New-onset asthma and the effect of environment and occupation among farming and nonfarming rural subjects

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Background: Many factors, including environmental exposures, have been related to the increase in the prevalence of asthma, but only few have been tested for in longitudinal studies.
Objective: We studied farming students to determine whether their environment during childhood and as adults was a factor determining subsequent onset of asthma.
Methods: From 1994 to 1998, new cases of asthma were identified by means of an annual posted questionnaire followed by a telephone interview in a prospective cohort consisting of 1964 farming-school students and 407 nonfarming subjects aged 16 to 26 years. For each case, we selected a control subject from the cohort with no asthma in a case-based design, and all underwent an interview and a clinical examination.
Results: We found 122 new cases of asthma. In a multiple regression model the odds ratio for new asthma was 3.3 (95% CI, 1.7-6.3) for smoking; 3.4 (95% CI, 1.6-7.0), 2.5 (95% CI, 1.1-5.3), and 7.0 (95% CI, 1.2-41.6) for exposure to swine, dairy production, and welding, respectively; and 11.7 (95% CI, 2.4-56.4) for bronchial hyperresponsiveness at baseline. Being born and raised on a farm significantly reduced the risk odds ratio (0.5 [95% CI, 0.3-0.98]), whereas atopy had no influence.
Conclusion: Exposure to swine and dairy confinements, welding, smoking, and bronchial hyperresponsiveness are risk factors for nonallergic asthma, and being born and raised on a farm reduces the subsequent risk. These findings support the theory that immune and inflammatory responses can be influenced by environmental exposure to early childhood, reducing the risk of asthma later in life. (J Allergy Clin Immunol 2011;128:761-5.)

Key words: *Farming, bronchial hyperresponsiveness, smoking, welding, hygiene hypothesis*

Abbreviations used
BHR: Bronchial hyperresponsiveness
COPD: Chronic obstructive pulmonary disease
OR: Odds ratio
TLR2: Toll-like receptor 2

Several studies have shown a high and increasing prevalence of asthma in the Western world during the last 2 to 3 decades, but there is uncertainty as to whether the prevalence of asthma is still increasing or has leveled off.[1] Many factors, including environmental exposures, have been related to the increase in the prevalence of asthma, but only a few risk factors have been tested for in longitudinal studies. However, cross-sectional studies in farmers have not all shown an increase in the prevalence.[2] Farming students in Denmark come from mixed backgrounds, with only half being raised on a farm, and they are exposed to a wide variety of allergens, organic dust, and toxins, all at high intensity. Therefore we have undertaken a longitudinal study of farming students to determine whether their environment during childhood and as adults was a factor determining the subsequent onset of asthma.

METHODS

Between 1992 and 1994, all of the 1964 farming-school students in Denmark who were in their second of 3 terms (mean age, 19.2 years; range, 16-26 years) together with 407 nonfarming rural subjects recruited from conscripts into the army were invited into a prospective cohort designed to study the risk factors for asthma development. The nonfarming rural subjects were living in a parish of no greater than 10,000 inhabitants, and they had no intention of making a career in farming. During the following 5 years, we identified all potential new cases every year and invited these cases and equally many control subjects for a clinical examination. The identification of potential cases was performed with a 2-step screening procedure, including (1) the annual screening questionnaire and (2) a telephone interview with all participants who reported at least 1 symptom indicative of asthma. The clinical examination at follow-up was exactly the same as during the baseline examination and included spirometry, tests for bronchial hyperresponsiveness (BHR), and skin prick tests. During the follow-up period, we performed the same interview on symptoms as at baseline plus an in-depth interview of work exposures at the time of first symptoms with a maximal delay of 1 year. The control subjects were asked for the work exposures at the middle of the preceding year.

For each new case, we selected a control subject from the cohort at the same time in a case-based design. We found 122 new cases of asthma and included 122 control subjects, of whom only 116 agreed to participate. We used the same definition of asthma as in the cross-sectional baseline study of the cohort,[3] which was a positive answer to at least one of 4 major questions (Have you been told by a doctor that you have asthma? Do you have asthma? Have you ever had asthma? Do you ever wheeze?) and 2 positive answers from a group of 10 symptom questions presented in Table I.

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A detailed occupational history was obtained for each employment period, together with a smoking history and information about place of birth, place of upbringing, and the start of asthma-like symptoms. For farming students, we asked for the type and number of animals in stables/confinement buildings to which they were exposed. Exposure to production animals was defined as hours of work each week in confinement or stable buildings. All were asked if welding was undertaken when performing their job. If welding was undertaken for more than a quarter of their working week, then the job was characterized as including a welding exposure. Skin prick tests were performed with a panel of 8 common inhalant allergens (Soluprick ALK; ALK-Abelló, Copenhagen, Denmark) extended with allergens from storage mites (*Tyrophagus putrescentiae*, *Acarus siro*, and *Lepidoglyphus destructor*) and molds (*Alternaria alternata* and *Cladosporium herbarum*). The test panel used was the same as at baseline. The extracts were placed on the skin of the forearm in 2 columns 50 mm apart. The skin was penetrated with a lancet, and after 10 minutes, the test was read as the greatest diameter of any wheal. Atopic status was diagnosed if the subject had 1 or more positive skin prick test responses (≥3 mm), and disposition to asthma was diagnosed if 1 or both parents had asthma.

FEV_1 and forced vital capacity were recorded in accordance with American Thoracic Society guidelines[4] by using the same dry wedge spirometer (Vitalograph, Buckingham, United Kingdom) as in the earlier cross-sectional study at baseline.[3] BHR was measured by using the method of Yan et al[5] with calibrated DeVilbiss No. 40 nebulizers (DeVilbiss Healthcare, Somerset, Pa) delivering a cumulative dose of 1.44 mg of histamine chloride; FEV_1 was recorded with a pneumotachograph the temperature and humidity of which were stabilized by the use of a fan.[6] Of the 238 participants, 8 refused to have their BHR measured, and 26 had missing data about being raised on a farm.

Univariate analysis was undertaken for categorical variables by using χ^2 tests in 2×2 tables. A *t* test was performed for comparison of continuous variables. Multivariate analysis was undertaken with logistic regression for categorical variables. Included in the model were skin prick test results, FEV_1, and bronchial responsiveness values at baseline[3] and the calculated cumulative exposure variables for each type of occupational exposure based on the questionnaire. The window of exposure for new cases of asthma was calculated as the years from the study's start at baseline up to the year before the start of the symptoms and half the year of debut. A probability of 5% or less was taken as significant.

TABLE I. List of 10 symptoms used in relation to diagnosing asthma

Do you ever have chest tightness?
Do you wake up in the morning with a tight chest?
Do you wake up in the night with wheeze?
Do you cough on waking in the morning?
Do you wake with a cough?
Do you wheeze when exposed to cold air?
Do you wheeze with exercise?
Do you wheeze when exposed to pollen?
Do you wheeze by exposure to animals?
Do you use asthma drugs?

RESULTS

There were 122 new cases of asthma identified, with 107 of these being from the farming students and 15 from the nonfarming rural subjects. Of the subjects with new asthma, 87% were male compared with 91% of the nonasthmatic subjects being male. Table II describes the demographic characteristics of the 112 subjects with new asthma (cases) and the 116 subjects who had not had asthma (control subjects). The age distribution was the same in cases and control subjects. Among farming students, the sex and atopy distribution was the same in cases and control subjects. All nonfarming rural subjects were male, and their prevalence of atopy was not significantly higher than among the farming students, both for cases and control subjects. There were significantly more smokers and subjects with BHR at baseline among the cases than among the control subjects. Significantly more of the control subjects among the farming students were raised on a farm compared with the cases with new-onset asthma. The frequency of being involved with dairy production was the same for cases and control subjects among the farming students at the time of the onset of symptoms for cases or retesting for control subjects; however, significantly more cases were involved in swine production than was true for the control subjects. Among the nonfarming rural subjects, involvement with welding as an occupation was significantly more prevalent among cases than control subjects, but none were exposed to swine or dairy production.

Table III lists the occupation held at the time of onset of asthma-like symptoms, with most of the farming-school students remaining in farming (90% of subjects with asthma and 73% of subjects with no asthma). None of the nonfarming rural subjects were occupied in farming, with most having jobs in industry and support services. Table IV shows the variables significantly associated with new cases of asthma in multivariate analyses adjusted for atopy, sex, disposition for asthma, and hay fever. The risk factors most strongly associated with new-onset asthma were baseline BHR (OR, 11.72; 95% CI, 2.44-56.44) and welding exposure (OR, 6.99; 95% CI, 1.17-41.57), followed by swine production (OR, 3.37; 95% CI, 1.63-6.97), smoking (OR, 3.26; 95% CI, 1.70-6.27), and dairy production (OR, 2.47; 95% CI, 1.14-5.34). Being raised on a farm significantly reduced the risk of new-onset asthma (OR, 0.50; 95% CI, 0.25-0.98). FEV_1 at baseline was not a risk factor for new-onset asthma. Stratifying for atopy did not change the estimates for either the atopic subjects or the nonatopic subjects, and the explained variance was the same in the 3 multivariate models (atopy adjusted $R^2 = 0.36$ as shown, R^2 for atopic subjects $= 0.32$, and R^2 for nonatopic subjects $= 0.33$; data not shown).

DISCUSSION

We have identified that baseline BHR, smoking, swine and dairy production, and welding all increase the risk of onset of asthma in young adults. More importantly, we also found that being raised on a farm significantly reduced the subsequent risk of asthma. This is the first evidence from a longitudinal study of environmental exposure protecting against the subsequent development of asthma.

Several cross-sectional studies in children have shown less atopy, hay fever, and asthma present in children raised on a farm compared with that seen in children raised elsewhere, and data from our initial cross-sectional study on this cohort, when they were about 20 years old,[7] found that the protective effect was also present in young adults. In Norwegian farmers[8] the prevalence of both allergic and nonallergic asthma was lower (4%) than that found among rural (5.7%) and urban (7.6%) populations. They also found from multiple regression analysis that there was a significantly reduced risk in farmers for both atopic (OR, 0.33) and nonatopic (OR, 0.60) asthma, suggesting a protective effect of

TABLE II. Demographic characteristics and the distribution of atopy and BHR among subjects with new-onset asthma (cases) and those without asthma (control subjects)

	Farming students		Nonfarming rural subjects	
	Cases (n = 107)	Control subjects (n = 102)	Cases (n = 15)	Control subjects (n = 14)
Age (y [SE])	21.7 (0.38)	22.6 (0.42)	21.8 (0.39)	22.5 (0.40)
Sex, male/female	91/16	92/10	15/0	14/0
Raised on a farm, no. (%)	26 (29.5)	46 (48.4)*	3 (20.0)	2 (14.3)
Smokers, no. (%)	59 (55.1)	27 (26.5)*	7 (46.7)	2 (14.3)
Atopy, no. (%)	30 (28.0)	28 (27.5)	9 (60.0)	6 (42.9)
BHR, no. (%)	19 (18.4)	2 (2.0)*	3 (21.4)	1 (7.7)
Type of exposure at the time of symptom onset or retesting				
Dairy production, no. (%)	33 (30.8)	26 (25.5)	0	0
Swine production, no. (%)	58 (54.2)	36 (35.3)*	0	0

*$P < .009$, cases versus control subjects among farming students.

TABLE III. Occupations held at the time of onset of asthma-like symptoms

	Farming students		Nonfarming rural subjects	
	Cases (n = 107)	Control subjects (n = 102)	Cases (n = 15)	Control subjects (n = 14)
Farming, no. (%)	96 (0.90)	73 (0.72)	0 (0.00)	0 (0.00)
Industry, no. (%)	1 (0.00)	9 (0.09)	0 (0.00)	2 (0.14)
Construction, no. (%)	0 (0.00)	3 (0.03)	1 (0.07)	0 (0.00)
Support services, no. (%)	3 (0.03)	0 (0.00)	4 (0.27)	4 (0.29)
Military, no. (%)	0 (0)	2 (0.02)	2 (0.13)	0 (0.00)
School, no. (%)	3 (0.03)	8 (0.08)	1 (0.07)	5 (0.36)
Unemployment, no. (%)	0 (0)	0 (0.00)	0 (0.00)	0 (0.00)
Other, no. (%)	3 (0.03)	2 (0.02)	0 (0.00)	1 (0.07)
Welding, no. (%)	1 (0.001)	1 (0.001)	7 (0.47)	2 (0.14)

Welding indicates more than 25% of work hours/week.

TABLE IV. Results from multivariate logistic regression analysis predicting onset of new asthma showing ORs with 95% CIs and significance level ($R^2 = 0.32$)*

Variable	OR	95% CI
Smoking	3.26	1.70-6.27
BHR	11.72	2.44-56.44
FEV_1	0.81	0.57-1.16
Swine production	3.37	1.63-6.97
Dairy production	2.47	1.14-5.34
Welding	6.99	1.17-41.57
Raised on a farm	0.50	0.25-0.98
Constant	0.91	

*Adjusted for atopy (OR, 1.33; 95% CI, 0.63-2.80), sex, disposition for asthma (OR, 2.33; 95% CI, 0.71-7.43), and hay fever. The variables BHR, FEV_1, and atopy are values measured at baseline.[3]

farming, although the authors stated that healthy worker selection might play a role.

The protective effect of farming exposure during childhood might be mediated through an increased tolerance toward endotoxin and other stimulants of the innate immune defense. The swine-confinement environment contains high amounts of microorganisms and their metabolites. A study looking at polymorphisms of the toll-like receptor 2 gene *(TLR2)* found that farmers' children with a T allele in *TLR2*/−16934 had significantly less asthma than children with genotype AA,[9] but this was only seen in farmer's children who were being raised on a farm and was not seen in the children of nonfarming parents. This finding was independent of the presence of atopy. The TLR2 receptor interacts with bacteria, yeasts, and parasites, all substances highly present in the farming environment. This might therefore suggest that the protective effect against asthma from being raised on a farm is due to a gene-environment interaction not only related to endotoxin modification of immune responses but more generally to the microbiological environment.

Of all the measures taken at baseline, the presence of BHR was the factor most strongly predictive of new-onset asthma in our subjects. This agrees with the results from the Spanish European Community Respiratory Health Survey study,[10] which was a longitudinal population-based study comprising 1640 subjects aged 20 to 44 years. Other recently published population-based epidemiologic studies[11,12] looking at the incidence of asthma and possible predictive factors had no data on BHR. However, an 11-year follow-up study from Switzerland[13] enrolling 4852 subjects found BHR to be a risk factor for both asthma and chronic obstructive pulmonary disease (COPD) and also for accelerated loss of lung function. Similar findings were observed in a Danish study[14] of 408 children and adolescents in which asymptomatic BHR was the strongest risk factor for the development of asthma.

Smoking significantly increased the risk of new asthma in our study, but data from previous published population-based studies have shown conflicting results. Torén et al[12] found a small increased risk for asthma during smoking person-years, and Wang et al[15] observed an interaction between smoking and bronchial airway responsiveness that increased the risk of new-onset asthma

in adulthood. A study of Danish adults found that asthma was significantly associated with current smoking.[16] In contrast to these findings from a cross-sectional study, results from longitudinal population-based studies in Denmark and Spain[10,17] did not find smoking to be a risk factor for new-onset asthma. Misclassification because of selection bias using questionnaire-based diagnosis of asthma might explain the heterogeneity of results concerning the relationship between smoking and asthma. In nonsmokers asthma-like symptoms are more likely to receive a diagnosis of asthma than in smokers[18] and, together with the healthy smoker effect,[19] introduce a differential bias, tending to underestimate asthma among smokers. However, the use of self-reported asthma might introduce differential bias, tending to overestimate the risk among smokers because smokers have been reported to have more severe asthma than nonsmokers.[20] A further differential bias might be introduced by wrongly diagnosing a case as asthma instead of COPD, with this error being more likely in smokers than nonsmokers. However, the present cohort is young, with a relatively short smoking exposure, indicating that the risk of COPD among our smokers should be very low.

We found that swine and dairy production and welding were identified as occupational risk factors for new-onset asthma. In a study of asthma prevalence and risk factors for respiratory diseases among 7752 farmers from across Europe, it was found that pig farmers had the highest risk for asthma symptoms.[21] A Norwegian study[8] found a higher prevalence for asthma in pig farmers (OR, 1.6) compared with that seen in farmers without livestock. Although exposure studies from different types of animal housing[2] found higher exposure levels of dust, bacteria, endotoxin, and ammonia in swine-confinement buildings than in cow stables, dairy production has also been associated with increased risk of asthma. In a study of 1015 Swedish dairy farmers, the prevalence of asthma increased from 5.3% to 9.8% during a period of 12 years (1984-1996).[22] Farming significantly increased the risk of asthma (OR, 1.53; $P = .0004$) among dairy farmers from central New York.[23] However, there is no uniform association between dairy production exposure and asthma. French data[24] suggest no increased risk of cumulative self-reported asthma and current asthma between dairy farmers and nonexposed control subjects (5.3% and 1.5% vs 3.4% and 1.3%, respectively). Welding as a cause of occupational asthma has been reported in short reports from Finland and Spain,[25-27] with a focus on metal arc welding and welding of stainless steel, and English surveillance data of occupational asthma rank welding as the most frequent cause (9%).[28] Few epidemiologic studies have been published analyzing the association between welding and asthma. Two cross-sectional studies[29,30] have shown conflicting results. The study from the United States did not find any association,[29] whereas in the study from Iran,[30] the prevalence of asthma was higher in welders than in nonwelders. In a recent published European 9-year follow-up study (the European Community Respiratory Health Survey II)[31] of 316 subjects, welding at work was not associated with asthma symptoms.

Selection of subjects to the farming school might partly explain the protective effect of being raised on a farm. We have looked at asthma prevalence among our farming-school students on entry to a career into the farming schools and their siblings who were not involved in farming. In those sibling pairs who were both raised on a farm, the prevalence of asthma was the same, whereas in those sibling pairs who were raised outside of a farm, the asthma prevalence was significantly higher among the siblings who did not take up farming than in those who became farming students.[32] This indicates that the probability that a sibling raised off a farm takes up a career in farming is affected by whether they have asthma. We therefore think that the protective effect of being raised on a farm is not explained by an effect of selection out of the farming trade.

The risk for new asthma was not related to the sex of the farming students. Because our data in the multiple regression model include very few female subjects, we might be unable to exclude a true effect of sex on the incidence of asthma. Hormonal factors and the sex-dependent difference in airway caliber have been suggested to explain this finding.[33] The reasons we have found no unequivocal link between sex and the development of asthma might be that female farming-school students are a selected group that must meet the physical demands of farming. Thus in terms of their airway caliber, they might match the male farming students more closely than would a randomly selected sample of European women.

Atopy did not influence the risk of new-onset asthma in the present study, whereas in several population-based longitudinal studies, atopy has been found to be a risk factor.[11,12,15] In cross-sectional studies in farming populations,[34,35] asthma or atopy as a child has been associated with asthma. However, asthma in Scandinavian farming populations most often is nonatopic,[8] and in our cohort positive skin prick test responses for common inhalant allergens were less common in the farming students than in the control subjects,[7,16] indicating a less pronounced influence of atopy on adult asthma among Scandinavian farmers.

This study presents a novel finding that childhood farming exposure can protect young adults who do not have asthma from subsequently having nonallergic asthma during a 5-year follow-up. This finding needs to be considered alongside the theory that too clean an environment during childhood subsequently leads to a higher prevalence of allergic phenotypes.[36,37] The mechanism behind the protective effect of childhood exposures is not yet known. In this study we find protection against nonallergic asthma, and this raises the possibility that the mechanism for this protection might not be solely through the regulation of allergic pathways.

We conclude that exposure to swine and dairy confinements, welding, smoking, and BHR are risk factors for asthma, and for the first time, we have shown in a longitudinal study that having being raised on a farm significantly protects young adults who were free from asthma from subsequently having asthma. This protective effect from farming exposure relates to the timing of the exposure, and we speculate that environmental modulation during childhood of immune or inflammatory responses might be important in causing this protective effect.

Clinical implications: Being raised on a farm protects young adults from having new nonallergic asthma (novel findings), whereas exposure to swine and dairy confinements, welding, smoking, and BHR increases the risk.

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