Original article

Rising prevalence of asthma is sex-specific in a US farming population

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Background: Asthma prevalence is increasing worldwide in most populations, likely due to a combination of heritable factors and environmental changes. Curiously, however, some European farming populations are protected from asthma, which has been attributed to their traditional lifestyles and farming practices.

Objective: We conducted population-based studies of asthma and atopy in the Hutterites of South Dakota, a communal farming population, to assess temporal trends in asthma and atopy prevalence and describe the risk factors for asthma.

Methods: We studied 1325 Hutterites (ages 6-91 years) at 2 time points from 1996 to 1997 and from 2006 to 2009 by using asthma questionnaires, pulmonary function and methacholine bronchoprovocation tests, and measures of atopy.

Results: The overall prevalence of asthma increased over the 10- to 13-year study period (7.5%-11.1%, $P = .049$), whereas the overall prevalence of atopy did not change (45.0%-44.8%, $P = .95$). Surprisingly, the rise in asthma was only among females (5.8%-11.2%, $P = .02$); the prevalence among males remained largely unchanged (9.4%-10.9%, $P = .57$). Atopy, which was not associated with asthma risk in 1996 to 1997, was the strongest risk factor for asthma among Hutterites studied in 2006 to 2009 ($P = .003$).

Conclusions: Asthma has increased over a 10- to 13-year period among Hutterite females and atopy has become a significant risk factor for asthma, suggesting a change in environmental exposures that are either sex limited or that elicit a sex-specific response. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Asthma, atopy, farming exposures, prevalence*

The prevalence of asthma has increased in most developed countries over the last 30 years.[1,2] In the United States, the prevalence of asthma rose from 3.1% to 7.4% between 1980 and 2007, with increases in both children (4.3% to 9.1%) and adults (2.8% to 7.3%).[3-7] This rise has been variously attributed to concurrent increases in immunization and antibiotic use,[8-12] obesity and sedentary lifestyles,[13,14] proinflammatory diets,[15-17] and air pollution[18,19] and to decreases in exposure to microbes in infancy,[20,21] duration of breast-feeding,[22-24] and family sizes,[25-27] among other factors.

In contrast, children raised on traditional European farms are protected from asthma,[28-32] suggesting that farming exposure in early life offers protection from asthma and atopy.[33] This farm-specific protection has been attributed to endotoxin exposure *in utero* and in early childhood[29,34,35] and possibly to exposure to cattle barns and raw (unpasteurized) milk in particular.[29,31,36,37] Curiously, this protective effect has not been consistently observed in children raised on US farms,[38,39] possibly due to differences in farming practices in the United States and Europe that include type of livestock, residential proximity to farm animals, farm size, use of antibiotics in livestock feed, and other farming practices that may be relevant to asthma susceptibility.[33,39]

In this paper we report the results of a cross-sectional study of asthma and allergic sensitization at 2 time points spanning 10 to 13 years in a US farming community, the Hutterites of South Dakota. The Hutterites are a religious isolate who originated in the South Tyrol in the 1500s and, after migrations throughout Europe over the next 300 years, settled in the United States in the 1870s. This population offers unique advantages for genetic studies because they live on large communal farms (called colonies), which ensures that environmental exposures are relatively uniform among individuals. Relevant to the study of pulmonary disease, smoking is prohibited (and rare) in this population. Although their farming practices are automated and state of the art, the Hutterites retain a traditional lifestyle that has changed little over many decades. For example, TVs, radios, and Internet access are forbidden, nearly all food is raised or grown on the colony, family sizes are large, and children are educated through the 8th grade in 2-classroom schoolhouses on the colony.

We have been conducting genetic studies of asthma in the Hutterites since 1993 and have reported significant sex-specific genetic architecture for asthma-associated quantitative traits in this population.[40-44] Here, we describe sex- and age-specific changes in asthma prevalences between 1996 and 2009 and describe the changing role of atopy in determining asthma risk.

METHODS

Study population

Approximately 900 Hutterites migrated from Europe in the 1870s to what is now South Dakota and settled on 3 communal farms, called colonies.[45] The Hutterites have remained reproductively isolated since arriving in the United

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States; however, because of a high natural fertility rate and desire for large families, they subsequently spread across the upper midwestern United States and western Canada.[45-48] Today, there are more than 35,000 Hutterites living on approximately 350 colonies, each of which is composed of 20 to 30 families. The more-than 1200 subjects in our studies live in South Dakota and are related to each other in a 13-generation, 3671-person pedigree with 64 founders. The mean kinship coefficient among these individuals is 0.035, slightly greater than that of first cousin once removed.

The Hutterites of South Dakota are highly productive poultry, pork, beef, and dairy farmers, though colonies vary with respect to the number and variety of livestock raised and farm acreage. The average colony encompasses 4000 square acres of land, and in addition to the farm facilities includes the Hutterite homes, communal kitchen and dining room, laundry, mechanical shops, schoolhouse, and church. Unlike European farmers, Hutterite women, infants, and young children rarely visit the animal barns, which are located at a distance from their homes, school, church, and dining room.

Although early life exposures, particularly in infancy, are very similar among boys and girls, Hutterite children begin the transition to sex-specific roles on the colony during their school years, with women eventually assuming responsibility for childcare, cooking, cleaning, sewing, and gardening and men taking on different jobs that include working with livestock (hogs, beef and dairy cows) or poultry (turkeys and chickens), raising crops (soybean, wheat, and corn), or performing technical or administrative jobs.

Phenotyping studies

Phenotyping studies were conducted in 1996 to 1997 and in 2006 to 2009 during visits to South Dakota colonies in the winter months (end of October through early March), the least busy season for farmers. Nine colonies were visited during each phase, of which 8 were visited during both phases (a total of 10 colonies). All Hutterites aged 6 years and older who were present on the days of our visits were invited to participate in these studies. Participation in each colony was greater than 95%, providing an unbiased cross section of the Hutterite population (age 6 years and older). In addition, Hutterites from other colonies in South Dakota, Minnesota, and North Dakota who were present on the days of our visits were invited to participate in our studies. In 1996 to 1997, 597 individuals completed asthma studies and 687 individuals completed skin prick testing; in 2006 to 2009, 841 individuals completed asthma studies and 937 individuals completed skin prick testing. Of these individuals, 309 were studied for asthma and 361 were studied for atopy at both time points. Methacholine bronchial challenges were not performed on pregnant or lactating women or if there were other medical contraindications (eg, prescribed beta-blockers), and therefore, asthma status could not be determined in these individuals. The combined sample size is 1187 Hutterites from 10 communal farms (colonies) in South Dakota studied between 1996 and 2009 and 138 visitors to those colonies (total number with asthma or atopy diagnosis n = 1325).

Subjects were evaluated by using a modified protocol from the Collaborative Study on the Genetics of Asthma.[40,49] All Hutterites aged 15 years and older and mothers of children younger than 15 years were interviewed by a pulmonologist or an asthma nurse by using a standardized symptom and clinical history questionnaire for asthma and atopy. A diagnosis of asthma required the following 3 elements: (i) the presence of at least 2 symptoms (wheezing, cough, or shortness of breath), (ii) a positive methacholine bronchial challenge test ($PC_{20} \leq 10$ mg/mL) or 15% improvement in baseline FEV_1 following inhalation of albuterol, and (iii) a doctor's diagnosis either prior to or at the time of our studies. Of the 45 diagnosed asthmatic subjects in 1996 to 1997, 25 (56%) had a prior physician's diagnosis of asthma and of the 59 individuals diagnosed in 2006 to 2009, 17 (29%) had a prior physician's diagnosis of asthma.

The presence of atopy was determined by a positive skin test reactivity to 1 or more of the tested allergens (Greer; Lenoir, NC).[40] The allergen panel included dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), pollen/grasses (*Ambrosia artemisiifolia*, *Artemisia vulgaris*, *Lolium perenne*, *Quercus alba*, *Betula verrucosa* [1996-1997 only] or *Poa pratensis*, *Betula nigra* [2006-2009 only]), pet danders (*Felis domesticus*, *Canis familiaris*), cockroaches (*Blattella germanica*, *Periplaneta americana*), and molds (*Aspergillus fumigatus*, *Cladosporium herbarum*, *Alternaria tenuis*) as well as negative (saline) and positive (histamine) controls. The area from skin prick wheal reactions (15 minutes after puncturing of the skin) was estimated by calculating the elliptical area by using the widest diameter measured and the diameter of the perpendicular axis. Significant skin reactivity was defined as a wheal area greater than 9 mm^2 and greater than that observed for the negative control in the presence of a visible response to histamine.

Prior to initiating our studies, consent was obtained from all adults and from mothers of children aged 18 years or younger and assent was obtained from Hutterites 18 years and younger. These studies were approved by the University of Chicago's Institutional Review Board.

Statistical analysis

The overall, sex-, and age-specific (by decade) prevalences of asthma and atopy were compared by using Fisher exact tests. *P* values (threshold <.05) are considered significant. *P* values from analyses comparing prevalences between the 2 time points are not corrected for the relatedness between individuals in the sample and are, therefore, slightly anticonservative. To ensure that the 2 samples were not interdependent, participants who were studied at both time points were included in the 1996 to 1997 sample but not in the 2006 to 2009 sample in all analyses. This also resulted in samples of similar sizes, making comparisons more readily interpretable.

To gauge the effects of risk factors on asthma, we analyzed both data sets (1996-1997 and 2006-2009) separately by using a binary variance component method. This method was developed in the context of general linear mixed models by using a logit link function and is specifically designed to estimate the effects of relevant factors on the risk of a binary trait by using data from large pedigrees with a complex lineage.[50] We modeled the effects of age, sex, atopy, number of older siblings, and genetics on the development of asthma by using a backward, stepwise selection method (threshold *P* value < .05) to identify the model that best fit each data set. In addition, we examined interaction effects between the significant risk factors. For each time period in our study, the estimates of the parameters from the best fitting model were then used to estimate the risk of asthma.

RESULTS

The demographic and clinical characteristics of our study population are shown in Table I; the sex- and age-specific prevalences of asthma and atopy in 1996 to 1997 and 2006 to 2009 are shown in Tables II and III, respectively. The overall prevalence of asthma increased over this short time period from 7.5% in 1996 to 1997 to 11.1% in 2006 to 2009 ($P = .049$). However, the increase in the prevalence of asthma was present only in females, in whom the prevalence nearly doubled, rising from 5.8% to 11.2% ($P = .02$). In contrast, the overall prevalence of asthma in males remained largely unchanged (9.4% in 1996-1997 and 10.9% in 2006-2009, $P = .57$). Although the overall prevalence of asthma was highest among children younger than 11 years at both time points (23.7% and 21.3%, respectively, $P = .81$), the largest increases in asthma were observed in the 11- to 30-year-old cohorts (increase from 6.2% to 11.6% among 11- to 20-year-olds, $P = .08$, and from 4.0% to 12.7% among 21- to 30-year-olds, $P = .047$). The cohorts aged 30 years and older had overall low prevalences of asthma that were similar between the 2 time points. Thus, the increase in asthma prevalence was confined to females and to individuals who were aged between 11 and 30 years during 2006 to 2009.

The observed overall rise in asthma was not coupled with a change in the overall prevalence of atopy in the Hutterites (Table III), which was 45.0% in 1996 to 1997 and 44.8% in 2006 to 2009 ($P = .95$), both lower than the 54.3% prevalence of atopy reported in the US population.[51] The prevalence of atopy also did not change significantly in males or females between 1996 and

TABLE I. Demographic and clinical characteristics of the study samples in 1996-1997 and 2006-2009

	Unaffected	Symptoms only	BHR only	Asthma	All
1996-1997	**n = 395**	**n = 62**	**n = 73**	**n = 45**	**n = 597**
Percent female	54	48	53	40	52
Age (y)	27 (17, 41)	33 (20, 42)	17 (12, 33)	22 (10, 37)	26 (16, 41)
BMI (kg/m^2)	24 (20, 28)	26 (23, 31)	23 (17, 27)	24 (17, 27)	24 (20, 28)
Percent predicted FEV_1	103 (15)	100 (12)	96 (18)	94 (10)	101 (15)
Percent predicted FVC	107 (15)	104 (11)	104 (17)	105 (11)	106 (14)
Mean FEV_1/FVC	82 (8)	82 (8)	80 (11)	78 (9)	81 (9)
Total IgE (kU/L)	20 (9, 50)	31 (8, 93)	14 (6, 36)	96 (24, 350)	23 (10, 77)
≥1 +SPT, n (%)	161 (41)	32 (52)	39 (53)	20 (45)	252 (44)
≥3 +SPT, n (%)	76 (19)	16 (26)	20 (27)	12 (27)	124 (22)
Asthmatic mother, n (%)	20 (8)	2 (5)	6 (12)	7 (22)	35 (8)
Asthmatic father, n (%)	30 (12)	8 (18)	9 (20)	9 (27)	58 (15)
No. of older siblings	3 (1, 6)	3 (1, 7)	3 (2, 6)	2 (1, 4)	3 (1, 5)
2006-2009	**n = 243**	**n = 78**	**n = 119**	**n = 59**	**n = 532**
Percent female	50	64	51	54	54
Age (y)	19 (14, 38)	49 (17, 32)	11 (9, 16)	20 (10, 14)	17 (12, 35)
BMI (kg/m^2)	23 (20, 28)	26 (20, 30)	19 (17, 23)	22 (17, 24)	22 (19, 27)
Percent predicted FEV_1	101 (13)	97 (13)	95 (12)	94 (12)	98 (13)
Percent predicted FVC	104 (14)	98 (14)	96 (12)	103 (13)	102 (14)
Mean FEV_1/FVC	85 (7)	85 (7)	87 (8)	83 (8)	85 (8)
Total IgE (kU/L)	8 (18, 44)	9 (18, 43)	26 (8, 66)	62 (23, 298)	23 (9, 61)
≥1 +SPT, n (%)	105 (43)	35 (45)	47 (39)	36 (61)	223 (45)
≥3 +SPT, n (%)	71 (29)	25 (32)	33 (28)	35 (59)	164 (33)
Asthmatic mother, n (%)	9 (6)	2 (5)	10 (10)	13 (32)	37 (10)
Asthmatic father, n (%)	9 (5)	3 (7)	17 (17)	11 (27)	42 (11)
No. of older siblings	3 (1, 5)	2 (1, 5)	2 (1, 4)	2 (1, 4)	3 (1, 5)

For mean values, the standard deviation is presented in parentheses; for median values, the first and third interquartile values are presented in parentheses.
BHR, Bronchial hyperresponsiveness; *BMI*, body mass index; *FVC*, forced vital capacity; *SPT*, skin prick test.

TABLE II. Prevalence of asthma in 1996-1997 and 2006-2009

	1996-1997 (no. asthma/ total)	Prevalence	2006-2009 (no. asthma/ total)	Prevalence	*P* value
Overall	45/597	7.5%	59/532	11.1%	**.049**
Males	27/286	9.4%	27/247	10.9%	.57
Females	18/311	5.8%	32/285	11.2%	**.02**
Age (y)					
≤10	9/38	23.7%	17/80	21.3%	.81
11-20	11/177	6.2%	27/232	11.6%	.08
21-30	5/126	4.0%	7/55	12.7%	**.047**
31-40	10/97	10.3%	2/65	3.1%	.126
41-50	5/83	6.0%	2/52	3.8%	.70
>50	5/76	6.6%	4/48	8.3%	.73

Individuals studied for asthma at both time points are included only in the 1996-1997 groups (n = 309). *P* values are calculated by using a Fisher exact test but are not corrected for relatedness of individuals in the sample. *P* values of <.05 are in boldface.

2009. Surprisingly, however, we saw a dramatic age-specific decrease in atopy prevalence in children aged 10 years and younger, with skin prick reactivity dropping from 57.1% in 1996 to 1997 to 33.3% in 2006 to 2009 ($P = .001$). In contrast and unlike the trends for asthma, the prevalence of atopy remained relatively unchanged (~50%) among Hutterites aged 11 to 30 years but increased in individuals older than 30 years from 32% to 37% in 1996 to 1997 to 44% to 50% in 2006 to 2009 (Table III).

To evaluate whether the effects of risk factors for asthma changed between the 2 time points, we assessed the effects of age, sex, atopy, and number of older siblings in each sample by using a multivariate model that also included a component that models the contribution of genetic factors to the risk of asthma. All analyses at each time point revealed a strong genetic component to the development of asthma ($P < .001$). However, other risk factors for asthma differed in the 1996 to 1997 and 2006 to 2009 samples (Table IV). In the earlier study period, being male ($P = .056$) and/or having fewer older siblings ($P = .033$) contributed to asthma risk; age and atopy were not significant during this time period. However, in the more recent study period, sex and number of older siblings were no longer significant predictors of asthma, whereas atopy ($P = .003$) and younger age ($P = .004$) were significant. That sex is not a significant predictor of asthma in 2006 to 2009 is attributed to the fact that the prevalences of asthma between males and females are similar in the more recent sample (ie, the females "caught up" to the males during the later time period); the association with "younger age" in the later period reflects the increased prevalence in the 11- to 30-year-old cohorts. The lack of association with "number of older siblings" in the later cohort was surprising, but likely reflects the large effects of atopy and age that may have reduced our power to detect the older sibling effect. None of the interaction terms between the significant covariates at either time point was significant. The age-specific risks for Hutterites with and without atopy are shown in Fig 1 for the 2006 to 2009 sample.

DISCUSSION

The prevalence of asthma has risen over the last decade in the Hutterites, similar to other "westernized" populations.[2] In the Hutterites, the rise in asthma was disproportionate in females

TABLE III. Prevalence of atopy in 1996-1997 and 2006-2009

	1996-1997 (no. atopic/ total)	Prevalence	2006-2009 (no. atopic/ total)	Prevalence	*P* value
Overall	309/687	45.0%	258/576	44.8%	.95
Males	156/316	49.4%	118/268	44.0%	.21
Females	153/371	41.2%	140/308	45.5%	.28
Age (y)					
≤10	40/70	57.1%	44/132	33.3%	**.001**
11-20	106/199	53.3%	105/220	47.7%	.28
21-30	69/138	50.0%	26/51	50.9%	1.00
31-40	38/119	31.9%	36/72	50.0%	**.02**
41-50	27/82	32.9%	23/47	48.9%	.09
>50	29/79	36.7%	24/54	44.4%	.47

Individuals studied for atopy at both time points are included only in the 1996-1997 groups (n = 361). *P* values are calculated by using a Fisher exact test but are not corrected for relatedness of individuals in the sample. *P* values of <.05 are in boldface.

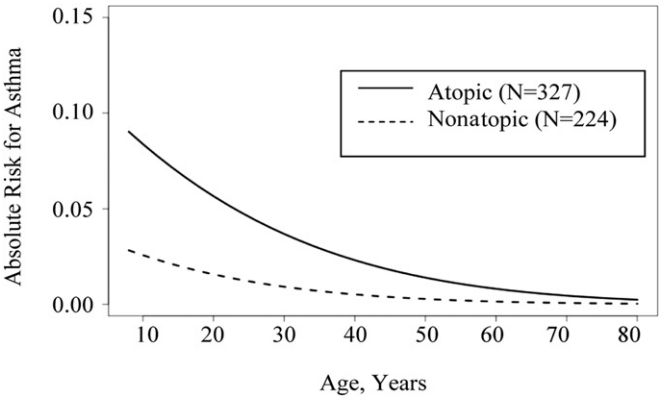

FIG 1. Absolute age-specific risks for asthma by atopic status in 2006 to 2009.

TABLE IV. Multivariate analysis of risk factors for asthma in 1996-1997 and 2006-2009

Covariates	Estimate (SE)	Odds ratio (95% CI)	*P* value
1996-1997			
Constant	−3.45 (0.83)		**<.001**
Sex	−0.97 (0.51)	0.38 (0.14-1.03)	.056
No. of older siblings	−0.18 (0.09)	0.83 (0.71-0.98)	**.033**
Genetic component*	2.58 (0.58)		**<.001**
2006-2009			
Constant	−6.82 (1.62)		**<.001**
Age	−0.08 (0.03)	0.92 (0.87-0.98)	**.004**
Atopy†	2.22 (0.73)	9.22 (2.19-38.85)	**.003**
Genetic component*	3.79 (0.84)		**<.001**

Only those covariates that are close to the significance threshold ($P < .05$) are listed. Those covariates with $P < .05$ are shown in boldface.

*The genetic component is an estimate of the variability in asthma risk that can be attributed to genetics.

†Atopy is defined as a positive skin prick test response to any of 13 tested aeroallergens (see the Methods section).

and in the subset of the population between the ages of 11 and 30 years. The female-specific rise in asthma prevalence mirrors data from the National Health and Nutrition Examination Survey,[5,6] as well as from other international epidemiological studies.[52-55] In the National Health and Nutrition Examination Survey, US asthma prevalences have consistently been higher in females than in males (4.6% vs 3.3%, respectively, in 1996-1997 based on symptoms, and 8.6% vs 6.9%, respectively, in 2006-2008 based on a physician's diagnosis).[3] However, in contrast to the National Health and Nutrition Examination Survey data, there was virtually no change in asthma rates among Hutterite males during this time period.

In the Canadian National Public Health Study, Ghosh et al[53] investigated asthma prevalence by sex, age, and urban/rural residence from 1996 to 2001. They also reported a trend toward increased asthma in women over time, particularly in the 15 to 34 years age group, whereas boys in the 0 to 14 years age group consistently had the highest overall prevalence of asthma. Female sex was also associated with a greater incidence of new asthma cases in the European Community Respiratory Health Survey of young adults who were unaffected at age 20 to 44 years in 1990 to 1995 but developed asthma in the interval between 1998 and 2003. However, atopy was not a significant risk factor for new-onset asthma in that study, in contrast to our findings in the Hutterites.[52] In all the aforementioned studies, both female sex and young to midadulthood appear to be important elements that allow for the development of asthma.

A genetic component contributing to asthma risk in the Hutterites was highly significant in the multivariate analyses of both the 1996 to 1997 and 2006 to 2009 samples ($P < .001$). Although the multivariate method used in this study does not allow a direct measure of the changes in genetic risk, the strong genetic predisposition to asthma and the increased prevalence observed in this population over a relatively short time period are findings similar to those of a recent Danish twin cohort study.[56] In that study, an increase in the heritability of asthma over a similarly short (decadelong) time period was observed, in particular among females. The investigators proposed a change in the penetrance of asthma risk alleles as a result of changing environmental exposures as a plausible mechanism. We suggest a similar mechanism for the sex- and age-specific changes in asthma prevalence in the Hutterites over a 10- to 13-year interval.

For example, a change in common practices (such as a shared occupational exposure among women) may underlie the increase in asthma and allergic sensitization over the last 10 to 13 years. Although we do not know the specific exposure, it is notable that during this same time period the Hutterite women stopped using homemade soaps for cleaning their houses and started to purchase commercial cleaners, which have been associated with occupational asthma in other populations.[57] For instance, exposure to quaternary ammonium compounds, such as those found in many common cleaners (eg, Pine-Sol and Lysol), induced a nonspecific IgE response to common aeroallergens and concurrent respiratory symptoms compatible with asthma in a study of pig farmers.[58] Cleaning chemicals are thought to act as low-molecular-weight haptens that complex with other proteins (including allergens) and thus drive a nonspecific IgE response.[59] This would support an immunologic basis for the rise in asthma prevalence in women and may represent an unmasking of an underlying genetic predisposition to asthma.

Lastly, we note the unexpected observation of a significant decrease in atopy in children aged 10 years and younger (from 57.1% to 33.3%; Table III) between 1996 to 1997 and 2006 to 2009, without a corresponding change in the prevalence of asthma (Table II). This observation suggests that the trigger for asthma in the youngest age group is not directly tied to an allergic response

as measured by the skin prick test. A similar discordance was seen in the increase in asthma prevalence among 11- to 30-year -olds without a corresponding change in the prevalence of atopic sensitization. These observations underscore that atopic sensitization remains a relatively common condition in the Hutterites. Although sensitization did not correlate with asthma risk in the earlier study, it became an important risk factor for the development of asthma in the 2006 to 2009 sample, particularly in the younger age groups (Fig 1). These combined observations reflect the fact that the overall decrease in atopy in children in the later time period occurred disproportionally in the nonasthmatic children.

While the causes of the increased prevalence of asthma in this farming community are at present still unknown, our observation of the increased asthma prevalence that is confined solely to females and individuals aged 11 to 30 years of age is intriguing. Whether this represents a response to an exposure that is unique to this community or an exposure that is common to many populations (such as household cleaners) remains to be determined, but nonetheless extends the spectrum of environmental factors that may be contributing toward the worldwide rise in asthma prevalence in developed countries. Furthermore, this epidemiological study underscores the importance of future efforts to untangle important gene by environment interactions that may bear on sex- and development-specific observations of disease prevalence.

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Key messages

- **Asthma has increased significantly in a South Dakota farming population, but only in females.**
- **Hutterite females and males are now similarly affected by a high prevalence of asthma.**
- **Atopy and younger age were independent risk factors for asthma among Hutterites studied in 2006 to 2009 compared with 1996 to 1997.**

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