protective effects are still unclear, but innate immune responses are believed to play a key role. In particular, it has been hypothesised that bacterial endotoxin and/or other microbial exposures associated with animal contact and/or consumption of unpasteurised milk may activate innate immune pathways through expression of Toll-like receptors (TLRs) and CD14.[10] These exposures may thereby suppress Th_2 cell expansion and the development of IgE-antibodies and Th_2 dependent diseases, including allergic asthma, hay fever and eczema.[11] Although it has been suggested that these protective effects should primarily arise from exposures during the first years of life[12], little is known as to whether this period is critical, and/or whether later and prenatal exposures may also play a role. One recent study in Europe reported that maternal exposure to the farm environment during pregnancy was more strongly associated with atopic sensitisation and innate immunity than were current exposures.[10] These results suggest that farming-related exposures during pregnancy may modulate immune responses and possibly reduce disease occurrence in the offspring. Other studies have shown protective effects on atopy and asthma of dietary factors during pregnancy such as fish, apple and vitamin D.[13-15] The converse has been suggested for maternal smoking and prenatal exposures to insecticides.[16-18]

In this cross sectional study we assessed the effects of current, early and prenatal farming exposures in children from dairy, sheep & beef, and horticulture farms, and a rural non-farming control population.

MATERIALS AND METHODS

Study design and population

The methods for the study were based on those of the European study on atopy and asthma in farmers children, known as the PARSIFAL study.[19] The current study involved a survey of 2,509 farming families and 1,001 non-farming families of working age. In the current paper we will present the findings in children.

Farming families living in the lower half of the North Island were randomly selected from a national database of farms in New Zealand. We aimed for equal numbers of dairy, sheep & beef, and horticulture farming families. However, there are relatively fewer horticultural farms (crop farms and orchards), resulting in lower numbers for this group. A rural control group of non-farmers from the same region (adults aged 25-49) were randomly chosen from the New Zealand Electoral Roll, and those with children were included in the analyses for the current paper.

Subjects were asked to complete a postal survey for themselves and their children (if any) aged 5 – 17 years. A maximum of two children were included per household; in case the family had more than two children within the specified age range we selected the two oldest children. The oldest children were chosen because wheeze in younger children is less clearly associated with asthma.[20] Those who had not responded to the postal survey after three reminders were asked to complete the questionnaire(s) by telephone. An overview of the recruitment, exclusions, and refusals is presented in figure 1. All subjects gave written informed consent, and the study was approved by the Massey University Human Ethics Committee (WGTN protocol 02/105).

Questionnaire

The symptom prevalence was assessed by using a standardised questionnaire based on the International Study of Asthma and Allergies in Childhood (ISAAC) postal questionnaire.[21] We focussed on the following questions, “Has your child had wheezing or whistling in the chest in the past 12 months?”, “Has your child ever had asthma?”, “In the past 12 months, has your child taken any medicines, pills or other medication for asthma?”, “Has your child ever had hay fever?”, and “has your child ever had eczema?”.

In the same questionnaire we assessed “environmental” exposures such as diet, and contact with animals and/or hay and grain products. The questions used to assess farm exposures are summarised in Table 1 and focus on three time periods in the child’s life, i.e. “current”, “life-time” and “prenatal” exposures. “Current exposures” relate to exposures in the previous 12 months; “life-time exposures” relate to exposures at any stage in live, and “prenatal exposures” relate to exposures of the mother during pregnancy. For current and prenatal exposures we also assessed the frequency of the exposures and for life-time exposures we made a distinction between exposures before and after 2 years of age (Table 1). We did not collect information on life time exposure to grain and hay products and consumption of unboiled milk.

Table 1. Questions used to assessing current, life time, and prenatal farm exposures.

Type of exposure	Timing of exposure	Question*	Answers
Farm animals	Current	In the last 12 months, how often on average did your child have contact with farm animals?	never; < once a week; ≥ once a week; ≥ once a day
	Life time exposure	Does or did your child have at least once a week contact with any of the following animals (Cattle, sheep, horses, pigs, poultry, goats, working dogs) at any stage in their life?	Yes; no
		In which period did your child have regular contact (at least once a week) with these animals?	0-24 months; older than 24 months
	Prenatal exposure	How often did the mother have contact with farm animals during the pregnancy?	never; < once a week; ≥ once a week; ≥ once a day
Grain/hay	Current	In the last 12 months, how often on average did your child go into a building containing agricultural products, like grain or hay?	never; < once a week; ≥ once a week; ≥ once a day
	Prenatal exposure	How often did the mother have contact with farm animals during the pregnancy	never; < once a week; ≥ once a week; ≥ once a day
Unboiled farm milk	Current	At this time, how often does your child drink unboiled milk, fresh from the farm	never; sometimes

* Contact with animals was defined as physically touching the animals or being in a shed where the animals are housed (while the animals were in there) or being in yards at the time animals were in there.

Statistical analyses

Chi-square and t-tests were performed to test differences in prevalence and mean levels respectively. We calculated crude and adjusted prevalence odds ratios using logistic regression analyses. Since we included children from the same household (with a maximum of two) the data were not completely independent. Therefore, we applied "clustered robust standard errors"[22] using the family unit as the cluster variable.

Multiple logistic regression models were constructed by adding one exposure variable at a time, commencing with the main exposure variables (i.e. those relating to farming exposure) followed by the potential confounders that showed the strongest effects in univariate analyses. At each step, odds ratios were checked for signs of confounding, and standard errors were checked for signs of multicollinearity. Due to multicollinearity between animal exposures and grain/hay exposures we could not assess the effect of each of these exposures independently (i.e. these could not be included in the same multiple regression model). Since most evidence points toward the potential protective effects of animal contact we selected exposure to animals as the main exposure variable in the final multivariate model. The final model consisted of variables representing animal exposures at different time points (i.e. exposures in the past 12 months, exposures in the first two years and after the first two years, and exposures of the mother during pregnancy) as well as several potential confounders (age, sex, ethnicity, mother's education level, smoking in the house, farm type, and parental asthma, hay fever and eczema). Apart from exposures to grain/hay no other problems of multicollinearity were observed for any of the other exposure variables and/or confounders. In particular, agreement between variables representing animal exposures at different time points was relatively low. For example the Kappa statistic for animal contact in the last 12 months and animal contact of the mother during pregnancy was only 0.24 (95% CL, 0.22-0.26). In addition to the potential confounders noted above we also tested the following variables: number of siblings, previous and current paracetamol use, antibiotic use, current and previous cat and/or dog ownership, vaccinations, body mass index, and dietary factors. However, these did not affect the associations between farming exposure and symptoms and were therefore not included in the final model.

We also assessed the independent and joint effects of current and prenatal exposure. For that purpose we dichotomised prenatal and current exposure, with "frequent exposure" being defined as contact with animals once a day or more (compared with contact less than once a day). We subsequently made comparisons between those who were frequently exposed in both periods, those that were only currently exposed, and those who were exposed in utero but not currently; the reference group consisted of children who had no exposure in both periods.

RESULTS

The 2,509 farming families (response, 77.8%) and 1,001 reference families (response, 67.0%) that participated included 1,333 farmers' children and 566 reference children (Figure 1). Compared with the farmers' children the reference group had a higher proportion of Māori and Pacific children; they also had more smokers in the house, and more siblings or parents with asthma, hay fever, and eczema. Children of dairy farmers had more siblings than the children in the reference group (Table 2).

Symptoms were less prevalent in farmers' children, the odds ratios were statistically significant for wheeze in the last 12 months, asthma ever, and eczema ever. These effects were most pronounced for livestock farmers (Table 3). Univariate regression analyses to assess specific farming related "exposures" that could explain these differences showed that contact with farm animals in the first two years of life was inversely associated ($p<0.05$) with all symptoms; a dose-response association was also demonstrated with animal contact in the past 12 months (Table 4). Similar dose-dependent associations were found for having been in a building containing farm products such as hay and grain. Children whose mothers had frequent exposure to farm animals during pregnancy were also less likely to have symptoms, with a dose-response trend for hay fever and eczema. Current wheeze, asthma ever, and asthma medication were also less prevalent (compared to the never exposed group), but these effects were only observed for children whose mothers had been exposed infrequently (less than once a week) and frequently (at least once a day). No effect was seen for the children whose mothers had been exposed at an intermediate frequency (at least once a week, but less than once a day). A similar non-linear pattern was seen for having been in a building with farm products such as grain and hay. There were no apparent differences in risk according to the types of animals that pregnant mothers and children were exposed to (cattle, sheep, pigs, etc; data not shown). Consumption of raw milk fresh from the farm was also inversely associated with asthma symptoms, hay fever and eczema (Table 4).

Table 2. Demographic, general characteristics and exposures to farm animals and unboiled fresh farm milk stratified for farm and reference children.

	Reference	Farm (all)	horticulture	Sheep and beef	Dairy
Number of children (n)	566	1333	241	552	540
Age (years, SD)	11.00 (3.56)	11.20 (3.49)	11.44 (3.50)	11.14 (3.56)	11.15 (3.43)
Height (m, SD)	1.49 (0.22)	1.50 (0.22)	1.52 (0.20)	1.50 (0.21)	1.49 (0.22)
Weight (kg, SD)	45.97 (19.14)	45.15 (17.69)	45.28 (16.29)	44.97 (18.61)	45.28 (17.38)
Siblings (n)	2.07 (1.35)	2.06 (1.13)	1.89 (0.99)	1.98 (1.09)	2.22 (1.22)†
Sex (% males)	51.2	52.1	49.0	53.4	52.2
Ethnicity					
New Zealand European (%)	65.2	95.0†	94.6†	94.9†	95.2†
Maori (%)	32.1	4.7	4.6	5.1	4.4
Pacific Islander (%)	2.7	0.3	0.8	0.0	0.4
Maternal education					
Secondary (%)	59.4	48.7†	40.2†	46.1†	55.2
University (%)	37.1	48.6	56.8	51.0	42.6
Current smoking in the household (%)	35.8	20.3†	13.8†	24.1†	19.3†
Reported asthma in parents (%)	36.3	28.7†	25.3†	28.6†	30.3*
Reported hay fever in parents (%)	59.5	58.0	67.1*	54.3	57.2
Reported eczema in parents (%)	48.3	39.1†	40.8	37.2†	40.2†
Exposure of the child to farm animals ≥ once a week					

Never	67.9	12.1†	42.8†	5.8†	4.9†
Only in the first two years of life	13.1	63.9†	25.8†	71.2†	73.3†
Only after the first two years of life	19.0	24.0†	31.4†	23.0†	21.9†
Exposure of the child to farm animals in the last 12 months					
Never	50.9	7.7†	34.0†	1.6†	2.0†
< once a week	38.2	23.4†	41.1†	20.5†	18.4†
≥ once a week	6.0	32.4†	10.4†	36.3†	38.2†
≥ once a day	4.9	36.6†	14.5†	41.6†	41.3†
Unboiled milk from farm currently					
Yes	3.1	19.0†	0.8	5.1	41.0†
Exposure of the mother to farm animals					
Never	95.5	41.0†	83.4†	31.0†	32.1†
< once a week	1.6	11.6†	10.4†	14.0†	9.7†
≥ once a week	0.7	15.6†	0.8†	20.8†	17.0†
≥ once a day	2.1	31.8†	5.4†	34.2†	41.0†

* P<0.05; † P<0.01; compared to reference group

Table 3. Prevalence and crude odds ratios (OR) and 95% confidence intervals (CI) of asthma symptoms, hayfever and eczema in farming and reference children.

	Reference N=566	Farm (all) N=1333		Horticulture N=241		Sheep and beef N=552		Dairy N=540	
	%	%	OR [95% CI]	%	OR [95% CI]	%	OR [95% CI]	%	OR [95% CI]
Wheeze in last 12 months	25.1	19.5	0.72 [0.56-0.93]†	22.4	0.86 [0.59-1.25]	20.7	0.78 [0.58-1.05]	17.0	0.61 [0.45-0.83]†
Asthma medication in last 12 months	22.5	19.1	0.81 [0.63-1.05]	20.7	0.90 [0.61-1.35]	19.5	0.84 [0.62-1.14]	17.8	0.75 [0.54-1.03]
Asthma ever	34.2	28.5	0.77 [0.61-0.96]*	34.9	1.03 [0.75-1.42]	26.5	0.69 [0.53-0.91]†	27.6	0.74 [0.56-0.97]*
Hay fever ever	27.7	26.1	0.92 [0.73-1.17]	33.8	1.33 [0.94-1.89]	26.0	0.92 [0.69-1.22]	22.8	0.77 [0.58-1.03]
Eczema ever	37.3	30.2	0.73 [0.58-0.91]†	35.3	0.92 [0.66-1.28]	29.2	0.69 [0.53-0.91]†	29.1	0.69 [0.53-0.90]†

* $p<0.05$; †$p<0.01$; compared to reference group

Table 4. Crude odds ratios (OR) and 95% confidence intervals (CI) for the associations between farm exposures and asthma symptoms, hay fever and eczema (Total n=1898)

	Wheeze in last 12 months	Asthma medication in last 12 months	Asthma ever	Hay fever ever	Eczema ever
Exposure of the child	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
Life time exposure to farm animals ≥ once a week					
In first two years versus never (n=908)‡	0.67 [0.51-0.88]†	0.75 [0.57-0.99]*	0.70 [0.55-0.89]†	0.69 [0.54-0.90] †	0.65 [0.51-0.82]†
After first two years versus never (n=421)‡	0.73 [0.52-1.02]	0.79 [0.56-1.10]	0.76 [0.56-1.02]	0.96 [0.71-1.29]	0.97 [0.73-1.29]
Current exposure to farm animals (last 12 months)					
< once a week versus never (n=527)	1.08 [0.79-1.48]	1.05 [0.76-1.45]	0.87 [0.65-1.15]	0.87 [0.65-1.18]	1.08 [0.81-1.43]
≥ once a week versus never (n=464)	0.66 [0.47-0.93]*	0.66 [0.46-0.94]*	0.61 [0.45-0.82]†	0.61 [0.44-0.84]†	0.87 [0.64-1.19]
≥ once a day versus never (n=514)	0.66 [0.47-0.93]*	0.57 [0.41-0.81]†	0.55 [0.41-0.74]†	0.52 [0.38-0.71]†	0.65 [0.48-0.89]†
Current exposure to grain/hay (last 12 months)					
< once a week versus never (n=760)	0.83 [0.64-1.08]	0.77 [0.59-1.00]	0.66 [0.53-0.84]†	0.82 [0.64-1.04]	0.79 [0.62-1.00]*
≥ once a week versus never (n=338)	0.57 [0.40-0.80]†	0.67 [0.47-0.95]*	0.64 [0.47-0.86]†	0.66 [0.47-0.91]*	0.56 [0.41-0.77]†
≥ once a day versus never (n=152)	0.72 [0.45-1.15]	0.61 [0.38-0.98]*	0.59 [0.39-0.89]*	0.63 [0.41-0.98]*	0.64 [0.43-0.96]*
Current consumption of unboiled farm milk (n=263)	0.61 [0.41-0.90]*	0.53 [0.34-0.82]†	0.67 [0.48-0.92]*	0.66 [0.46-0.93]*	0.62 [0.45-0.85]†
Exposure of the mother during pregnancy					
Exposure to farm animals during pregnancy					
< once a week versus never (n=163)	0.47 [0.28-0.80]†	0.68 [0.43-1.07]	0.69 [0.46-1.02]	0.79 [0.55-1.14]	0.80 [0.55-1.16]
≥ once a week versus never (n=211)	0.94 [0.64-1.38]	0.90 [0.63-1.31]	0.85 [0.61-1.19]	0.65 [0.45-0.94]*	0.64 [0.46-0.89]†
≥ once a day versus never (n=433)	0.49 [0.36-0.67]†	0.54 [0.39-0.74]†	0.50 [0.39-0.66]†	0.53 [0.40-0.70]†	0.51 [0.39-0.68]†
Exposure to grain/hay during pregnancy					
< once a week versus never (n=345)	0.56 [0.40-0.79]†	0.61 [0.43-0.86]†	0.60 [0.45-0.78]†	0.65 [0.49-0.87]†	0.68 [0.52-0.90]†
≥ once a week versus never (n=182)	0.69 [0.45-1.05]	0.73 [0.48-1.11]	0.76 [0.52-1.10]	0.61 [0.41-0.91]*	0.51 [0.34-0.75]†
≥ once a day versus never (n=179)	0.53 [0.33-0.83]†	0.50 [0.31-0.81]†	0.49 [0.34-0.71]†	0.53 [0.35-0.79]†	0.50 [0.34-0.74]†

* p<0.05; †p<0.01; ‡ Reference category: children with no contact to animals

We subsequently conducted multiple regression analyses (Table 5) to establish which of the farming-related exposures were independent predictors of the lower prevalence of asthma symptoms, hay fever and eczema. However, since animal, and grain/hay exposures were highly correlated we were not able to test both exposures independently, and therefore chose to include only animal contact (see above). The protective effect of maternal exposures during pregnancy remained almost unchanged after adjustment for potential confounders for all study outcomes. Current exposure of the child to farm animals remained protective for asthma medication, asthma ever and hay fever, whereas significant associations were no longer found for wheeze and eczema. In addition, contact with farm animals during the first two years of life of the child was no longer associated with symptoms. Raw milk was also no longer significantly associated with symptoms. Further adjustments for number of siblings, previous and current paracetamol use, antibiotics, current and previous cat and/or dog ownership, vaccinations, body mass index, and dietary factors did not significantly alter the results (data not shown).

For all symptoms, the strongest reduced risks were in those children with both prenatal and current exposure to farm animals (wheeze, OR 0.48, CL 0.28-0.80; asthma medication, OR 0.50, CL 0.30-0.82; asthma ever, OR 0.50, CL 0.33-0.76; hay fever ever OR 0.47, CL 0.30-0.73; eczema ever, OR 0.46, CL 0.30-0.70) (Figure 2). Children with prenatal exposure only had an intermediate risk (wheeze OR 0.62, CL 0.39-0.99; asthma medication OR 0.72, CL 0.45-1.17; asthma ever OR 0.65, CL 0.43-099, hay fever ever OR 0.55, CL 0.36-0.85; eczema ever OR 0.82, CL 0.53-1.26), whereas those with only current exposure had no or only a slightly reduced risk (wheeze OR 0.90, CL 0.60-1.34; asthma medication OR 0.77, CL 0.52-1.14; asthma ever OR 0.97, CL 0.67-1.40; hay fever ever OR 0.80, CL 0.56-1.14; eczema ever OR 0.92, CL 0.65-1.32, respectively). The joint effect of prenatal and current farming exposure more than explained the protective effect of farming (table 3). In fact, after adjustment for prenatal and current exposure the effect of farming disappeared with most odds ratios close to or just above unity (data not shown).

Table 5. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between farming and various selected "exposures" and asthma symptoms, hay fever and eczema. Associations were adjusted for age, sex, ethnicity, mother's education level, smoking in the house, farm type, and parental asthma, hay fever and eczema, and all other variables in the model (Total n=1769).

	Wheeze in last 12 months	**Asthma medication in last 12 months**	**Asthma ever**	**Hay fever ever**	**Eczema ever**
Exposure of the child	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
Life time exposure to farm animals ≥ once a week					
first two years versus never (n=908)	0.90 [0.58-1.19]	1.27 [0.82-1.95]	1.27 [0.85-1.89]	1.13 [0.75-1.72]	1.03 [0.69-1.55]
after first two years versus never (n=421)	0.76 [0.49-1.19]	1.04 [0.67-1.62]	0.98 [0.66-1.45]	1.24 [0.82-1.88]	1.16 [0.79-1.71]
Current exposure to farm animals (last 12 months)					
< once a week versus never (n=498)	1.22 [0.82-1.82]	0.98 [0.65-1.47]	0.81 [0.56-1.17]	0.69 [0.47-1.03]	1.08 [0.75-1.54]
≥ once a week versus never (n=425)	0.76 [0.44-1.33]	0.49 [0.28-0.86]*	0.59 [0.37-0.94]*	0.42 [0.25-0.71]†	1.01 [0.61-1.67]
≥ once a day versus never (n=478)	0.80 [0.46-1.42]	0.47 [0.27-0.82]†	0.60 [0.37-0.98]*	0.44 [0.26-0.74]†	0.82 [0.49-1.37]
Current consumption of unboiled farm milk (n=242)	0.90 [0.55-1.47]	0.66 [0.39-1.11]	0.88 [0.59-1.31]	0.87 [0.57-1.35]	0.91 [0.62-1.35]
Exposure of the mother during pregnancy					
Exposure to farm animals during pregnancy					
< once a week versus never (n=156)	0.38 [0.21-0.71]†	0.56 [0.33-0.96]*	0.60 [0.38-0.96]*	0.67 [0.42-1.07]	0.68 [0.43-1.06]
≥ once a week versus never (n=195)	1.31 [0.82-2.10]	1.13 [0.70-1.83]	1.07 [0.71-1.60]	0.66 [0.42-1.04]	0.75 [0.49-1.16]
≥ once a day versus never (n=399)	0.53 [0.35-0.80]†	0.63 [0.41-0.97]*	0.53 [0.36-0.76]†	0.51 [0.35-0.75]†	0.58 [0.40-0.84]†

* p<0.05; †p<0.01

DISCUSSION

In this cross-sectional study we found that symptoms of asthma and eczema were less prevalent in farmers' children than in rural reference children. More interestingly perhaps, we demonstrated dose-response associations for maternal exposure to farm animals and/or grain and hay products during pregnancy, and hay fever and eczema in their children. A reduced risk for asthma symptoms and asthma medication use was also shown but no clear dose-response association was found. The strongest protective effects were demonstrated for those children whose mothers had frequent exposures to farm animals during pregnancy and who were also currently exposed.

The finding that farmers' children have less asthma, hay fever and eczema has been demonstrated in several other studies.[1, 2, 9, 11, 19] It has recently also been shown that *prenatal* farm exposures are associated with an increased expression of receptors of innate immunity (TLR2, TLR4 and CD14) and a decrease in atopic sensitisation in children; asthma, wheeze and hay fever symptoms were also reduced, but these associations were weak and not statistically significant.[10] Our study is therefore the first to demonstrate a direct link between exposures in utero and a strong and significant reduction in asthma symptoms, hay fever and eczema. These observations were consistent for all study outcomes after adjusting for several known risk/protective factors including parental asthma, hay fever and eczema. Due to the cross-sectional design of the study we cannot exclude the possibility of recall bias. However, this is unlikely to explain our findings because it would require the parents to have knowledge of the potential protective effects of prenatal farm exposures. We tested for non-response bias by comparing the symptom prevalences obtained in the initial postal survey and in the follow-up telephone survey (in those who did not respond to the postal survey) and found no differences in prevalence between the two surveys for the farming population (data not shown). In the reference population the prevalence was somewhat higher for those who completed the survey by phone. However, this is unlikely to explain the protective effects that we observed since it implies that the slightly higher non-response in the reference population would have led to an underestimation of the symptom prevalence in that population and consequently in a reduction of the observed protective effect. In any case, the response was reasonable (78% for farmers and 67% for the reference population) limiting the potential for significant non-response bias.

Since the differences in ethnicity between the reference and the farmers population were substantial (Table 2) we also repeated the analyses excluding all Māori and Pacific Island children but this did not significantly change the results (data not shown). Similarly, restricting the analyses to only the farming population did not change the observed associations between early and current farm-related exposures and asthma symptoms, hay fever and eczema (data not shown). Our findings therefore are robust and are unlikely to be explained simply due to general (non-farm related) differences between farming and non-farming families.

The most consistent results were found with prenatal exposures, but as demonstrated in multiple regression models (Table 5) current exposures were also independently associated with asthma medication, asthma ever, and hay fever (wheeze in the last 12 months also showed a reduced risk, but this did not reach statistical significance). Moreover, we found the strongest protective effects in those children with both prenatal and current exposure (Figure 2). Consistent with this finding, studies in adult farmers have shown that the combination of childhood and current farm exposure was associated with the lowest risk of allergic sensitisation,[6] hay fever,[7] and asthma.[8] The latter study,[8] which was based on the parents of the children in the current study, also showed a dose-dependent inverse association between the combined number of years of farm exposure in childhood and adulthood and asthma symptoms. The combined evidence of these studies suggests that current exposures may play a role in the continued protection of allergic disease later in life. This is plausible since there is substantial evidence that the immune system is not "fixed" after the first years of life and that "immune deviation" may take place throughout life,[23, 24] although others have argued that immunologic reactivity expressed in childhood is already fully established in infancy and early childhood.[12] However, due to its cross-sectional design which was based on questionnaire data only, our study is not ideally suited to assessing the effects of timing of exposure. Also, because we included children of different ages (5-17 years), "current exposures" do not refer to the same period in life for every child, further complicating the assessment of the importance of timing of exposure.

Interestingly, protective effects were demonstrated not only for asthma and hay fever, but also for eczema. The level of agreement between asthma ever and eczema ever (Kappa, 0.24; 95% CL 0.19-0.28) and hay fever ever and eczema ever (Kappa, 0.17; 95% CL 0.13-0.22) was low suggesting that the protective effects on eczema are real and were not due to high agreement with the other health outcomes.

Maternal exposure was inversely associated with all symptoms, but a dose-response trend was only found for hay fever and eczema. For asthma symptoms we found inverse associations for both the “low” and “high” exposure groups, but no association was found for the “intermediate” exposure group. The same pattern was observed when we adjusted the analyses for potential confounders (table 5). The reasons for this are unclear. It is also not clear how maternal exposures during pregnancy affect asthma, hay fever and eczema manifestation in the offspring. One option is that maternal immune responses to farm exposures (through cytokine production) may prime the developing foetal immune system.[25] Alternatively, foetal priming to environmental antigens in utero may play a role.[26] Moreover, it has been suggested that environmental exposures may affect gene expression during development in utero which could have long-term effects on the immune system in later life.[10] The evidence for any of these potential explanations is, however, weak, and further prospective studies are needed to conclusively elucidate the underlying immunological mechanisms.

Animal contact is likely to play a role in the observed protective effects in our study and those of others.[2, 9, 10] In our study, however, animal contact was also strongly associated with other farm exposures such as hay and grain. Both animals and hay/grain products are associated with high exposures to micro-organisms and in particular bacterial endotoxin,[27] and prenatal farming exposure has also been shown to be associated with an up regulation of several innate immune receptors specific for microbial products (TLRs and CD14).[10] Exposure to micro-organisms and microbial products may therefore be an important intermediate factor and has been suggested to up-regulate (through innate immune activation) Th_1 and down-regulate Th_2 lymphocyte immunity, thereby suppressing the development of IgE-antibodies and Th_2 dependent diseases, including allergic asthma, hay fever and eczema.[28] The evidence for this is limited however, and a study in farmers children did not support the hypothesis that microbial exposures in famers children skew the Th1/Th2 balance toward Th1 responses[11] Alternatively, microbial exposure may enhance the activity of T regulatory cells resulting in a down-regulation of *both* Th_2 and Th_1 immunity.[28] However, the potential role of regulatory T cells has so far not been studied in the context of farm exposures. Other studies in non-farming populations have also shown inverse associations between bacterial endotoxin exposure in infancy and wheeze and asthma at a later age emphasising the potential role of endotoxin exposure in these protective effects.[29] However, despite microbial exposure being a plausible reason for the reduced risk, farm exposures in new Zealand are likely to be different from those in Europe. In particular, in New Zealand livestock is kept out in the field year round, whereas in Europe they are kept in stables for at least part of the year. New Zealand farm children with frequent contact to animals are therefore likely to be less highly exposed than their counterparts in Europe. Therefore, other factors associated with contact to farm animals may also be relevant.

As previously shown in other studies[2, 10, 30] we found that consumption of raw milk fresh from the farm was inversely associated with all studied outcomes. However, when we adjusted for other farm exposures the protective effects largely disappeared. Consumption of raw farm milk therefore not appears to be a significant protective factor in our study.

In conclusion, prenatal farm exposures may protect against symptoms of asthma, hay fever and eczema in farmers' children. The results of this study also suggest that continued exposure later in life may be required to maintain optimal protection, but confirmation from prospective studies is required to confirm this.

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FIGURE LEGENDS

Figure 1: Flow diagram describing subject recruitment, exclusion and refusals. * The response was based on the number of responders divided by the total number of eligible families.

Figure 1:

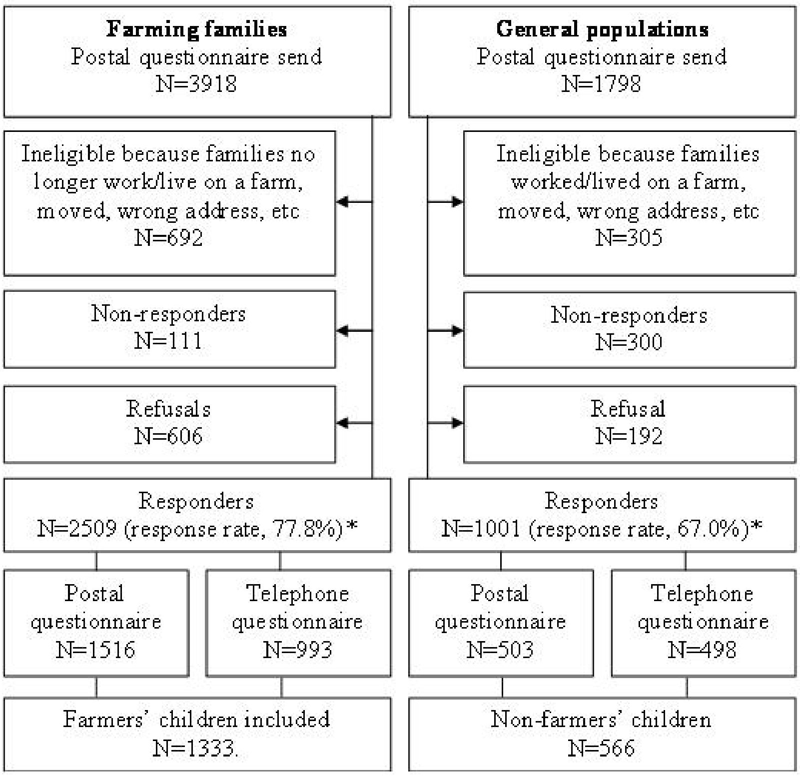

Figure 2. Adjusted odds ratios for the independent and joint effects of current and prenatal animal exposure: O, never exposed (n=1124; reference group); Δ only currently exposed (n=247); □ only prenatal exposure (n=168); ◊ current and prenatal exposure (n=231). The analyses were adjusted for age, sex, ethnicity, smoking in the house, mother's education, farm type, raw milk consumption, parental asthma, hay fever and eczema.