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

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ABSTRACT: The aim of the present study was to assess which factors contribute to the lower prevalence of allergic diseases in farmers' children, and the importance of timing of exposure.

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

Farmers' children had a lower incidence of 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 nonlinear 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 2 yrs was not associated with symptoms, after controlling for prenatal exposure. A combination of prenatal and current exposure was most strongly associated with wheeze (odds ratio (OR) 0.48, 95% confidence interval (CI) 0.28–0.80), asthma medication (OR 0.50, 95% CI 0.30–0.82), asthma ever (OR 0.50, 95% CI 0.33–0.76), hay fever (OR 0.47, 95% CI 0.30–0.73) and eczema (OR 0.46, 95% CI 0.30–0.70).

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.

KEYWORDS: Asthma, farming, hygiene hypothesis, prenatal, timing

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 T-helper cell (Th) type 2 expansion and the development of immunoglobulin (Ig)E antibodies and Th2-dependent diseases, including allergic asthma, hay fever and eczema [11]. Although it has been suggested that these protective effects 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. A 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 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 opposite has been suggested for maternal smoking and prenatal exposures to insecticides [16–18].

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

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STATEMENT OF INTEREST
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MATERIALS AND METHODS

Study design and population

The methods for the present study were based on those of the European study on atopy and asthma in farmers' children, known as the Prevention of Allergy – Risk factors for Sensitisation in children related to Farming and Anthroposophic Lifestyle (PARSIFAL) study [19]. The current study involved a survey of 2,509 farming families and 1,001 nonfarming families of working age. The findings in children are presented.

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

Subjects were asked to complete a postal survey for themselves and their children aged 5–17 yrs (if any). A maximum of two children were included per household; if the family had more than two children within the specified age range, the two oldest children were selected, 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 (Palmerston North, New Zealand; WGTN protocol 02/105).

Questionnaire

The symptom prevalence was assessed using a standardised questionnaire based on the International Study of Asthma and Allergies in Childhood (ISAAC) postal questionnaire [21]. The current authors 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, ''environmental'' exposures were assessed, 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 exposures during three time periods in the child's life: current, lifetime and prenatal. ''Current exposures'' relate to exposures in the previous 12 months; ''lifetime exposures'' relate to exposures at any stage in life; and ''prenatal exposures'' relate to exposures of the mother during pregnancy. For current and prenatal exposures, the frequency of the exposures was also assessed, and for lifetime exposures a distinction was made between exposures before and after 2 yrs of age (table 1). Information was not collected on lifetime exposure to grain and hay products and consumption of unboiled milk.

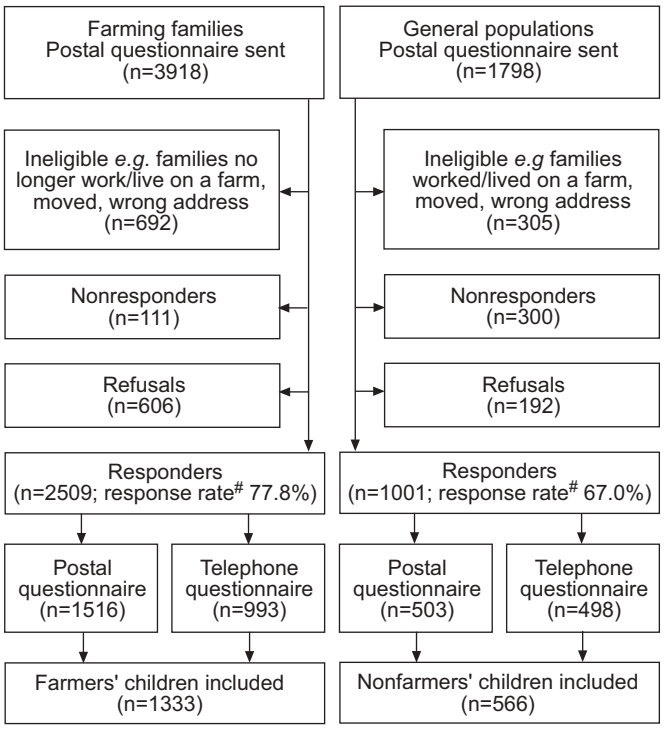

FIGURE 1. Flow diagram describing subject recruitment, exclusion and refusals. #: the number of responders divided by the total number of eligible families.

Statistical analyses

Chi-squared tests and unpaired t-tests were performed to test differences in prevalence and mean levels, respectively. Crude and adjusted prevalence odds ratios (ORs) were calculated using logistic regression analyses. Since children from the same household were included (with a maximum of two per household), the data were not completely independent. Therefore, clustered robust standard errors [22] were applied, 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, ORs 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, the effect of each of these exposures could not be assessed 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, exposure to animals was selected 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 2 yrs of life and after the first 2 yrs, 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

TABLE 1 Questions used to assess current, lifetime 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; less than once a week; at least once a week; at least once a day
	Lifetime 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 or 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?	Aged 0–2 yrs; >2 yrs
	Prenatal exposure	How often did the mother have contact with farm animals during the pregnancy?	Never; less than once a week; At least once a week; At least once a day
Grain or 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; less than once a week; at least once a week; at least once a day
	Prenatal exposure	How often did the mother have contact with farm animals during the pregnancy?	Never; less than once a week; at least once a week; at least 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 were housed (while the animals were in there) or being in yards at the time animals were in there.

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% confidence interval (CI) 0.22–0.26). In addition to these potential confounders, the following variables were also tested: 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.

The independent and joint effects of current and prenatal exposure were also assessed. For that purpose, prenatal and current exposure were dichotomised, with ''frequent exposure'' being defined as contact with animals at least once a day (compared with contact less than once a day). Subsequently, comparisons were made between those who were frequently exposed in both periods, those who 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 either period.

RESULTS

The 2,509 farming families and 1,001 reference families that participated (response rates of 77.8 and 67.0%, respectively) included 1,333 farmers' children and 566 reference children (fig. 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 ORs 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 2 yrs of life was inversely associated with all symptoms ($p<0.05$). 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 with 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 nonlinear 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 to which pregnant mothers and children were exposed (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).

Subsequently, multiple regression analyses were conducted (table 5) in order 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, it was not possible to test both exposures independently;

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
Children n	566	1333	241	552	540
Age yrs	11.00±3.56	11.20±3.49	11.44±3.50	11.14±3.56	11.15±3.43
Height m	1.49±0.22	1.50±0.22	1.52±0.20	1.50±0.21	1.49±0.22
Weight kg	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**
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**
Māori	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 household	35.8	20.3**	13.8**	24.1**	19.3**
Reported conditions in parents					
Asthma	36.3	28.7**	25.3**	28.6**	30.3*
Hay fever	59.5	58.0	67.1*	54.3	57.2
Eczema	48.3	39.1**	40.8	37.2**	40.2**
Exposure of child to farm animals at least once a week					
Never	67.9	12.1**	42.8**	5.8**	4.9**
Aged 0–2 yrs	13.1	63.9**	25.8**	71.2**	73.3**
Aged >2 yrs	19.0	24.0**	31.4**	23.0**	21.9**
Exposure of child to farm animals in last 12 months					
Never	50.9	7.7**	34.0**	1.6**	2.0**
Less than once a week	38.2	23.4**	41.1**	20.5**	18.4**
At least once a week	6.0	32.4**	10.4**	36.3**	38.2**
At least 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 mother to farm animals					
Never	95.5	41.0**	83.4**	31.0**	32.1**
Less than once a week	1.6	11.6**	10.4**	14.0**	9.7**
At least once a week	0.7	15.6**	0.8**	20.8**	17.0**
At least once a day	2.1	31.8**	5.4**	34.2**	41.0**

Data are presented as mean±SD or %, unless otherwise stated. *: $p<0.05$; and **: $p<0.01$, compared with the reference group.

therefore, the current authors chose to include only animal contact. 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 2 yrs of life 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, 95% CI 0.28–0.80; asthma medication: OR 0.50, 95% CI 0.30–0.82; asthma ever: OR 0.50, 95% CI 0.33–0.76; hay fever ever: OR 0.47, 95% CI 0.30–0.73; eczema ever: OR 0.46, 95% CI 0.30–0.70; fig. 2). Children with prenatal exposure only had an intermediate risk (wheeze: OR 0.62, 95% CI 0.39–0.99; asthma medication: OR 0.72, 95% CI 0.45–1.17;

TABLE 3 Asthma symptoms, hay fever and eczema in farming and reference children

	Reference prevalence %	Farm							
		All		Horticulture		Sheep and beef		Dairy	
		Prevalence %	OR (95% CI)	Prevalence %	OR (95% CI)	Prevalence %	OR (95% CI)	Prevalence %	OR (95% CI)
Subjects n	566		1333		241		552		540
Wheeze[#]	25.1	19.5	0.72 (0.56–0.93)**	22.4	0.86	20.7	0.78 (0.58–1.05)	17.0	0.61 (0.45–0.83)
Asthma medication[#]	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)**

[#]: in the last 12 months. *: $p<0.05$; and **: $p<0.01$, compared with the reference group.

asthma ever: OR 0.65, 95% CI 0.43–099; hay fever ever: OR 0.55, 95% CI 0.36–0.85; eczema ever: OR 0.82, 95% CI 0.53–1.26), whereas those with only current exposure had no or only a slightly reduced risk (wheeze: 0.90 (0.60–1.34); asthma medication: OR 0.77, 95% CI 0.52–1.14; asthma ever: OR 0.97, 95% CI 0.67–1.40; hay fever ever: OR 0.80, 95% CI 0.56–1.14; eczema ever: OR 0.92, 95% CI 0.65–1.32). 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 ORs close to or just above unity (data not shown).

DISCUSSION

In the present cross-sectional study, symptoms of asthma and eczema were found to be less prevalent in farmers' children than in rural reference children. Perhaps more interestingly, dose–response associations were demonstrated 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.

Several other studies have demonstrated that farmers' children have less asthma, hay fever and eczema [1, 2, 9, 11, 19]. It has also been shown recently 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 [10]. Asthma, wheeze and hay fever symptoms were also reduced, but these associations were weak and not statistically significant [10]. Therefore, the present study is 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 the possibility of recall bias cannot be excluded. However, this is unlikely to explain the findings, since it would require the parents to have knowledge of the potential protective effects of prenatal farm exposures. Nonresponse bias was tested for by comparing the symptom prevalence obtained in the initial postal survey and in the follow-up telephone survey (in those who did not respond to the postal survey), and no differences in prevalence were found 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 observed, since it implies that the slightly higher nonresponse 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 nonresponse bias.

Since the differences in ethnicity between the reference and the farmers population were substantial (table 2), the analyses were also repeated 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). Therefore, the present findings are robust and are unlikely to be explained simply due to general (farm unrelated) differences between farming and nonfarming 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, the strongest protective effects were found in those children with

TABLE 4 Associations between farm exposures and asthma symptoms, hay fever and eczema[#]

	Subjects n	Wheeze[¶]	Asthma medication[¶]	Asthma ever	Hay fever ever	Eczema ever
Exposure of the child						
Lifetime exposure to farm animals[+,§,f]						
Aged 0–2 yrs	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)**
Aged >2 yrs	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[¶,§]						
Less than once a week	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)
At least once a week	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)
At least once a day	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 or hay[¶,§]						
Less than once a week	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)*
At least once a week	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)**
At least once a day	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	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						
Farm animals[§]						
Less than once a week	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)
At least once a week	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)**
At least once a day	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)**
Grain or hay[§]						
Less than once a week	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)**
At least once a week	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)**
At least once a day	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)**

Data are presented as crude odds ratio (95% confidence interval), unless otherwise stated. [#]: 1,898 subjects in total; [¶]: in the last 12 months; [+]: at least once a week; [§]: given category *versus* never; [f]: reference category was children with no contact with animals. *: $p<0.05$; **: $p<0.01$.

both prenatal and current exposure (fig. 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 study by DOUWES *et al*. [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 against 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 immune deviation may take place throughout life [23, 24], although others have argued that immunological reactivity expressed in childhood is already fully established in infancy and early childhood [12]. However, due to its cross-sectional design that was based on questionnaire data only, the present study is not ideally suited to assessing the effects of timing of exposure. Also, because children of different ages (5–17 yrs) were included, ''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 (κ 0.24, 95% CI 0.19–0.28) and hay fever ever and eczema ever (κ 0.17, 95% CI 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, inverse associations were found for both the ''low'' and ''high'' exposure groups, but no association was found for the ''intermediate'' exposure group. The same pattern was observed when the analyses were adjusted 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 possibility 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

TABLE 5 Association between farming and selected exposures and asthma symptoms, hay fever and eczema[#]

	Subjects n	Wheeze[¶]	Asthma medication[¶]	Asthma ever	Hay fever ever	Eczema ever
Exposure of the child						
Lifetime exposure to farm animals[+,§]						
Aged 0–2 yrs	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)
Aged >2 yrs	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[¶,§]						
Less than once a week	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)
At least once a week	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)
At least once a day	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	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						
Farm animals[§]						
Less than once a week	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)
At least once a week	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)
At least once a day	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)**

Data are presented as odds ratio (95% confidence interval), unless otherwise stated. [#]: adjusted for age, sex, ethnicity, mother's education level, smoking in the house, farm type, and parental asthma, hay fever and eczema, as well as all other variables in the model (1,769 subjects in total); [¶]: in the last 12 months; [+]: at least once a week; [§]: given category *versus* never. *: $p<0.05$; **: $p<0.01$.

could have long-term effects on the immune system in later life [10]. However, the evidence for any of these potential explanations is weak, and further prospective studies are needed to elucidate the underlying immunological mechanisms conclusively.

Animal contact is likely to play a role in the observed protective effects in the current study and those of others [2, 9, 10]. However, in the present study, 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 microorganisms, particularly bacterial endotoxin [27], and prenatal farming exposure has also been shown to be associated with an upregulation of several innate immune receptors specific for microbial products (TLRs and CD14) [10]. Exposure to microorganisms and microbial products may, therefore, be an important intermediate factor and has been suggested to upregulate Th1 (through innate immune activation) and downregulate Th2 lymphocyte immunity, thereby suppressing the development of IgE antibodies and Th2-dependent diseases, including allergic asthma, hay fever and eczema [28]. However, the evidence for this is limited, and a study in farmers' children did not support the hypothesis that microbial exposures in farmers' children skew the Th1/Th2 balance toward Th1 responses [11]. Alternatively, microbial exposure may enhance the activity of regulatory T-cells, resulting in a downregulation of both Th2 and Th1 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 nonfarming 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 all 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. Hence, other factors associated with contact to farm animals may also be relevant.

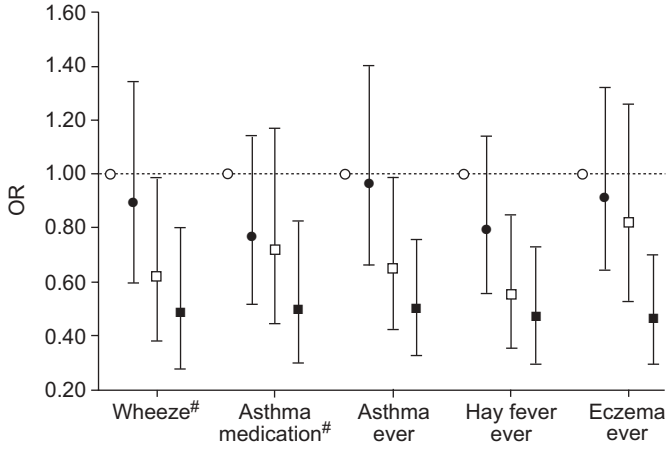

FIGURE 2. Adjusted odds ratios (OR) with 95% confidence intervals for the independent and joint effects of current and prenatal animal exposure. The analyses were adjusted for age, sex, ethnicity, smoking in the house, mother's education level, farm type, raw milk consumption, and parental asthma, hay fever and eczema. [#]: in last 12 months. ○: never exposed (reference group), n=1124; ●: only currently exposed, n=247; □: only prenatal exposure, n=168; ■: current and prenatal exposure, n=231.

As previously shown [2, 10, 30], the present study found that consumption of raw milk fresh from the farm was inversely associated with all studied outcomes. However, when other farm exposures were adjusted for, the protective effects largely disappeared. Thus, consumption of raw farm milk does not appear to be a significant protective factor in the current study.

In conclusion, prenatal farm exposures may protect against symptoms of asthma, hay fever and eczema in farmers' children. The results of the present 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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