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Low prevalence of atopy in young Danish farmers and farming students born and raised on a farm

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Summary

Background Recent studies have shown that in several countries atopic sensitization to common allergens (common atopy) and atopic symptoms are markedly less prevalent in children living on a farm, compared with non-farm children living in the same rural areas. Living conditions on farms may, however, vary largely between different countries. It is also not yet known whether the 'protective' effect of a farm environment can also be found in adults.

Materials and methods Common atopy and respiratory health were assessed by skin prick tests (SPT), questionnaire and measurement of bronchial hyper-responsiveness (BHR) in the Sund Stald (SUS) study, a cohort study on respiratory health in Danish farming students and conscripts from the same rural areas as controls. Results of SPT were confirmed by IgE serology in all SPT+ subjects and a subset of SPT– subjects. Prevalences of common atopy, respiratory symptoms and bronchial hyper- responsiveness were compared for farmers and controls, and for those who had or had not lived on a farm in early childhood.

Results In multiple logistic regression analyses adjusting for ever smoking and a familial history of allergy, both being a farmer (ORs 0.62–0.75) and having had a farm childhood (ORs 0.55–0.75) appeared to contribute independently to a lower risk of sensitization to common allergens as assessed by SPT and IgE serology. A farm childhood was also inversely associated with high total IgE (OR 0.68), presence of respiratory symptoms (ORs 0.69–0.79) and BHR (OR 0.61) in these analyses. Direction and strength of the association between being a farmer and respiratory symptoms or BHR varied widely (ORs 0.69–1.28).

Conclusion The 'anti-atopy' protective effect of a farm childhood could be confirmed in Danish farming students: prevalences of positive SPT, specific and total IgE, allergic symptoms and BHR were lower in those being born or raised on a farm. Past exposure to the farm environment in early childhood may therefore also contribute to a lower risk of atopic sensitization and disease at a later age.

Keywords atopy, Denmark, farm childhood, farming, IgE, skin prick tests, young farmers
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Introduction

In several recent reports a markedly lower prevalence of atopy has been demonstrated in farm children, who appeared to have a two to three times lower risk of being atopic compared with their peers in the same rural areas and visiting the same schools but not living on a farm [1–5]. In these studies atopy was defined as self-reported symptomatic atopic disease, including hay-fever, doctor-diagnosed asthma or recurrent wheezing [1–5], and/or as type I sensitization to common, non-farm-associated allergens such as dust mites, pollens and pets as assessed by IgE serology [1] or skin prick tests [3,5]. In one study, non-specific airway hyper-responsiveness was also shown to be less prevalent among those who lived on a farm [5].

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These findings are remarkable as the farm environment is well known for its high levels of exposure to airborne organic dusts containing a wide variety of antigenic and potentially allergenic proteins of plant, animal and microbial origin [6–9]. As in traditional farming the work and home environment are usually closely associated, high allergen exposure levels are likely for all who live on a farm, also when not directly involved in farm work, such as children. Apart from typical farm-associated allergens, 'common allergens', such as those from pets or house dust mites, are usually also abundant in the farm home environment [10–12]. With regard to common outdoor allergens, such as pollen and mould spores, it seems very likely that farmers and their family members are on average exposed to at least equal and probably higher allergen levels than non-farming subjects in a rural or urban environment.

As farm environments may show considerable differences between various countries and/or regions, confirmation of these findings from different farming communities is of major importance. Although at least five such studies have been

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published, three came from the same geographical region – Switzerland [1], Bavaria [2] and Austria [3] – and mainly involved children living at relatively small family farms with mixed types of agriculture. Three studies included skin prick tests (SPT) [3,5] or specific IgE measurements [1], while the Bavarian study was completely based on questionnaire data [2]. The Finnish study found the 'anti-atopy' effect of a farm childhood in a questionnaire study among first-year university students [4], which suggests that the effect would last into young adulthood; unfortunately this study did not include objective tests for the presence of atopy (SPT or IgE serology).

We have investigated atopic sensitization to common allergens, symptoms of respiratory allergy and bronchial hyperresponsiveness (BHR) in the SUS project, a Danish cohort study [13] in which respiratory health status and its development are studied in up to 2000 farming students and young farmers, and a control group of 400 conscripts coming from and living in the same rural areas. Data were analysed with regard to where subjects had lived in childhood, and their current status as a farmer or farming student, or as a non-farming control.

Materials and methods

Population

In 1992–94 all 2478 second-year students of farming schools ('farmers') in Denmark were invited to participate in the study, and at baseline 1734 male and 230 female students were enrolled. A control group was recruited in 1994 of 407 conscripts of the Danish military service (controls), who all indicated that they lived in rural areas, but were not currently involved in farm work, nor intended to start a farming career. Details of the recruitment and selection of study participants, response rates, as well as various relevant and general characteristics, such as prevalence of smoking, percentage females, mean age, familial history of allergy, working experience with farm animals, etc., have been described in a previous report in which also the mean lung function and prevalences of various respiratory symptoms and the presence of bronchial hyper-responsiveness at baseline were analysed [13]. Parents of farming students completed an additional questionnaire on smoking habits, family size and the prevalence of allergy among parents and grandparents.

After data on approximately 800 farmers had been collected, the baseline health and living environment questionnaire was modified to include a question on where the study subject had lived during childhood ('Were you born and raised on a farm?'). Respondents were classified as 'farm child' if they answered yes to being born and raised on a farm, and as 'not farm child' if they were not. In total 1028 male and 138 female farmers and all 407 controls answered this question.

Atopy: skin prick tests

All individuals were skin prick tested with 14 allergens, including the common, i.e. not specifically farm-associated, allergens house dust mite, cat, dog, pollen from grass (mix of five species), birch, and mugwort (*Artemisia*), and various common moulds. The panel further included known or presumed 'farm-related' allergens such as animal allergens from pigs, cows and/or horses, and three different storage mites [13,14]. In all subjects, reactions to a negative (saline) and positive (histamine 5 mg/mL) control were also assessed. A weal diameter of at least 3 mm was regarded as a positive response, provided that the weal diameter of the negative control did not exceed 1 mm, and the weal diameter of the positive control was also at least 3 mm.

Atopy on the basis of positive skin prick tests was defined as at least one positive SPT to one of the five common allergens, house dust mite, grass pollen, birch pollen, cat or dog; this parameter was designated 'SPT(5)'.

Atopy: IgE serology

Blood samples had been taken at the start of the study and serum had been frozen in aliquots at $-80\,^{\circ}C$. Total IgE and specific IgE antibodies to the common allergens house dust mite, grass pollen (mix of two species), birch pollen, cat and dog, and to an allergen extract of storage mites (three species) were measured by enzyme immunoassays [15]. Only a subset of sera was selected: from all subjects in the whole cohort who had shown at least one positive SPT to any of the 14 allergens in the test panel ($n = 768$; 32%) and a random selection of 100 subjects with negative results for all tested allergens.

Allergen-specific IgE was assessed with 1/10 diluted sera in duplicate allergen-coated microwells. A serum was considered positive if the optical density at 492 nm in both wells exceeded the mean OD_{492} in the control wells by >0.050. If the OD_{492} in only one of the duplicate wells reached this level, the test was repeated. If the result of the second test was still inconclusive, the serum was considered positive if the mean value of both wells exceeded the mean OD_{492} in the control wells by >0.050. A total of 409 sera were re-tested on a second occasion, and a concordance of negative and positive findings of $>90\%$ was found, with practically all discordant results in sera with borderline reactions. Atopy on the basis of specific IgE tests, 'IgE(5)', was defined as at least one positive test for one of the five common allergens.

Total IgE was measured by sandwich EIA, with sera diluted 1/10, 1/20 and 1/40, and as calibration standard the IgE standard for the Pharmacia CAP system [15]. Although total IgE levels in both populations showed a log-normal distribution, the values were dichotomized and 'high total IgE' was defined as a serum IgE level of >100 kU/L. A total of 406 sera were re-tested on a second occasion. The mean percentage difference between the two values found in this series was 13%; with regard to the classification as 'high' or 'normal', a concordance of 97% was found, with practically all discordant results for sera with total IgE levels between 80 and 120 kU/L.

Respiratory symptoms and bronchial hyper-responsiveness

The baseline health and living environment questionnaire included questions on respiratory symptoms and doctor-diagnosed diseases.

Wheeze was diagnosed when subjects reported having ever wheezed. Asthma was defined as described previously [13]. Non-work-related rhinoconjunctivitis was diagnosed when subjects reported upper airway or eye symptoms that were worse at home or after contact with pollen or in spring, summer or autumn.

Bronchial hyper-responsiveness was measured as described previously [13] with calibrated DeVilbiss no. 40 nebulizers (DeVilbiss, Somerset, PA, USA) delivering a cumulative dose of 1.44 mg histamine. Subjects whose FEV_1 fell by 20% or

Table 1. Demographic characteristics of study population according to current working life as a farmer and living on a farm in childhood

	Controls ($n = 402$)	Farmers, no farm childhood ($n = 494$)	Farmers, farm childhood ($n = 505$)
Smoker (%)	132 (32.8)	185 (37.5)**	116 (23.0)
Ex-smoker (%)	1 (0.3)*	22 (4.5)	12 (2.4)
Age (± SD)	19.5 (± 0.9)*	19.2 (± 1.2)	19.4 (± 1.4)
Familial history of allergy (%)†	33 (8.2)	28 (5.7)	30 (5.9)
Normalized years with pigs‡	0.0 (± 0.0)*	1.0 (± 2.3)**	2.0 (± 5.1)
Normalized years with cattle‡	0.0 (± 0.0)*	1.7 (± 2.8)**	4.8 (± 5.3)
No. siblings (%)**,§			
0		17 (4.2)	12 (2.7)
1		198 (48.6)	117 (26.7)
2		111 (27.3)	180 (41.0)
≥ 3		81 (19.9)	130 (29.6)

*$P < 0.05$ farmers vs. controls. **$P < 0.05$ farmers with a farm childhood vs. farmers without a farm childhood.
†A familial history of allergy was diagnosed if two or more people among siblings or parents had an allergic disease.
‡Calculated from job history and standardized to years of 52 weeks/year and 40 h/week. Median (± interquartile range).
§Only farmer subjects were asked how many siblings they had; 407 farmers without a farm childhood and 439 farmers with a farm childhood answered this question.

more of the largest FEV_1 recorded at baseline or after 0.9% saline were considered as having bronchial hyper-responsiveness (BHR).

Statistical analyses

All statistical analyses were performed using SAS (version 6.12). In order to obtain a satisfactory match with the rural controls ($n = 407$) only male farmers aged under 26 were selected for further analysis ($n = 1691$). Information on childhood residence, smoking behaviour and familial history of allergy was available for 999 male farmers (59%) and 402 controls (99%). BHR was measured in 987 male farmers and 380 controls. Due to the exclusion of subjects with a positive SPT reaction to the buffer control or a negative reaction to histamine, relations with SPT(5) could be analysed in 988 male farmers and 399 controls. Since IgE was measured in a selected sub-population the relations with IgE(5) and 'high total IgE' could be analysed in only 302 male farmers and 143 controls. Alternative cut-off values were tested but had only little impact on the associations reported in this paper.

Combined effects of being a farming student ('farmer') and of a farm childhood were analysed in multiple logistic regression analyses (PROC LOGISTIC) with an adjustment for (ever) smoking and a familial history of allergy. No adjustment for age was made in this truncated sample of young persons. Results were calculated and expressed as odds ratios with 95% confidence intervals.

Results

Main population characteristics for both subgroups of farmers and for controls are given in Table 1. Controls were slightly older than farmers and more often reported a familial history of allergy. Within the group of farmers, farmers with a farm childhood smoked less often and tended to have more siblings than farmers without a farm childhood. Working experience with cattle and pigs was most extensive in farming students who had been born on a farm, while controls had spent only limited time with farm animals.

Prevalences of positive SPT reactions are shown in Fig. 1 for farmers who had ($n = 501$) or had not ($n = 487$) lived on a farm during childhood, and for the whole group of conscripts ($n = 399$). For practically all allergens the prevalence of sensitization was markedly lower for farmers than for controls and, within the group of farmers, lower for those who had lived on a farm during childhood than for those who had not been a farm child. Interestingly, even sensitization to typical 'farm-related' allergens, such as storage mites and hair, danders or urinary proteins from farm-animals, showed a lower prevalence among farmers than among controls. As a result, the prevalence of a positive SPT to 'any common allergen' ('SPT(5)') was significantly lower in farmers than in conscripts and, within farmers, significantly lower in those who had lived on a farm during childhood when compared with those who had not (Table 2).

Wheeze was reported significantly less often by farmers than controls, but prevalences of asthma, rhinoconjunctivitis and BHR were similar (Table 2). However, within the group of farmers prevalences of respiratory symptoms and BHR were much lower in those who had lived on a farm during childhood when compared with those without a farm childhood. Prevalences of wheeze and asthma were therefore lowest in farmers with a farm childhood when compared with both conscripts and farmers without a farm childhood, while prevalences of rhinoconjunctivitis and BHR were highest in farmers without a farm childhood.

Conscripts were shown as one group as only a small proportion (44 out of 402) had lived on a farm during childhood. Prevalences of sensitization in this subgroup were in general similar to those found in farmers without a farm childhood history, e.g. a positive SPT to 'any common allergen' ('SPT(5)') was found in 10 (22.7%) of the 44 conscripts with a farm childhood (not shown), compared with 110 (22.6%) of 487 farmers with no farm childhood (Table 2). In contrast, prevalences of respiratory symptoms and BHR were very similar for conscripts who had or had not lived on a farm during childhood.

There were no differences in smoking behaviour, age and working experience with cattle between the selected sample in which specific and total IgE was measured and the rest of the population. However, a familial history of allergy was more

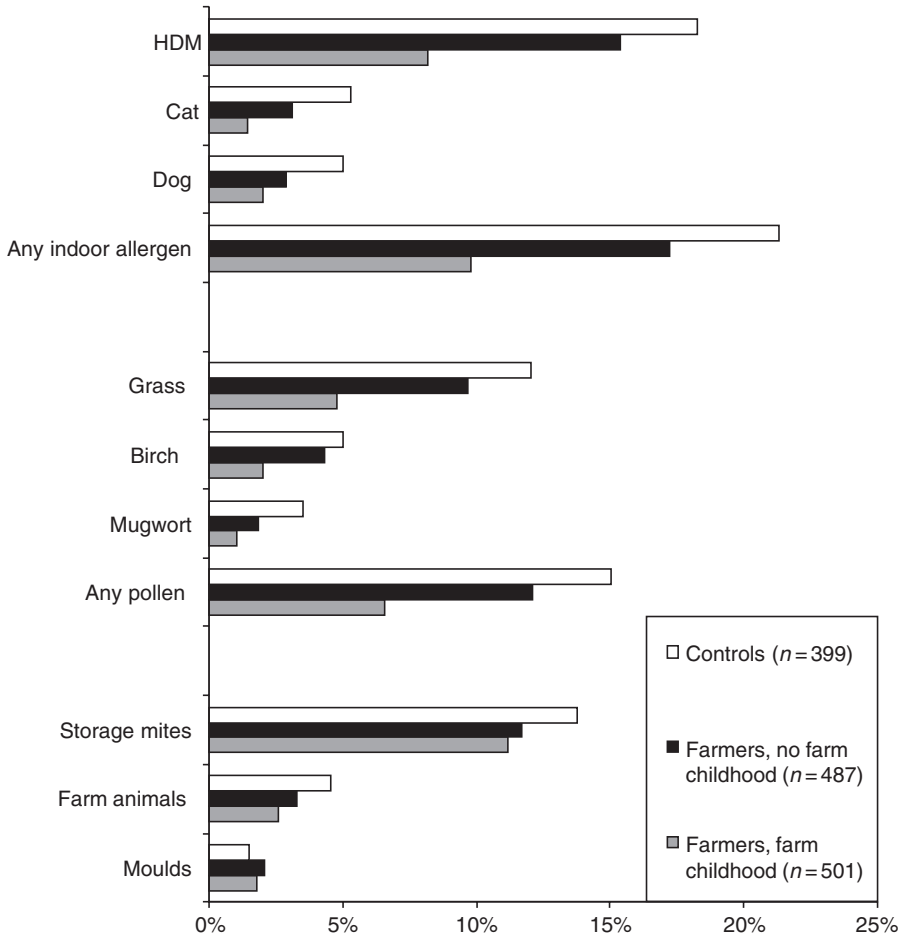

Fig. 1. Sensitization against common and work-related allergens in young male adults in a rural environment. Prevalences of positive SPT in rural controls, farmers not born and raised on a farm, and farmers born and raised on a farm.

Table 2. Common atopy and respiratory health in study population according to current working life as a farmer and living on a farm in childhood

	Controls†	Farmers, no farm childhood†	Farmers, farm childhood†
SPT(5)‡	108/399 (27%) *	110/487 (23%) **	67/501 (13%)
Wheeze	50/402 (12%)*	53/494 (11%)**	27/505 (5%)
Asthma	33/395 (8%)	43/492 (9%) **	26/499 (5%)
Rhinoconjunctivitis	53/402 (13%)	78/494 (16%)	59/505 (12%)
BHR	31/380 (8%)	54/490 (11%) **	32/497 (6%)

*$P < 0.05$ farmers vs. controls. **$P < 0.05$ farmers with a farm childhood vs. farmers without a farm childhood. †Results are given as the number of subjects with a given characteristic (*n*) divided by the number of subjects for which the information was available (*N*). ‡Positive SPT to one of the five common allergens, house dust mite, grass pollen, birch pollen, cat or dog.

Table 3. Common atopy as defined by serology in restricted study population according to current working life as a farmer and living on a farm in childhood

	Controls†	Farmers, no farm† childhood	Farmers, farm childhood†
IgE(5)‡	101/141 (72%)*	99/161 (61%)	71/137 (52%)
High total IgE§	83/143 (58%)	94/164 (57%)**	60/138 (43%)
Total IgE			
GM (± GSD)	110 (± 4.0)	109 (± 5.3)	78 (± 4.9)

*$P < 0.05$ farmers vs. controls. **$P < 0.05$ farmers with a farm childhood vs. farmers without a farm childhood. †Results are given as the number of subjects with a given characteristic (*n*) divided by the number of subjects for which the information was available (*N*), except where indicated. ‡Positive IgE test to one of the five common allergens, house dust mite, grass pollen, birch pollen, cat or dog. §Serum IgE level of > 100 kU/L.

common, the average number of siblings lower, and working experience with pigs less extensive, in the former group (not shown). Because subjects with positive SPT responses were over-represented in this sample, frequencies of positive IgE EIA tests and total IgE levels were high (Table 3). Association of positive IgE tests with farm childhood and being a farming student, however, showed a very similar pattern to that for positive SPTs. Relations for the various individual allergens were also similar, although no clear differences between groups were found for storage mite IgE sensitization.

A high concentration of total IgE (i.e. > 100 kU/L) was strongly associated with positive SPT reactions, OR

Table 4. Present working life as a farmer and living on a farm in childhood as determinants of common atopy in young male adults in a rural environment. Multiple (logistic) regression analyses of the relation of both determinants with three atopy parameters, with adjustment for smoking habits and a familial history of allergy

Atopy parameter	Determinant	OR	95% confidence interval	*P*
SPT(5)*	Farmer vs. control	0.75	[0.55–1.01]	< 0.06
($n = 1387$)	Farm childhood	0.55	[0.40–0.76]	< 0.001
	(Ever) smoking	0.97	[0.73–1.28]	> 0.8
	Familial history of allergy	3.16	[2.02–4.93]	< 0.001
IgE(5) †	Farmer vs. control	0.62	[0.39–0.98]	< 0.05
($n = 439$)	Farm childhood	0.71	[0.46–1.10]	> 0.1
	(Ever) smoking	0.81	[0.53–1.22]	> 0.3
	Familial history of allergy	1.75	[0.87–3.52]	> 0.1
High total IgE‡	Farmer vs. control	0.90	[0.58–1.39]	> 0.6
($n = 445$)	Farm childhood	0.68	[0.44–1.04]	< 0.08
	(Ever) smoking	0.84	[0.56–1.25]	> 0.3
	Familial history of allergy	1.68	[0.90–3.16]	> 0.1

*Positive SPT to one of the five common allergens, house dust mite, grass pollen, birch pollen, cat or dog. †Positive IgE test to one of the five common allergens, house dust mite, grass pollen, birch pollen, cat or dog. ‡Serum IgE level of > 100 kU/L.

(95%CI) = 4.0 (2.6–6.2), and with demonstrable IgE antibodies to common allergens, OR (95%CI) = 7.4 (4.7–11.8). Levels of total IgE were significantly lower in farmers who had lived on a farm during childhood, both compared with farmers who had not and compared with rural controls (Table 3). The latter two groups showed no difference, however.

In univariate analyses smoking, a familial history of allergy, the number of siblings and working experience with cattle and pigs were all significantly associated with atopy, symptoms or BHR (not shown). However, only smoking and a familial history of allergy were included in further multiple regression analyses in which the combined effects of being a farmer and having a farm childhood were assessed. Information on the number of siblings was available only for farming students. Adjusting for the number of siblings had no effect on the association between a farm childhood and prevalences of symptoms or BHR when analyses were restricted to farmers, and only slightly weakened the association with the prevalence of SPT(5) (not shown). Working experience with pigs and cattle was highly associated with being a farmer and having had a farm childhood. When included in one model, the strength of associations between the latter parameters and wheeze, SPT(5) and IgE(5) slightly decreased, while associations with rhinoconjunctivitis became stronger (not shown).

Results of these regression analyses confirmed that both being a farmer and a farm childhood contributed significantly to a lower risk of atopy defined either as at least one positive SPT ('SPT(5)') or as at least one positive specific IgE test ('IgE (5)'). For 'high total IgE', the OR for a farm childhood was below 1 but only borderline significant, while the OR for being a farmer was much less pronounced (Table 4). Also, in classical regression analysis only a weak, and not statistically significant, inverse relation was found between (log-transformed) levels of total IgE and being a farmer or having had a farm childhood (not shown). For respiratory health parameters, a negative association was found between prevalences of wheeze, asthma, rhinoconjunctivitis and BHR and a farm childhood, although this was significant only for the latter two. Current working life as a farmer showed only non-significant trends towards lower risks for wheeze and asthma and higher risks for rhinoconjunctivitis and BHR (Table 5).

Discussion

Our findings confirm and extend other recent studies in which atopy was shown to be markedly less prevalent among children living or raised on a farm [1–4]. In a population of Danish farming school students and, as controls, conscripts from the same rural areas, the prevalence of positive SPT and/or IgE tests to common allergens was lowest in farmers who in childhood had lived on a farm, intermediate in farmers without a farm childhood and controls with a farm childhood, and highest in controls without a farm childhood. Total serum IgE level was also lowest in farmers with a farm childhood, but was not significantly different between controls and farmers without a farm childhood. Prevalences of atopic symptoms in the whole group of farmers were not consistently different from those in non-farming rural controls, but were significantly lower in farmers with, than in farmers without, a farm childhood.

Several questions can be raised regarding the validity of the results. Investigation of atopy prevalences was not the primary objective of the SUS project [13,14] and the design of the study might therefore not have been completely adequate. The question regarding the childhood home environment was added to the questionnaire after data on approximately 800 farming students had already been collected, and part of the original study population could thus not be included in our analyses. Prevalences of positive SPTs, respiratory symptoms and BHR in this group were, however, similar to those in the analysed population, and it therefore seems unlikely this could have biased the observed relations between atopy and childhood home environment.

Information on several potential confounders, such as antibiotic use, socio-economic status, attending day-care and number of siblings, was not or only partly available. Adjusting for such confounders changed the effect estimates for several atopic symptom parameters in some of the other studies in farm

Table 5. Present working life as a farmer and living on a farm in childhood as determinants of respiratory health status in young male adults in a rural environment. Multiple logistic regression analyses of the relation of both determinants with respiratory symptoms and BHR, with adjustment for smoking habits and a familial history of allergy

Symptom	Determinant	OR	95% confidence interval	*P*
Wheeze	Farmer vs. control	0.69	[0.46–1.05]	< 0.09
($n = 1401$)	Farm childhood	0.68	[0.43–1.06]	< 0.1
	(Ever) smoking	3.41	[2.33–4.99]	< 0.001
	Familial history of allergy	2.66	[1.50–4.71]	< 0.001
Asthma	Farmer vs. control	0.92	[0.57–1.47]	> 0.7
($n = 1386$)	Farm childhood	0.79	[0.49–1.27]	> 0.3
	(Ever) smoking	2.43	[1.60–3.68]	< 0.001
	Familial history of allergy	3.18	[1.75–5.77]	< 0.001
Rhino-conjunctivitis	Farmer vs. control	1.24	[0.86–1.79]	> 0.2
	Farm childhood	0.70	[0.49–0.99]	< 0.05
($n = 1401$)	(Ever) smoking	1.04	[0.75–1.44]	> 0.8
	Familial history of allergy	2.83	[1.74–4.59]	< 0.001
BHR	Farmer vs. control	1.28	[0.82–2.02]	> 0.2
($n = 1367$)	Farm childhood	0.61	[0.39–0.95]	< 0.03
	(Ever) smoking	1.34	[0.90–1.98]	> 0.1
	Familial history of allergy	1.39	[0.70–2.78]	> 0.3

children [1–3,5], but had almost no effect on estimated ORs for atopic sensitization [1,3,5]. In our study, adjusting for the number of siblings within the group of farmers only slightly changed the estimated ORs for atopy in relation to a farm childhood (not shown). We therefore conclude that the 'protective' effect of a farm childhood against atopic sensitization and related respiratory symptoms can also be found in Denmark.

While most earlier studies investigated atopy in primary school children, our data show that the 'anti-atopy effect' of a farm childhood can still be found in young adulthood, also within a population of which currently all subjects are exposed to the farm environment. The Finnish study [4] investigated students of nearly the same age as our farmers and controls and also indicated that the farm childhood effect can still be observed in young adulthood. However, since atopy was defined as self-reported atopic disease during any period in life, the reported low ORs might have been due mainly to associations with a history of atopy, and not with current atopic illness. Our data refer to the current or recent health status and found similar relations with SPT or IgE serologic results, and thus confirm more definitely that the farm childhood-related anti-atopy effect would continue into adulthood.

Another new finding might be the association of a present working life as a farmer with a lower prevalence of atopy, independent of a farm childhood history. Many earlier studies have noticed a low prevalence among farmers of atopy, defined as typical type I allergic illness such as hayfever or asthma-like symptoms, and/or as atopic sensitization to common allergens [16–19]. It has been suggested that this low prevalence might be due to a strong healthy worker effect, with atopic teenagers being less likely to start a farming career with its known risks of high dust and allergen exposures [20]. The low prevalence of a familial history of atopic disease in farming students compared with controls (Table 1) may indeed support such an explanation. On the other hand, healthy worker selection would be driven primarily by (a history of) experienced allergic symptoms, and not directly by atopic sensitization, as long as the subject does not know his/her SPT or serologic results. In our study, however, negative associations between 'being a farmer' and symptoms were hardly found (Tables 2 and 5) and were much less pronounced than those with SPT or IgE test results. Thus, although a 'healthy worker' effect for respiratory symptoms or BHR can not be ruled out, the data suggest that also recent and current exposure of young adults to a farm environment may contribute to a lower risk of atopic sensitization to common aeroallergens.

A clear distinction between 'atopic sensitization' and 'atopic symptoms' or 'atopic disease' may also explain why – according to some critical comments [20] – the effect of a farm childhood would be most pronounced for hayfever and pollen sensitization, and much less for asthma, wheezing and indoor allergen sensitization. In our and many others' experience, self-reported hayfever shows in population studies a very strong association with positive pollen-specific SPT or IgE tests, while associations of self-reported wheezing and 'asthma' with indoor allergen sensitization are, although highly significant, in general much weaker. Apparently, much of self-reported wheezing and 'asthma' is of a non-atopic nature, and thus a relatively poor indicator of atopic sensitization compared with hayfever. In fact, the studies that included SPT or IgE serology have, just as our own study, found that a farm childhood is particularly associated with a low prevalence of atopic sensitization, not only to pollen but just as much also for indoor allergens [1,3], while relations with reported symptoms show less consistent patterns.

Given the currently high global prevalences of atopic diseases, it is of great importance to identify the farm environment-associated factors that would account for 'protection against atopy'. A genetic healthy farmer selection over a number of generations is unlikely [3], and thus external exposure factors must play a key role. Stimulation of the developing immune system towards Th1-dominated responses by microbial agents such as endotoxins has been proposed as a plausible

explanatory mechanism [21–23]. Gereda et al. [24] indeed showed a negative association between house dust endotoxin levels and the prevalence of atopic sensitization in young children in a non-farm community, and increased levels of endotoxin in house dust from farmers' homes, particularly on farms with livestock such as pigs, cows and horses, have been reported [25]. If the presumed immune modulation of atopic responsiveness occurs via systemic mechanisms, exposure to endotoxins or similar agents via the gastrointestinal tract (GIT) may, however, be important as well, and a different diet of farm children, e.g. frequent consumption of non-pasteurized milk with enhanced levels of (other) microbial pro-inflammatory or immune-modifying agents, would be another plausible explanation [21,23,26–28].

On the other hand, if modulation of atopic immune responses to aeroallergens occurs primarily at the respiratory mucosae, exposure to airborne microbial agents would be more relevant. Thus, further epidemiological and experimental studies are required to identify the most relevant environmental or dietary factors that would account for the much lower prevalence of atopy in farming communities. Elucidation of the underlying mechanisms will be of major importance for a better understanding of the relations between changing environmental and dietary exposures and the risks of atopic sensitization and disease.

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