Atopy and allergic respiratory disease in rural Poland before and after accession to the European Union

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Background: In 2003, we recorded a striking difference in the prevalence of atopy between village and small-town populations in southwest Poland. Nine years later, we undertook a second survey of the same area.

Objective: We sought to assess whether rapid changes in farming practices, driven by accession to the European Union in 2004, were accompanied by an increase in atopy, asthma, and hay fever in these villages.

Methods: In 2012, we surveyed 1730 inhabitants older than 5 years (response rate, 85%); 560 villagers and 348 town inhabitants who had taken part in the earlier survey. Participants completed a questionnaire on farm-related exposures and symptoms of asthma and hay fever. Atopy was assessed by using skin prick tests.

Results: In 2012, far fewer villagers had contact with cows (4% vs 24.3% in 2003) or pigs (14% vs 33.5%), milked cows (2.7% vs 12.7%), or drank unpasteurized milk (9% vs 35%). Among the villagers, there was a significant increase at all ages in the prevalence of atopy between 2003 and 2012 both in the total population (7.3% vs 19.6%, $P < .0001$) and among those who took part in both surveys (7.9% vs 17.8%, $P < .0001$). Among the townspeople, the prevalence of atopy did not change substantially (20% vs 19.9% and 21.7% vs 18.5%, respectively). Hay fever increased 2-fold in the villages (3.0% vs 7.7%) but not in the town (7.1% vs 7.2%); there was little or no change in asthma prevalence in the villages (5.0% vs 4.3%) or town (4.3% vs 5.0%).

Conclusions: We report a substantial increase in atopy at all ages and in a remarkably short period of time in a Polish population whose farm-related exposures were dramatically reduced after their country's accession to the European Union. (J Allergy Clin Immunol 2014;133:1347-53.)

Key words: *Atopy, asthma, farming exposures, changes in farming practices*

In 1970, Peter Preston[1] posed the following question: "Is the atopic syndrome a consequence of good hygiene?" If this was the case, he argued that "the manifestations of atopy … would have appeared in given areas only after standards of hygiene … had been raised to high levels." His hygiene hypothesis was later developed by Strachan[2] and has been proposed as a central explanation for some of the geographic and temporal distributions of atopy and associated conditions, such as asthma, rhinitis, and eczema, in the last few decades. Although there are some notable anomalies,[3] the global patterns are broadly consistent with the hypothesis that asthma increases as countries become more Western, urban, and cleaner. In this context particular attention has been paid to the apparently protective effects of a childhood spent on a farm, most notably in Alpine village families in which those children born to dairy farmers have lower rates of hay fever and atopy than their neighbors from nonfarming families.[4] Although these findings have been reproduced many times in Western countries, the underlying causes remain unclear.[5]

In 2003, we undertook a survey (Alegro 1) of atopy, asthma, and rhinitis in the inhabitants of a region of lower Silesia, Poland.[6] Among those living in Sobotka, an unremarkable town of just 4000 inhabitants, the prevalence of atopy was 20%, with a peak (35%) in those 11 to 20 years of age, a pattern very like that in the United Kingdom and similar countries. In contrast, among those living in any of 7 small villages, each no more than 10 km from the town, the prevalence of atopy was just 7%, a figure less than any recorded elsewhere in Europe and varying little by age. At that time, 55% of villagers (but <1% of those living in Sobotka) described themselves as living on farms, although "smallholdings" might be a better description. A quarter had regular or occasional contact with cows, a third had regular or occasional contact with pigs, and 35% reported that they drank unpasteurized cow's milk.[7] We could not discern a "farm effect" among the village families, probably because, as we argued, every villager was sufficiently exposed to the protective effect or effects attributed elsewhere to farming, irrespective of whether they were farmers themselves.

In 2004, Poland acceded to the European Union, a condition of which was the national adoption of the Common Agricultural Policy. As a result, it immediately became uneconomic for village farmers in Silesia to keep small numbers of cows or other large farm animals. Figures provided by the Veterinary Office in Wrocław, for example (personal communication), show that between 2002 and 2007, the number of cows kept by households in the seven Alegro 1 villages decreased by 80%, from a total of 295 to 58; local agricultural census returns in 2002 and 2010 showed similar reductions in the numbers of farmed pigs.

We predicted that these changes would lead to an increase at all ages in the prevalence of atopy among the Alegro 1 villagers. Thus, in 2012, we undertook a second survey of the same populations, which was called Alegro 2.

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TABLE I. Characteristics of total surveyed populations in 2003 and 2012

	Sobotka			Villages				
	2003	2012	*P* value	2003	2012	*P* value	*P* value*	*P* value†
Eligible (no.)	784	927		1144	1076			
Surveyed, no. (%)	707 (90)	832 (90)	.77	993 (87)	898 (84)	.03	.02	<.001
SPT, no. (%)	691 (98)	808 (97)	.45	973 (98)	868 (97)	.07	.73	.59
Age (y), median (range)	40 (5-86)	46 (5-99)	<.001	34 (5-92)	40 (5-92)	<.001	.01	.003
Female sex, no. (%)	389 (55)	475 (57)	.41	526 (53)	487 (54)	.58	.40	.23
Household size, median (range)	4 (1-8)	3 (1-8)	<.001	5 (1-13)	4 (1-12)	<.001	<.001	<.001
Participated in both surveys, no.	348			560				
Birth order, no. (%), first born	280 (40)	334 (40)	.83	313 (32)	318 (35)	.07	<.001	.04
Live on a farm?, no. (%)	7 (1)	18 (2)	.07	547 (55)	452 (50)	.04	<.001	<.001
Regular or occasional contact with:								
Cows	3 (0.4)	2 (0.2)	.53	241 (24.3)	39 (4.3)	<.001	<.001	<.001
Pigs	6 (0.8)	9 (1.1)	.64	333 (33.5)	126 (14.0)	<.001	<.001	<.001
Poultry	25 (3.5)	27 (3.2)	.75	465 (46.8)	333 (37.1)	<.001	<.001	<.001
Sheep or goats	4 (0.6)	7 (0.8)	.52	32 (3.2)	28 (3.1)	.90	<.001	<.001
Horses	3 (0.4)	3 (0.4)	.84	8 (0.8)	17 (1.9)	.04	.44	<.001
Regular or occasional:								
Milking cows	0 (0)	1 (0.1)	.36	119 (12.0)	24 (2.7)	<.001	<.001	<.001
Cleaning barns or stables	4 (0.6)	17 (2.0)	.01	283 (28.5)	140 (15.6)	<.001	<.001	<.001
Collecting eggs	16 (2.3)	22 (2.6)	.63	341 (34.4)	255 (28.4)	.01	<.001	<.001
Drinking unpasteurized milk	37 (5.2)	42 (5.0)	.87	347 (34.9)	78 (8.7)	<.001	<.001	<.001

SPT, Skin prick test.
*χ^2 Test comparing Sobotka in 2003 and villages in 2003.
†χ^2 Test comparing Sobotka in 2012 and villages in 2012.

METHODS

We obtained approval for the survey from the Ethics Committee at the Wrocław Medical University; each participant provided signed consent, did so on behalf of their child, or both.

We used exactly the same instruments in the second survey, albeit delivered by a new set of 7 research nurses who were not informed of our hypothesis. We again invited all households in the 7 villages and in 2 areas of Sobotka to take part: all residents 5 years or older were eligible. Each person 15 years or older completed a questionnaire administered by a research nurse; mothers supplied information for younger children. We used standardized questions from the International Study of Asthma and Allergies in Childhood protocol[8] on symptoms of asthma and rhinitis; we also included questions on current and past exposure to farm animals. We invited everyone to undergo skin prick tests with extracts of the 4 common aeroallergens house dust mite, cat fur, mixed grass pollens, and tree pollens (ALK-Abelló, Hungerford, Berkshire, United Kingdom) and with negative (saline) and positive (histamine) control solutions. The nurses each surveyed approximately equal numbers of urban and village households.

Of 2003 eligible persons, 1730 (86%) took part in the survey. They were a little older than those who did not take part (median age, 42 vs 39 years) and were more often female (56% vs 37%). We surveyed 898 (84%) of 1076 eligible villagers, 868 (97%) of whom had a skin prick test; 560 of them had taken part in Alegro 1 (Table I). In Sobotka 927 were eligible for the survey; 832 (90%) took part, with 808 (97%) undergoing skin testing, and 348 had participated in the earlier survey. Those townspeople who participated in both surveys were 4 years older than those from the villages (median age in Sobotka, 48.6 years; median age in the villages, 44.5 years).

Villagers who took part in both surveys had a lower prevalence of atopy in 2012 than those who were surveyed only in 2012 (17.8% vs 22.6%); the converse was true in Sobotka, where the prevalence of atopy was a little higher among those who were surveyed twice (21.7% vs 18.6%).

In 2012, in both the village and town populations, there were no significant differences in mean skin prick test responses to histamine measured by the 7 study nurses. On average, the histamine responses were slightly higher than in the original survey, both in the townspeople (5.2 mm in 2012 vs 4.6 mm in 2003) and the villagers (5.6 mm in 2012 vs 5.0 mm in 2003).

We considered skin prick test responses to be positive if they induced a mean wheal diameter 3 mm or greater than the response to saline and considered a subject to be atopic if he or she had a positive response to 1 or more of the test allergens. We calculated crude and adjusted prevalence odds ratios[9] using logistic regression, adjusting for age, sex, first-born status, maternal age, current smoking, parental farming, and location (town/village; identified *a priori* as potential confounders) and including a "family" variable to account for any clustering effect. In analyses comparing the inhabitants of Sobotka and the villages, we also adjusted for living on a farm and associated exposures. All analyses were performed with the IBM SPSS Statistics 20 package (SPSS, Chicago, Ill).

RESULTS

Table I compares the characteristics of the participants living in Sobotka and those living in the villages. In 2012, as in 2003, very few families from Sobotka reported that they lived on a farm, and fewer had any regular or occasional contact with large farm animals or undertook farming tasks. In contrast, half of the village families in 2012 lived on a farm, a proportion only a little less than that in 2003. However, the nature of these farms was very different from the first survey. In 2012, few villagers had even occasional contact with cows (4%) or pigs (14%), and few (3%) continued to milk cows. Contact with poultry was also less common in 2012, but the difference from 2003 was smaller. The decrease in farm animal exposures was present at all ages (Fig 1). In 2012, just 9% of the village population reported that they regularly or occasionally drank unpasteurized milk, a figure less than that in 2003 (35%) and similar to that in the people of Sobotka at both time points.

The prevalence of atopy and associated respiratory allergies in 2012 is shown in Table II for the whole surveyed population and in Table III for those who had also taken part in the first survey (2003). The prevalence of atopy in 2012 was very similar in the village and town populations among all survey participants (19.6% [95% CI, 16.9% to 22.2%] vs 19.9% [95% CI, 17.2% to 22.7%]) and among those who participated in both surveys (17.8% [95% CI, 14.6% to 21.0%] vs 21.7% [95% CI, 17.3% to

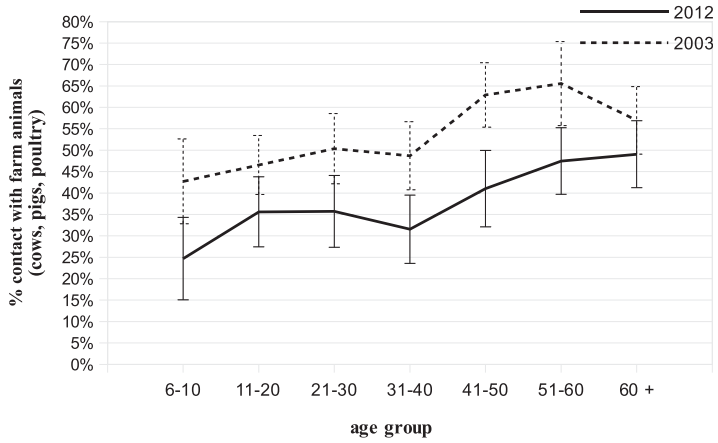

FIG 1. Age-specific exposure to farm animals (cows, pigs, and poultry) in the village population in 2003 and 2012.

26.1%]). Among the village inhabitants, the prevalence of atopy was significantly higher in 2012 than in 2003 in both the total surveyed population (19.6% vs 7.3%, $P < .001$) and in those who took part in both surveys (17.8% vs 7.9%, $P < .001$); in Sobotka it did not change in the total population (19.9% vs 20.0%, $P = .98$) and increased only slightly among those participating in both surveys (18.5 % vs 21.7%, $P = .30$). Similar increases in atopy among the villagers were seen for each of the test allergens.

The increase in the prevalence of atopy in the villages was present at all ages, although it was most pronounced up to age 50 years both in the total surveyed population and among those who took part in both surveys (Fig 2, *C* and *D*). In town inhabitants who were surveyed twice, the age-specific prevalences of atopy shifted, with the peak moving from the 11- to 20-year age group to the 21- to 30-year age group, but this merely reflected the time interval (9 years) between the 2 surveys (Fig 2, *B*).

In contrast to these findings, we did not observe any important temporal changes in either population in the prevalence of wheeze or rhinitis or diagnoses of asthma (Tables II and III). The prevalence of doctor-diagnosed hay fever increased 2-fold in the village population (3.0% vs 7.7%) but did not change in the town population (7.1% vs 7.2%). The increase in diagnosed hay fever in the village population was confined to those age 50 years or less and was particularly marked (approximately 5-fold) in those between 11 and 40 years of age. However, just 41% of those living in Sobotka and 44% of villagers who reported a doctor's diagnosis of hay fever had a positive skin prick test response to grass or tree pollens.

Table IV summarizes the associations between atopic status in 2012 and a series of farm-related exposures in the full surveyed population. In each case the odds ratios were generally consistent with a protective effect, but the strongest protective factors differed between the 2 time periods. In 2003, the strongest protective effects were from drinking unpasteurized milk, although there were also possible protective effects from contact with pigs and poultry and, to a lesser extent, cows. In 2012, the strongest protective effect was from contact with cows, but there were also possible protective effects from contact with pigs and animal-related activities, such as milking cows, cleaning barns, and collecting eggs. Living on a farm was protective in 2012, although not in 2003 (Table IV).

A further analysis (not shown in tables) confined to those villagers who had taken part in both surveys confirmed the 3-fold increase in the prevalence of atopy between 2003 and 2012. However, adjusting for a range of farm-related exposures (living on a farm; contact with cows, pigs, or poultry; and drinking unpasteurized milk) did not account for this increase; there was little or no change in the odds ratio comparing the prevalence between 2012 and 2003 when the analysis was adjusted for these farming-related factors, even though they individually showed protective effects. Table V summarizes analyses of "incident" cases of atopy (those who attended both surveys and were atopic in 2012 but not in 2003) in relation to individual measures of farm-related exposures in 2003/2012. Continuing residence on a farm and persistent exposure to farm animals (cows, pigs, or poultry) offered protective effects against the development of atopy.

DISCUSSION

As we hypothesized, there has been a steep increase over a period of just 9 years in the prevalence of atopy in these Silesian villages. The increase is evident at all ages and has eliminated the stark contrast between villagers and townspeople that was evident in 2003. On the other hand, there was little change in the prevalence of asthma symptoms or diagnosed asthma and only a modest increase in diagnosed hay fever (but not hay fever symptoms) in the villages. We found protective effects for living on a farm in 2012, as well as (nonsignificant) protective effects of farming-related exposures, including contact with cows, pigs, and poultry; milking cows; cleaning barns; and collecting eggs. However, adjusting for these factors made little change to the odds ratios when comparing atopy in the villages in 2012 and 2003.

Before considering the potential explanations for these striking findings, some possible sources of bias should be considered. The questionnaires used have been validated and widely used in international studies,[10] as have our methods for measuring atopy. We used identical methods in 2003 and 2012, making it highly unlikely that the changes between the surveys are due to methodological inaccuracies; it is very difficult to see how any such inaccuracies could have created differences between Sobotka and the villages in 2003 but not in 2012. The research nurses

TABLE II. Prevalence of atopy and associated conditions in 2003 and 2012 among the total population

	Total surveyed population					
	Sobotka			Villages		
	2003	2012	*P* value	2003	2012	*P* value
No.	691	808		973	868	
Atopy (any), no. (%)	138 (20.0)	161 (19.9)		71 (7.3)	170 (19.6)	
95% CI	17.0% to 23.0%	17.2% to 22.7%	.98	5.7% to 8.9%	16.9% to 22.2%	<.001
House dust mite, no. (%)	56 (8.1)	62 (7.7)	.76	35 (3.6)	90 (10.4)	<.001
Grass pollen, no. (%)	73 (10.6)	80 (9.9)	.67	35 (3.6)	77 (8.9)	<.001
Tree pollen, no. (%)	30 (4.3)	51 (6.3)	.09	10 (1.0)	44 (5.1)	<.001
Cat fur, no. (%)	38 (5.5)	54 (6.7)	.34	16 (1.6)	58 (6.7)	<.001
Wheeze/asthma, no.	707	832		993	898	
Have you had wheezing or whistling in the chest in last 12 mo?, no. (%)	54 (7.6)	32 (3.8)	.001	64 (6.4)	50 (5.6)	.42
Have you ever been told by a doctor that you have asthma?, no. (%)	35 (5.0)	36 (4.3)	.56	43 (4.3)	45 (5.0)	.48
No.	691	808		973	868	
Atopy and wheeze in last 12 mo, no. (%)	20 (2.9)	13 (1.6)	.09	10 (1.0)	12 (1.4)	.48
Rhinitis/hay fever, no.	707	832		993	898	
In last 12 mo, have you had a problem with sneezing or a runny or blocked nose or itchy eyes when you (your child) did not have a cold or flu?, no. (%)	329 (46.5)	318 (38.2)	.001	257 (25.9)	229 (25.5)	.85
Problem with sneezing or a runny or blocked nose or itchy eyes in April, May, June, or July	310 (43.8)	291 (35.0)	<.001	190 (19.1)	171 (19.0)	.96
Has a doctor ever told you that you have hay fever?, no. (%)	50 (7.1)	60 (7.2)	.92	30 (3.0)	69 (7.7)	<.001
No.	691	808		973	868	
Grass or tree pollen sensitization with rhinitis during pollen season (May, June, July), no. (%)	61 (8.8)	63 (7.8)	.47	18 (1.8)	33 (3.8)	.01

TABLE III. Prevalence of atopy and associated conditions in 2003 and 2012 among those who were surveyed in both years

	Population taking part in both surveys					
	Sobotka			Villages		
	2003	2012	*P* value	2003	2012	*P* value
No.	335	336		541	540	
Atopy (any), no. (%)	62 (18.5)	73 (21.7)		43 (7.9)	96 (17.9)	
95% CI	14.3% to 22.7%	17.3% to 26.1%	.30	5.7% to 10.2%	14.6% to 21.0%	<.001
House dust mite, no. (%)	26 (7.8)	32 (9.5)	.42	20 (3.7)	56 (10.4)	<.001
Grass pollen, no. (%)	32 (9.6)	36 (10.7)	.62	24 (4.4)	38 (7.0)	.07
Tree pollen, no. (%)	11 (3.3)	25 (7.4)	.02	5 (0.9)	18 (3.3)	.006
Cat fur, no. (%)	19 (5.7)	26 (7.7)	.29	9 (1.7)	33 (6.1)	<.001
Wheeze/asthma, no.	347	348		561	560	
Have you had wheezing or whistling in the chest in last 12 mo?, no. (%)	27 (7.8)	14 (4.0)	.04	33 (5.9)	34 (6.1)	.89
Have you ever been told by a doctor that you have asthma?, no. (%)	11 (3.2)	15 (4.3)	.43	24 (4.3)	30 (5.4)	.40
No.	335	336		541	540	
Atopy and wheeze in last 12 mo, no. (%)	9 (2.7)	5 (1.5)	.28	6 (1.1)	6 (1.1)	.997
Rhinitis/hay fever, no.	347	348		561	560	
In last 12 mo, have you had a problem with sneezing or a runny or blocked nose or itchy eyes when you (your child) did not have a cold or flu?, no. (%)	160 (46.1)	140 (40.2)	.12	149 (26.6)	141 (25.2)	.60
Problem with sneezing or runny or blocked nose or itchy eyes in April, May, June, or July	151 (43.5)	128 (36.8)	.07	109 (19.4)	106 (18.9)	.83
Has a doctor ever told you that you have hay fever?, no. (%)	23 (6.6)	26 (7.5)	.66	20 (3.6)	32 (5.7)	.09
No.	335	336		541	540	
Grass or tree pollen sensitization with rhinitis during pollen season (May, June, July), no. (%)	28 (8.4)	28 (8.3)	.99	12 (2.2)	18 (3.3)	.26

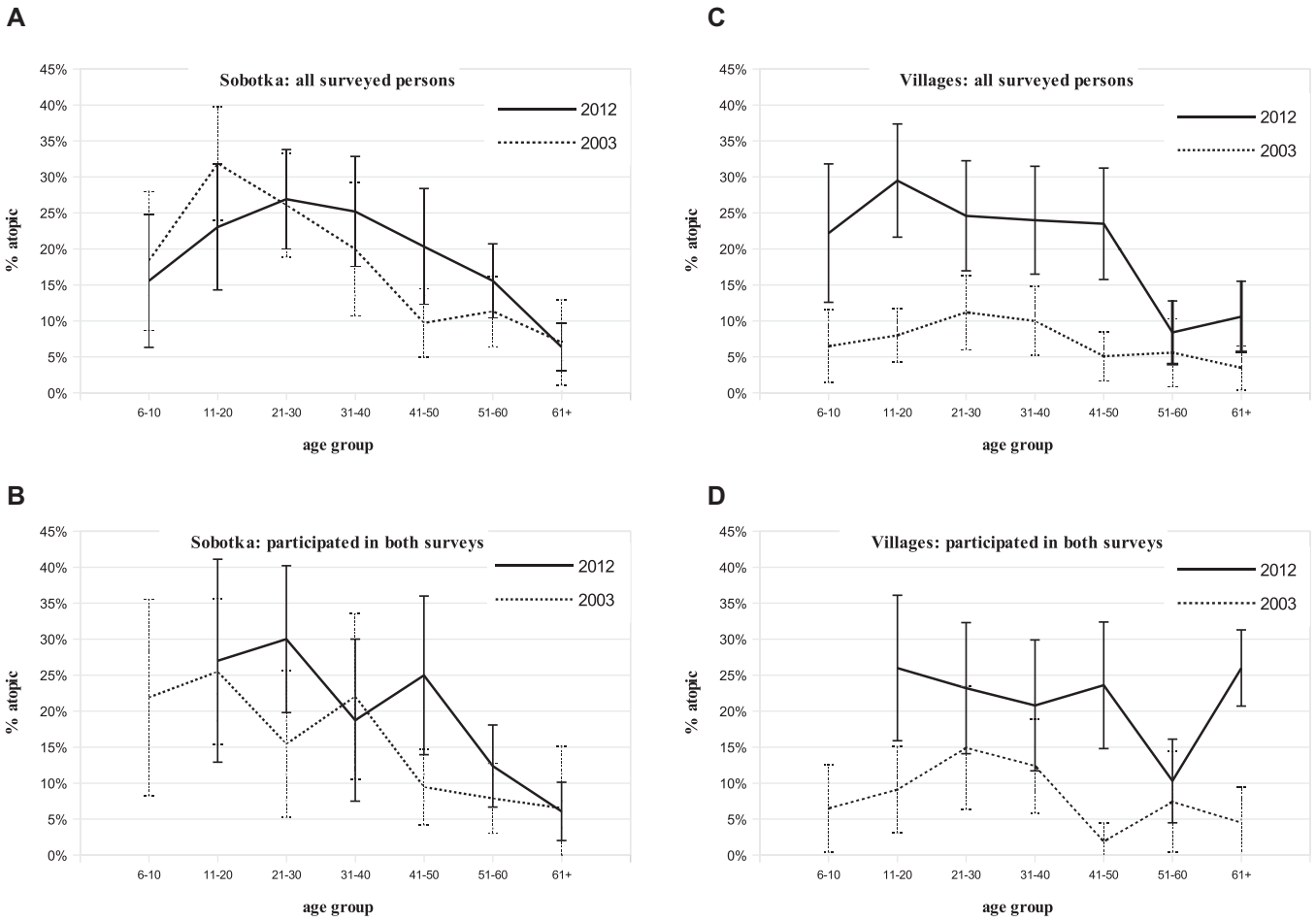

FIG 2. Age-specific prevalence of atopy in the Sobotka (**A** and **B**) and village (**C** and **D**) populations, 2003 and 2012, among the total surveyed population and those taking part in both surveys.

who administered the skin prick tests were not made aware of our hypothesis, and the findings in the town population indicate appropriate consistency both between and within the first and second surveys. In particular, the fact that the findings in Sobotka are very similar in 2003 and 2012 indicates that it is unlikely that misclassification of atopy could explain the marked changes in the villages between these 2 time points, nor can population movements explain the changes between 2003 and 2012. More than half of our 2012 survey participants had also been surveyed in 2003, and we obtained similar results whether we analyzed the full data set or just the subgroup who participated in both surveys.

What could explain these striking changes in the villages? There is an increasing and consistent body of evidence, albeit largely in children, that farm-related exposures are protective against atopy and associated conditions, such as asthma and hay fever. Thus we argue that the changes in the villages between 2003 and 2012 represented a reduction in those farming exposures that had been asserting a protective effect in 2003. However, although it is clear that the package of changes involved in farming protect against atopy, identifying the specific protective exposures has proved very difficult, probably because they are each closely associated with one another, although exposure to livestock, places where farm animals are housed, or both appear to be important,[11-15] as does consumption of unpasteurized milk products.[15-18]

TABLE IV. Odds ratios and 95% CIs for associations between atopy and farm-related exposures in 2003 and 2012: total village and Sobotka populations

	2003, aOR (95% CI)*	2012, aOR (95% CI)*
Population	n = 1664	n = 1676
Living on a farm	1.09 (0.67-1.75)	0.63 (0.43-0.94)
Contact with cows†	0.91 (0.48-1.69)	0.25 (0.06-1.11)
Contact with pigs†	0.78 (0.44-1.37)	0.53 (0.27-1.02)
Contact with poultry†	0.78 (0.48-1.27)	0.86 (0.56-1.32)
Milking cows†	1.34 (0.612.96)	0.74 (0.20-2.73)
Cleaning barns†	1.05 (0.58-1.88)	0.73 (0.41-1.29)
Collecting eggs†	0.94 (0.56-1.57)	0.78 (0.49-1.24)
Drinking unpasteurized milk†	0.71 (0.45-1.11)	0.99 (0.57-1.73)

aOR, Adjusted odds ratio.
*Adjusted for age, sex, first-born status, maternal age, current smoking, living in town/village, and parental farming and including a family clustering effect.
†Additionally adjusted for living on a farm.

Between 2003 and 2012, the introduction of the Common Agricultural Policy resulted directly in a major shift in Polish village farming practices, so that the keeping of large animals, in particular cows, became uneconomical and virtually disappeared. In our regression analysis, after adjustment for living on a farm, the strongest (albeit nonsignificant) protective effect on atopy was

TABLE V. Prevalence, crude and adjusted odds ratios, and 95% CIs for associations between farm-related exposures in 2003/2012 and new cases of atopy in 2012 (both town and villages, those who took part in both surveys and were not atopic in 2003)

	Atopy, new cases, no. (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Population, n = 771	99 (12.8%)		
Living on farm			
No in 2003 and no in 2012, n = 403	55 (13.6%)	1.00 (reference)	1.00 (reference)
Yes in 2003 and no in 2012, n = 72	14 (19.4%)	1.53 (0.80-2.92)	1.07 (0.51-2.50)
No in 2003 and yes in 2012, n = 53	11 (20.8%)	1.66 (0.81-3.41)	1.13 (0.52-2.21)
Yes in 2003 and yes in 2012, n = 243	19 (7.8%)	0.54 (0.31-0.93)	0.38 (0.20-0.72)
Contact with cows			
No in 2003 and no in 2012, n = 620	85 (13.7%)	1.00 (reference)	1.00 (reference)
Yes in 2003 and no in 2012, n = 121	13 (10.7%)	0.76 (0.41-1.41)	0.70 (0.36-1.33)
No in 2003 and yes in 2012, n = 10	0 (0.0%)		
Yes in 2003 and yes in 2012, n = 20	1 (5.0%)	0.33 (0.04-2.51)	0.25 (0.03-1.97)
Contact with pigs			
No in 2003 and no in 2012, n = 537	78 (14.5%)	1.00 (reference)	1.00 (reference)
Yes in 2003 and no in 2012, n = 140	13 (9.3%)	0.60 (0.32-1.12)	0.48 (0.25-0.93)
No in 2003 and yes in 2012, n = 22	3 (13.6%)	0.93 (0.27-3.21)	0.59 (0.17-2.12)
Yes in 2003 and yes in 2012, n = 72	5 (6.9%)	0.44 (0.17-1.12)	0.36 (0.14-0.95)
Contact with poultry			
No in 2003 and no in 2012, n = 430	58 (13.5%)	1.00 (reference)	1.00 (reference)
Yes in 2003 and no in 2012, n = 118	19 (16.1%)	1.23 (0.70-2.16)	0.97 (0.52-1.81)
No in 2003 and yes in 2012, n = 49	10 (20.4%)	1.65 (0.78-3.47)	1.27 (0.57-2.84)
Yes in 2003 and yes in 2012, n = 174	12 (6.9%)	0.48 (0.25-0.91)	0.41 (0.20-0.83)

OR, Odds ratio.
*Adjusted odds ratio for age, sex, first-born status, maternal age, current smoking, and living in town/village.

for the keeping of cows, a finding consistent with the temporal pattern we recorded with a reduction in regular or occasional contacts with cows decreasing from 24% in the villages in 2003 to 4% in 2012. However, further analysis indicated that the increase in atopy among the village families could not readily be explained by (reductions in) contact with cows or other farm-related exposures. Interestingly, the finding that farm residence was protective in 2012 but not in 2003 might indicate that the relevant protective exposures were, in the village populations, essentially ubiquitous in the earlier period but by 2012 had become more discreet. We are not aware of other major changes in village life, such as diet, beyond reductions in the consumption of unpasteurized milk during the interval between the 2 surveys. However, we recognize that the "natural experiment" design of our study cannot identify precisely which changes in village lifestyle and exposures are responsible for the changes in atopy prevalence.

Some might be surprised by the rapidity with which the prevalence of atopy has increased in the village population and by the observation that the increase was across all ages. Studies of immigrant populations suggest that increases in atopy and associated allergic conditions can occur within just a few years of migration and at any age,[19] suggesting that environmental exposures in industrialized countries (or the absence of environmental exposures that are common in developing countries) can favor the induction and exacerbation of asthma symptoms and that these effects do not occur solely in early life. The prevalence of atopy and hay fever among schoolchildren in Leipzig increased over a period of just 4 years, an increase that was less dramatic than we report and attributed to changes effected by the reunification of Germany.[20] Similarly, in the occupational setting the risk of sensitization to workplace aeroallergens and consequent asthma is highest within the first 2 or 3 years of new employment.[21] Our findings in Poland indicate that the atopic state is more plastic than many believe and that the importance of early-life exposures might have been overstated. Thus "allergy" can develop at any age, either in response to a newly encountered risk factor or in this case the removal of a putative protective exposure.

Our findings relate essentially to atopy and not clearly to incident asthma or hay fever. This is perhaps not surprising, given that we found little difference between Sobotka and the villages in the prevalences of these conditions in our original 2003 survey.[6] Then the striking difference was for atopy, and this is primarily what has changed between 2003 and 2012. The lack of any difference in clinical outcomes (between Sobotka and the villages) in 2003 and the lack of change between 2003 and 2012 might reflect the difficulties in establishing these diagnoses in this population by questionnaire, as evidenced, for example, by our finding that less than half of those with a diagnosis of hay fever had positive skin test responses to pollens. Alternatively, it might be that these clinical conditions take longer to manifest than does the immunologic state of atopy. It might be also that distinct exposures or mechanisms operate in the farm-related protection against asthma and atopy and that the changes between 2003 and 2012 involved reductions in exposure to factors that protect against atopy but are not strongly relevant to asthma and hay fever. This is not implausible because a majority of asthma cases do not involve atopic mechanisms.[22]

This is the first study of its kind to include a prospective dimension. If our interpretation is correct, then very rapid increases in atopy can occur as a direct result of "modernization," in this case the abrupt disruption of a centuries-old system of small-scale agriculture. It is likely that a similar process is underway in other parts of Europe and possibly elsewhere and even that what we have observed is at least in part a "microcosm"[23] of the temporal and geographic distributions of allergy and associated diseases on that continent. This would have major implications for the potential prevention of allergy, asthma, and

rhinitis not only in Western countries but also in low- and-middle-income countries, in which we are faced with the prospect of major increases in prevalence over the next few decades as these countries become more westernized and less rural.[24]

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Clinical implications: The study shows a substantial increase in atopy at all ages and in a remarkably short period of time in a Polish rural population whose farm-related exposures were dramatically reduced after their country's accession to the European Union. There was no change in atopy prevalence among the inhabitants of the nearby small town.

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