Farm living and allergic rhinitis from childhood to young adulthood: Prospective results of the GABRIEL study

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Background: Growing up on a farm is associated with a reduced prevalence of respiratory allergies in childhood. Whether this protective effect remains into adulthood is unknown.

Objectives: We aimed to prospectively investigate the relationship between farm exposure and prevalence of allergic rhinitis and wheeze from childhood to early adulthood.

Methods: Participants from phase 2 of the Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL) who were living in southern Germany (aged 6-11 years at baseline and 20-25 years at follow-up) were invited to complete a questionnaire on sociodemographic data, farm contact, respiratory symptoms, and potential confounders. Odds ratios (ORs) with 95% CIs were modeled by using generalized estimating equations.

Results: Of the 2276 phase 2 participants, 1501 (66%) answered the follow-up questionnaire, of whom 1333 could be included in the analyses. Living on a farm was associated with reduced prevalence of allergic rhinitis (OR with persistent farm living = 0.4 [95% CI = 0.2-0.6]; OR with farm living at baseline only = 0.4 [95% CI = 0.2-0.8]). The OR for development of symptoms from baseline to follow-up was almost 3 (OR = 2.7 [95% CI = 2.1-3.3]) irrespective of farm living. For symptoms of wheeze, no statistically significant association with farm living was observed.

Conclusions: The protective effect of farm living on allergic rhinitis persists from childhood to early adulthood. Continuing exposure over puberty does not add to the effect. This confirms that the window of opportunity for a protective effect might be found in childhood. (J Allergy Clin Immunol 2022;150:1209-15.)

Key words: *Asthma, allergic rhinitis, farming, rural environment, young adulthood, prospective cohort study*

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Abbreviations used
GABRIEL: Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community
GEE: Generalized estimating equation
OR: Odds ratio

Atopic diseases are a major global health concern.[1-4] To prevent them, determinants of their onset need to be understood. Farm living is among the environmental factors that have been shown to protect against allergies and asthma in children.[5-8] Microbial exposures recognized by the innate immune response are common in the farm environment and are thus discussed as causative agents of a changed adaptive immune response resulting in lower prevalence of respiratory allergies and asthma.[9-11] It has therefore been hypothesized that perinatal periods are relevant exposure time windows for the development of allergy symptoms from childhood to adulthood.[12] However, we have recently shown that exposures occurring in late childhood can also be relevant for specific disease trajectories, including symptoms of allergic rhinoconjunctivitis.[13]

The gut and lung microbiome are discussed as potentially cross talking with the human immune system and thus relevant for the development of allergies and asthma. Environmental microbial exposures contribute to the individual microbiota composition.[14] Differences in airway and gut microbiota composition have been shown between urban and rural infants, as well as between farm and nonfarm infants.[11,15] In this context, perinatal microbial exposures have been suggested as a window of opportunity for asthma and allergy prevention, as the association between early-life microbial exposures may persist until elementary school age.[11,15] Whether the protection remains during the transition from childhood to adulthood is still unknown, as so far only cross-sectional studies have been conducted. These studies support the hypothesis that growing up on a farm reduces the risk of allergic sensitization and allergic rhinitis in adulthood.[9,16-18] Whether puberty is an additional window of opportunity for the potentially beneficial effect of farm exposures in the teenage years is so far also unknown.

Evidence for a protective effect on asthma is less pronounced in adults.[9,16,19] This might be due to the fact that adult asthma is frequently characterized by neutrophilic inflammation rather than by eosinophilic response. Endotoxins, which are common in the farm environment, are a risk factor for neutrophilic airway inflammation; thus, the different phenotype might explain the divergent findings in children and adults.[9,19]

A better understanding of the development of atopic diseases across the lifespan of children growing up in rural areas would provide important implications for future prevention strategies and therapies. We therefore aimed to answer the following study questions: (1) do children raised on a farm have a lower prevalence of respiratory allergy symptoms and asthma in young adulthood than their rural counterparts not living on a farm? (2) does the magnitude of the effect change from childhood to adulthood? and (3) is the effect larger for children with constant exposure to farm environments than for those who moved away from the farm?

In order to answer these questions we did a prospective follow-up of the GABRIEL study in 2020. At baseline the GABRIEL study had recruited participants aged 6-11 years in 2006 from rural areas of southern Germany to identify agents in agricultural environments that are protective against asthma and allergies.[20]

METHODS

Study design and population

The original, cross-sectional GABRIEL study was conducted in several phases, as described in detail by Genuneit et al.[20] For our follow-up, the GABRIEL study population was restricted to study participants at the Bavarian study center. For phase 1 of the GABRIEL study, a population-based sample of 40,000 children (aged 6 to 10 years) were invited to the study via their elementary schools. Of the contacted parents, 56% agreed to participate. The questionnaire sought information on sociodemographic data, contact with farming, and symptoms and diagnoses of asthma and allergies. The latter questions were taken from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[21]

Eligible for phase 2 were all children whose parents were both born in Germany and had consented to dust sampling and blood withdrawal, including genetic analyses. The study population was divided into children living on a farm run by their parents, children not living on a farm but regularly visiting animal sheds or consuming farm milk, and children without farm contact. From each stratum, random samples were taken as described in Genuneit et al[20] to increase the number of exposed participants. The 2573 participants selected from Bavaria received a detailed parental questionnaire on farm contact.

The selected 2573 participants from Bavaria comprised the study population for the follow-up study presented in this article. In 2019, before the main follow-up study of 2020, we successfully tested the study design, contact methods, and questionnaire by inviting 50 randomly selected baseline participants. Invitation letters were sent via post to the parental address given at baseline. The addresses of participants whose letters could not be delivered were searched for via the relevant residents' registration offices. Nonresponders were sent up to 2 postal and up to 5 telephone reminders to complete the questionnaire.

Of the 2573 children who had been selected for phase 2 of the study, 89% completed the questionnaire and 2276 agreed to be recontacted, thus forming our follow-up study sample. Among these children, 164 had moved. For 140 of the 164 children, identification of the new address by the respective residents' registration office was possible. Of the 2252 baseline participants who were reached, 1501 (67%) completed the follow-up questionnaire. For 1341 individuals, we were able to merge data with that from the baseline questionnaire (Fig 1). The final study population consisted of 1333 study participants with baseline information on farm living.

Ethical approval and data protection

Ethical approval was obtained at baseline from the ethics committee of the Bavarian Chamber of Physicians and for follow-up from the ethics committee of the Medical Faculty of Ludwig Maximilian University of Munich. All parents (baseline) and all participants (follow-up) gave written informed consent for their participation in the study.

Questionnaires and variable definitions

The baseline questionnaires included questions on sociodemographics, farm exposures from the prenatal period to elementary school age, home environment, and symptoms of allergic diseases and asthma.[22] The 16-item follow-up questionnaire asked for sociodemographic data and data necessary to merge the baseline and follow-up data (eg, date of birth, sex, parental birth years, parental education, name of the elementary school, district in which the participant lived at baseline), smoking behavior, level of education, vocational training in agriculture, farm living, and respiratory symptoms (wheezing and

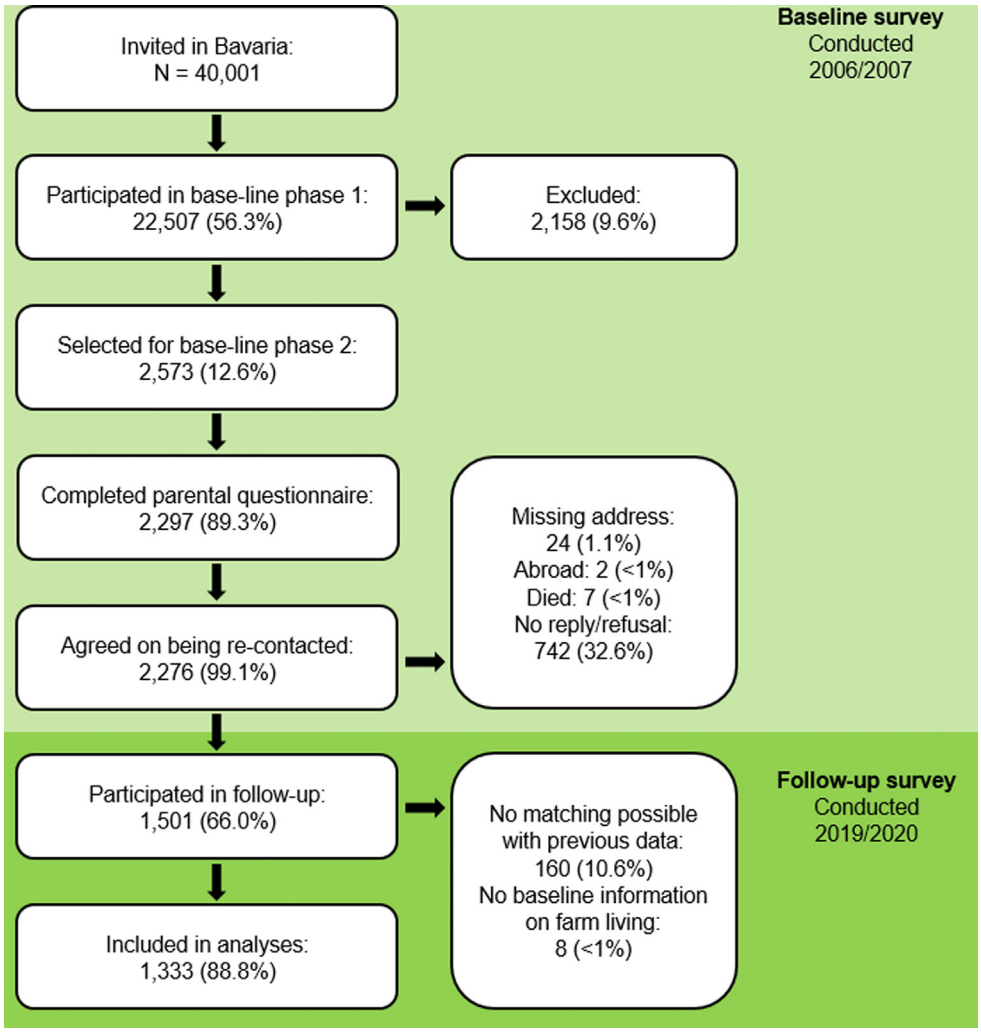

FIG 1. Flowchart of the recruitment process.

allergic rhinitis). Whenever possible, the same questions as in the baseline questionnaire were used. Questions on education, smoking, and respiratory symptoms were taken from the European Community Respiratory Health Survey questionnaire.[23]

Variable definition

Baseline farm living was considered present when each of 2 questions—Does your child live on a farm? and If yes, is the farm currently run by your family?—was answered affirmatively. Follow-up farm living was defined as an affirmative response to the question Do you currently live on a working farm?

The 12-month prevalence of allergic rhinitis at baseline was defined as a positive response to the questions In the past 12 months, has your child had problems with sneezing or with a running or blocked or itchy nose without having a cold? *AND* If yes, in the past 12 months, has your child had problems with itchy or running eyes together with these nose problems? At follow-up, allergic rhinitis was defined as a positive response to the question Have you had allergic rhinitis, for example, "hay fever," in the past 12 months?"

Baseline and follow-up wheezing symptoms were considered present if wheezing or whistling in the chest during the 12 months before the survey were reported.

As potential confounders, we took into account sex (female vs male), smoking status at follow-up (ever smoker vs never smoker), and parental level of education (low vs high). In accordance with the International Standard Classification of Education,[24] the parental level of education was categorized as high if at least 1 parent had achieved a vocational baccalaureate diploma (12 years of schooling) or high school certificate (13 years of schooling).

Statistical analyses

The baseline characteristics (absolute and relative frequencies) of the participants who were included in the follow-up analyses were compared with those of the participants who could not be included. Likewise, we descriptively compared absolute and relative frequencies of the variables under study according to whether the children were living or not living on a farm at baseline.

Thereafter, we assessed the association between baseline and follow-up farm exposure and symptom prevalence of allergic rhinitis and symptoms of wheeze by using generalized estimating equations (GEEs) for binomial outcome with logit link function. For this, we defined 3 exposure groups (living on a farm always, at baseline only, or never). Those with follow-up farm living only had to be excluded from the main GEEs owing to their low number (n = 20). For the results including the category of those with follow-up farm living only, see Table E2 (available in the Online Repository at www.jacionline.org). The clustering factor was the participants. Follow-up (baseline vs follow-up) was considered the inner subject effect, which means that each participant built a cluster and appeared twice in the data set: once at baseline and once at follow-up. Associations of change in

TABLE I. Description of the study population stratified for living on a farm at baseline (n = 1333)

Characteristic	No. missing	Living on a farm at baseline				
		No (n = 735)		Yes (n = 598)		
		No.	%	No.	%	*P* value*
Baseline questionnaire (2006)						
Sex (female)	0	369	50.2	311	52.0	.55
Age in 2006 (y)	0					.75
6†		109	14.8	96	16.1	
7		170	23.1	134	22.4	
8		191	26.0	139	23.2	
9		176	23.9	149	24.9	
10‡		89	12.1	80	13.4	
Low parental education§	17	439	60.6	478	80.9	<.001
Allergic rhinitis	5	76	10.4	23	3.9	<.001
Wheeze	25	85	11.7	46	7.9	.02
Follow-up questionnaire (2020)						
Ever smoking	2	167	22.8	113	18.9	.09
Current main activity	0					<.001
Student		277	37.7	158	26.4	
Vocational trainee		114	15.5	71	11.9	
Employed		288	39.2	313	52.3	
Other		56	7.6	56	9.4	
Living on a farm in 2020	4	20	2.7	391	65.8	<.001
Vocational training in agriculture (ever)	1	7	1.0	79	13.2	<.001
Allergic rhinitis	8	175	24.0	62	10.4	<.001
Wheeze	1	89	12.1	39	6.5	<.001

**P* value retrieved from a chi-square exact test.
†Includes a single 5-year-old participant in the farming group.
‡Includes a single 11-year-old participant in the farming group and 2 in the nonfarming group.
§None of those parents had achieved a high school degree.

symptom prevalence of allergic rhinitis and asthma with living on a farm were analyzed by including an interaction term between follow-up and farm living.[25] The following covariates were included in the models *a priori*: sex, parental level of education, and smoking status (at follow-up). Age was not included as a potential confounder, as age range was very limited and thus not considered relevant. Other farm-related factors (eg, vocational training in agriculture, contact to animal sheds) were not included owing to high collinearity with farm living. As only 0.4% of data were missing, complete case analyses were done. Statistical analyses were performed with SPSS software, version 26 (IBM, Armonk, NY).

RESULTS

The 1333 baseline participants who could be included in the analyses were more likely to be female, to have had farm contact at baseline, and to raise poultry and cultivate grains for sale than were those who were lost to follow-up (see Table E1 in the Online Repository at www.jacionline.org). In contrast, age distribution at baseline differed only slightly between the 2 groups. Participants were also less likely to report symptoms of wheeze or allergic rhinitis at baseline than were those who were lost to follow-up.

About half of the population was female, with age ranging between 6 and 11 years at baseline (19 and 24 years at follow-up). Age and sex were independent of baseline farm living (Table I). However, participants living on a farm at baseline were more likely to have parents with a lower educational attainment (81% vs 61%). Farm living was inversely related to symptoms of allergic rhinitis (4% vs 10% [$P < .001$]) and wheeze (8% vs 12% [$P = .02$]).

At follow-up, 66% of the participants who had lived on a farm at baseline continued to do so. In contrast, only 3% of those not living on a farm at baseline had moved to a farm. Farm living at baseline also increased the likelihood for vocational training in agriculture (13% vs 1% among nonfarm children). At the time of the follow-up survey, more than half of those who had lived on a farm at baseline were already employed (52%), whereas the majority of those without baseline farm living were still in training at a university (38%) or on the job (16%).

Between baseline and follow-up, the prevalence of allergic rhinitis symptoms had more than doubled in both groups (from 10% to 24% in participants without baseline farm contact and from 4% to 10% in participants with baseline farm contact). Although prevalence increased in both groups, it remained higher in those without baseline farm contact ($P < .001$). Rates of symptoms of wheeze remained similar and thus higher in those who did not live on a farm at baseline (12%) than in those who had lived on a farm (7% [$P < .001$]).

The adjusted GEE models showed that symptoms of allergic rhinitis at follow-up were less likely for children always living on a farm (odds ratio [OR] = 0.35 [95% CI = 0.20-0.62]) and for those who gave up farm living (OR = 0.36 [95% CI = 0.17-0.77]) than for those who had never lived on a farm. For wheezing, the ORs in the adjusted GEE models (Table II) remained in the same direction as in the unadjusted results (Table I), but the difference was no longer significant.

Accordingly, with the unadjusted results, the odds of development of symptoms between baseline and follow-up remained significant for allergic rhinitis (OR = 2.66 [95% CI = 2.10-3.38]) but not for wheeze (OR = 1.01 [95% CI = 0.76-1.35]) (Table II). A nonsignificant interaction term between farm living and follow-up indicated that the protective effect of farm living on allergic rhinitis and wheezing stayed constant over time, regardless of whether participants had lived on a farm all the

TABLE II. Results of the adjusted GEE models for the association between farm living and change in symptoms of allergic rhinitis and wheeze between baseline and follow-up (n = 1290)

	Rhinitis at follow-up			Wheeze at follow-up		
		95% CI			95% CI	
Variable	OR	Lower	Upper	OR	Lower	Upper
Farm living*						
Never	1			1		
At baseline only	0.36	0.17	0.77	0.82	0.47	1.41
Always	0.35	0.20	0.62	0.68	0.43	1.07
Study phase						
Baseline: 2006	1			1		
Follow-up: 2020	2.66	2.10	3.38	1.01	0.76	1.35
Interaction term: Farm living × study phase						
Never	1			1		
At baseline only	1.42	0.67	2.98	0.52	0.24	1.10
Always	0.83	0.48	1.41	0.97	0.56	1.70
Sex (female)	0.71	0.54	0.95	0.71	0.53	0.96
High level of parental education	0.97	0.72	1.31	1.23	0.90	1.68
Ever smoking at follow-up	0.89	0.62	1.28	1.96	1.41	2.71

GEE models are adjusted for all variables displayed.
*Participants who moved to a farm between baseline and follow-up were excluded owing to their small number (n = 20).

time or at baseline only. In other words, after having lived on a farm in childhood, there was no additional benefit from staying on the farm versus having moved away from the farm. Smoking at follow-up (OR = 2.0 [95% CI = 1.4-2.7]) was an additional risk factor for symptoms of wheeze. Results from the sensitivity analysis including the category of those with "follow-up farm living only" show that the main effects remained in the same direction (see Table E2 in the Online Repository at www.jacionline.org).

DISCUSSION

By following our cohort from childhood to adulthood, we were able to provide evidence that the protective effect of growing up on a farm on development of allergic rhinitis persists into young adulthood, even the if study participants had moved away from the farm after the age of 6 to 12 years. Likewise, we did not see an additional benefit of continued farm exposure from adolescence to young adulthood. The prevalence of allergic rhinitis symptoms more than doubled from childhood to adulthood irrespective of farm contact, although participants who had lived on a farm started from a lower prevalence level.

In accordance with Nwaru et al,[26] despite seeing a protective effect of farm living in childhood on rhinitis in adulthood, we could not confirm an association between farm living and wheeze symptoms. The reason for this might be the low prevalence of wheeze within the past 12 months in our study combined with the diverse phenotypes of asthma, given that microbial exposures in the farm environment are thought to mainly protect against atopic asthma. A study conducted in the United States found that asthma prevalence is comparable in farm and nonfarm children and even higher in children living on a farm on which swine were being raised—especially if antibiotics were used.[27] Those findings indicate that in further studies it will be necessary to distinguish the type of animals raised on a farm and the type of asthma.

Our results are consistent with previous, cross-sectional findings reporting an inverse association between growing up on a farm with nasal symptoms such as hay fever or allergic rhinitis in adulthood and, to a lesser extent, with asthma symptoms.[9,16,28] Overall, the prevalence of symptoms of allergic rhinitis and asthma were lower than in our recent studies carried out in urban populations of Germany.[13,29] Altogether, this confirms the hypothesis that farm living is inversely related to allergic diseases in childhood and adulthood.[15,16] We need to take into account the fact that in Canada, a study of school-age children showed that farm residency and farm activities were associated with hay fever; however, exposure to livestock had a protective effect on skin prick test sensitivity.[30] In line with those findings, we found in the baseline phase of the GABRIEL study that a specific type of farm typical for traditional farming (cows, cultivation) was protective against asthma, hay fever, and atopy.[22] Again, these findings show us that distinguishing the type of farming and farm activities is necessary for future studies, as has been pointed has been out by others.[31]

There are several possible explanations for the protective effect of farm life on atopic diseases. Intestinal microbiota may prevent atopic diseases by balancing the ratio of T_H1- and T_H2-type cells.[32] The GABRIEL study already showed that the microbiome of the nose in children with intense farm contact was richer.[33] In turn, children with asthma showed lower α- and β-diversity in the microbiome of their nose,[34] and dust samples from their rooms showed less diversity.[35] Furthermore, various authors have reported that the guts of infants raised on farms contain higher amounts of specific bacteria reducing inflammatory processes.[11,14,15,36,37] Therefore, dietary choices such as the consumption of unprocessed cow's milk may contribute to the farm effect.[38] Additionally, exposure to a highly diverse microbial environment on farms may influence the microbiome of the upper airways[11] and the gut.[12,14] However, results of the PASTURE birth cohort study carried out among European farm and nonfarm children indicate that although early-life exposure to diverse bacterial components is protective, successful maturation of the gut microbiome is key to protect against respiratory allergies and asthma.[11,33]

The finding that the odds for development of symptoms between baseline and follow-up did not interact with farm living

is important. It confirms previous results among children and cross-sectional studies in adults. Recent birth cohort studies indicate that exposure during the prenatal period and first year of life offer windows of opportunity to prevent respiratory allergies later in life.[11,12,36] However, in our study children were asked whether they lived on a farm at inclusion (when they were already 6 to 11 years old). Moreover, the absolute change in allergic rhinitis symptom prevalence was much larger in nonfarm participants than in farm participants, and one might ask whether exposure beyond childhood is necessary for this effect. Our data are compatible with the theory that the innate immune system also exhibits adaptive characteristics, a property that has been termed *trained immunity*.[39] We thus separated children who left farm living from children who continued to live on a farm. The effect estimates were similar for the 2 groups, indicating that the window of opportunity for farm exposure is during childhood, although whether this has to be early childhood is unclear. Unfortunately, because of the very small group of participants who moved to a farm between baseline and follow-up, we cannot provide evidence as to whether starting exposure later in life also protects against nasal allergy.

Having a large group of participants with childhood exposure provided enough statistical power to analyze the effect of persistent versus childhood exposure on symptoms of allergic rhinitis and wheezing. This is another advantage of our study in addition to its prospective nature. We were able to recontact the majority of our study population 14 years after the baseline study, and 66% agreed to participate, thus lowering the risk of selection bias. Previous analyses of the baseline study showed that participants with allergic symptoms were more likely to participate. However, this selection was not dependent on exposure status and thus was not expected to result in biased results. [20] In our follow-up nonresponder analyses, those with farm contact and those without symptoms were more willing to participate at follow-up, which might have introduced some selection bias. Although we were able to adjust for some potential confounders, we might have missed aspects such as further differences in dietary behavior that might also differ between those with persistent and those with childhood exposure. We also cannot rule out a "healthy farmer effect," meaning that families with allergic diseases might give up farming, thus not raising their children on a farm.[40] Nevertheless, careful analyses of the baseline study did not indicate any such healthy farmer effect in the GABRIEL baseline population.[20] The definition of symptoms of wheeze present in the past 12 months should be adequate for children, but it might bear some problems for adults who may wheeze simply because of a cold. Therefore, we might have overestimated the prevalence of wheezing in the adults. Misclassification of exposure and outcome might have happened, as they were assessed by questionnaire only. In terms of exposure, we had to rely on farm living as a proxy for endotoxin exposure at follow-up. However, assessing biologic markers during the course of this follow-up is planned. In terms of outcome, we cannot determine the exact age at which the allergy or asthma started. However, asking about the time of onset retrospectively might have led to recall bias. In our study, risk of recall bias was limited thanks to the prospective nature of the study, but awareness of symptoms might have differed by exposure status. Having said that, we are confident that this sort of bias did not distort our results considerably because carefully validated items were used.[1,23,25]

In conclusion, our study indicates that the protective effect of growing up on a farm against allergic rhinitis is set until school age and is sustained from there onward. The effect estimates for continued exposure to farm environments were similar to the effect estimates for exposure during childhood only. Therefore, our findings are in line with the hypothesis that the window of opportunity for allergy prevention by exposure to environments rich in microbial diversity lies somewhere in childhood. In future follow-ups, the upper airway microbiome should be analyzed and the results should be compared with the baseline microbiome data, thereby illuminating all aspects of farm life (eg, types of animals, crops) and outcome development.

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Key messages

- **Growing up on a farm is associated with reduced prevalence of allergic rhinitis from childhood to young adulthood.**
- **The odds of development of allergic rhinitis stay constant over time and do not depend on whether farm contact is continued, which supports evidence that the relevant window of opportunity occurs early in life.**
- **Evidence for symptoms of wheeze is less clear-cut, potentially owing to the diverse phenotypes of asthma.**

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TABLE E1. Comparison between baseline characteristics by participation in the follow-up analyses

		Participants of the follow-up survey included in the analyses				
		No (n = 1240)		Yes (n = 1333)		
Characteristic	No. missing	No.	%	No.	%	*P* value*
Sex (female)	0	543	43.8	680	51.0	<.001
Age in 2006 (y)	7					.05
6†		158	12.8	205	15.4	
7		272	22.1	304	22.8	
8		278	22.5	330	24.8	
9		340	27.6	325	24.4	
10‡		185	15.0	169	12.7	
Living on a farm in 2006	24	436	35.9	598	44.9	<.001
Animals		390	89.4§	538	90.0§	.477
Cows		244	56.0§	365	61.0§	.078
Pigs		131	30.0§	165	27.6§	.442
Sheep		30	6.9§	49	8.2§	.477
Poultry		156	35.8§	250	41.8§	.044
Horses		70	16.1§	89	14.9§	.662
Goats		32	7.3§	26	4.3§	.054
Rabbits		111	25.5§	166	27.8§	.392
Plants		345	79.1§	484	80.9§	.316
Grains for animals		289	66.3§	419	70.1§	.142
Corn		241	55.3§	352	58.9§	.195
Grain for sale		128	29.4§	229	38.3§	.002
Allergic rhinitis	11	137	11.1	99	7.5	.002
Wheeze	58	153	12.7	131	10.0	.04

**P* value retrieved from chi-square exact test.
†Includes a single 5-year-old participant in the farming group.
‡Includes a single 11-year-old participant in the farming group and 2 in the nonfarming group.
§Percentage among those who did live on a farm in 2006 (multiple answers are possible).

TABLE E2. Results of the adjusted GEE models for the association between farm living and change in symptoms of allergic rhinitis and wheeze between baseline and follow-up (n = 1310)*

	Rhinitis at follow-up			Wheeze at follow-up		
		95% CI			95% CI	
Variable	OR	Lower	Upper	OR	Lower	Upper
Farm living						
Never	1			1		
Always	0.35	0.20	0.62	0.52	0.30	0.89
At follow-up only	0.98	0.22	4.44	2.03	0.59	6.96
At baseline only	0.36	0.17	0.77	0.89	0.50	1.59
Study phase						
Baseline: 2006	1			1		
Follow-up: 2020	2.66	2.10	3.38	1.30	0.96	1.76
Interaction term: Farm living × study phase						
Never	1			1		
Always	0.83	0.48	1.41	1.29	0.72	2.29
At follow-up only	1.17	0.32	4.27	1.30	0.59	2.85
At baseline only	1.42	0.67	2.98	0.46	0.21	1.04
Sex (female)	0.71	0.54	0.94	0.84	0.61	1.14
High level of parental education	0.95	0.70	1.29	1.22	0.88	1.69
Ever smoking at follow-up	0.90	0.63	1.28	1.99	1.42	2.78

*GEE models are adjusted for all variables displayed here.