Protection from childhood asthma and allergy in Alpine farm environments—the GABRIEL Advanced Studies

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Background: Studies on the association of farm environments with asthma and atopy have repeatedly observed a protective effect of farming. However, no single specific farm-related exposure explaining this protective farm effect has consistently been identified.

Objective: We sought to determine distinct farm exposures that account for the protective effect of farming on asthma and atopy.

Methods: In rural regions of Austria, Germany, and Switzerland, 79,888 school-aged children answered a recruiting questionnaire (phase I). In phase II a stratified random subsample of 8,419 children answered a detailed questionnaire on farming environment. Blood samples and specific IgE levels were available for 7,682 of these children. A broad asthma definition was used, comprising symptoms, diagnosis, or treatment ever.

Results: Children living on a farm were at significantly reduced risk of asthma (adjusted odds ratio [aOR], 0.68; 95% CI, 0.59-0.78; *P* < .001), hay fever (aOR, 0.43; 95% CI, 0.36-0.52; *P* < .001), atopic dermatitis (aOR, 0.80; 95% CI, 0.69-0.93; *P* = .004), and atopic sensitization (aOR, 0.54; 95% CI, 0.48-0.61; *P* < .001) compared with nonfarm children. Whereas this overall farm effect could be explained by specific exposures to cows, straw, and farm milk for asthma and exposure to fodder storage rooms and manure for atopic dermatitis, the farm effect on hay fever and atopic sensitization could not be completely explained by the questionnaire items themselves or their diversity.

Conclusion: A specific type of farm typical for traditional farming (ie, with cows and cultivation) was protective against asthma, hay fever, and atopy. However, whereas the farm effect on asthma could be explained by specific farm characteristics, there is a link still missing for hay fever and atopy. (J Allergy Clin Immunol 2012;129:1470-7.)

***Key words:** Asthma, hay fever, atopic dermatitis, atopic sensitization, childhood, farming, farm milk, early life*

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Asthma and allergies constitute complex diseases; their cause involves both genetic and environmental determinants. Moreover, both diseases frequently have their onset in childhood and thus appear to comanifest. However, recent results from the GABRIEL Surveys contradict this concept of interdependent phenotypes. The GABRIEL Surveys were designed to identify key factors in the development of asthma using the latest research across a variety of disciplines, including genetics, epidemiology, and immunology (see Table E1 in this article's Online Repository at www.jacionline.org).[1-6] A genome-wide association study within the GABRIEL Surveys found no overlap in genes associated with asthma and total IgE levels.[1] Furthermore, within the GABRIEL Surveys, discrepant results were also observed for the protective role of microbial diversity within a farming environment.[2] Whereas the protective farm effect on childhood asthma could be explained by the overall diversity of bacteria and fungi from dust of farm and nonfarm children, this did not hold for atopy.

Previous studies on the protective effect of growing up on a typical Central European farm were fairly consistent with respect to hay fever and atopy. In contrast, results for asthma were quite heterogeneous. This potentially indicates that not all farms are the same and that specific farm characteristics are possibly of greater effect than farm exposure in general.[7-10] These previous studies mainly used questionnaires assessing the farm's characteristics but not the child's exposure. The aim of the current epidemiologic GABRIEL Advanced Studies was an in-depth analysis of the protective exposures within a farming environment both on asthma

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Supported by the European Commission as part of GABRIEL (a multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community), contract no. 018996 under the Integrated Program LSH-2004-1.2.5-1.

Disclosure of potential conflict of interest: M. Depner has received research support from the European Commission/European Research Council. A. Boznanski, H. Danielewicz, and D. Heederik have received research support from the European Commission. E. von Mutius has consulted for Novartis, GlaxoSmithKline, ALK-Abelló, and Protectimmune; has received a speaker's fee from InfectoPharm; has received research support from Airsonnett AB; and has served as a member of the Expert Panel for the UK Research Excellence Framework. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication August 31, 2011; revised March 15, 2012; accepted for publication March 16, 2012.

Available online April 24, 2012.

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0091-6749/$36.00

doi:10.1016/j.jaci.2012.03.013

Abbreviations used
aOR: Adjusted odds ratio
LCA: Latent class analysis

and atopy. This was based on a newly designed questionnaire aiming at disentangling the protective effect of a child's distinct farm exposures.

METHODS

Study design and population

The GABRIEL Advanced Surveys were conducted by 5 study centers in rural areas of southern Germany (Bavaria and Baden-Württemberg), Switzerland (9 German-speaking cantons), Austria (Tyrol), and Poland (Silesia) from winter 2006 to spring 2008.[5] Because of differences in study design, the Polish data will be reported separately. In the population-based phase I study a short recruiting questionnaire was distributed to parents of all schoolchildren through their elementary schools. In phase II stratified random samples of all children whose parents had given written informed consent to blood sampling, genetic analyses, and dust sampling were studied. Three strata were defined: (1) farm children (ie, children living on a farm run by the family); (2) exposed nonfarm children (ie, children not living on a farm but regularly exposed to stables, barns, or cow's milk produced on a farm); and (3) unexposed nonfarm children.

In all centers the ethics committees of the respective universities and the data protection authorities approved the study.

Questionnaires

The recruitment questionnaire in phase I assessed the prevalence of respiratory and allergic symptoms and diagnoses, socioeconomic status, family history of atopy, maternal smoking, and farm characteristics comprising types of animal breeding, cultivation, and animal feeding. A comprehensive questionnaire was handed out to parents in phase II assessing characteristics of asthma and detailed information on the child's farm-related exposures. All farm-related exposures were assessed for 5 time periods (pregnancy; first, second to third, and fourth to fifth years of life; and past 12 months) and 5 frequency categories per time period (never/almost never, about once a month, about once a week, about once a day up to 15 minutes, and about once a day longer than 15 minutes). The following exposures were assessed: contact with animals (cats, dogs, cows, pigs, poultry, sheep, and horses), stay in animal sheds (cow, pig, and poultry), contact with animal feed (straw, hay, grain, corn, grass, silage, pellet feed, and sugar beet), presence during parental farming activities (harvesting/kibbling/ensiling corn, harvesting/handling hay, ensiling grass, harvesting/threshing/kibbling grain, fieldwork, manuring, and spraying pesticides), stay in barn or fodder storage room, and consumption of cow's milk produced on the farm.

Asthma and other allergic illnesses

Asthma was defined as either current wheeze (parental reporting of wheeze in the past 12 months), a positive answer to the question "Did your child ever use an asthma spray?," or a doctor's diagnosis of asthma at least once or of wheezy bronchitis more than once. Atopic and nonatopic current wheeze was defined as current wheeze with or without atopic sensitization (see the definition below), respectively, by using the children without current wheeze as a common reference group. Severe wheeze was defined as wheeze in the past 12 months with multiple triggers and asthma inhaler use ever.

Hay fever was defined as either nasal symptoms with itchy or watery eyes in the past 12 months or a doctor's diagnosis of hay fever ever. Atopic dermatitis was defined as a doctor's diagnosis ever.

All questionnaire-based outcomes were reported in phase I except for severe wheeze, which was assessed in phase II, and atopic and nonatopic current wheeze because atopic sensitization was also only assessed in phase II.

Atopic sensitization

Blood samples were collected, and serum IgE antibodies against inhalant (*Dermatophagoides pteronyssinus*, cat, grass mix [sweet vernal grass, rye grass, timothy grass, cultivated rye, and velvet grass], birch, and mugwort) and food (egg white, cow's milk, fish, wheat, peanut, and soybean) allergens were measured in one central laboratory at the Robert-Koch-Institute, Berlin, Germany, by using the UNICAP 1000 (Phadia AB, Uppsala, Sweden). Atopic sensitization was defined as specific IgE antibodies of at least 0.7 kU/L against *D pteronyssinus*, cat, or birch or a positive reaction (0.35 kU/L) to the grass mix.

Statistical analyses

For further information on statistical analyses, see the Methods section in this article's Online Repository at www.jacionline.org.

For phase I, categorical variables are presented as relative frequencies; P values are based on the Pearson χ^2 test. A latent class analysis (LCA) was used to derive different types of farming, the association of which with outcomes was then analyzed by using logistic regression analysis. For phase II, all questionnaire-based farm-related exposures were dichotomized into presence or absence of the exposure based on an exposure frequency of at least once a week in a specific time period. Early-life exposure was then defined as the presence of the exposure in pregnancy or the first 3 years of life. Correlation between these farm-related exposure variables was assessed by using the Kendall tau-b correlation coefficient. Diversity of farm exposures was defined by summing up all dichotomous farm exposures and division into quartiles based on the weighted distribution in the study sample. Categorical variables are presented as weighted relative frequencies and compared over categories by using the Rao-Scott χ^2 test. Weighted logistic regression models were used to calculate associations between outcomes and farm-related exposures. Stepwise logistic regression analyses were calculated to assess final models containing the most relevant exposures. Combined effects of all dichotomized farm-related exposure variables defined as 4-level categorical variables were included in this process. All models were adjusted for farming, center, and potential confounders (family atopy, ≥2 siblings, sex, maternal smoking in pregnancy, and parental education). Statistical analysis was performed with SAS 9.2 software (SAS Institute, Inc, Cary, NC), and a P value of .05 was considered significant. Because of the exploratory character of the analysis, corrections for multiple testing were not performed.

RESULTS

In phase I, 132,518 recruitment questionnaires were distributed, of which 79,888 (60.3%) were returned. Of those, 34,491 (43.2%) parents provided written informed consent for blood sampling, genetic testing, and dust sampling. Their children were eligible for phase II (Fig 1); mean age was 8.7 ± 1.4 years. Of these, 9,668 were randomly selected for phase II by exposure stratum (ie, farm children, exposed nonfarm children, and unexposed nonfarm children), and 8,419 (87%) returned the detailed phase II questionnaire. Of these participants, 7,682 (91%) provided blood samples for measurements of specific IgE levels. Families participating in phase II were of higher education and had more allergic illnesses in the family, as also observed in other studies.[11]

A lower prevalence of asthma, hay fever, atopic dermatitis, and atopic sensitization was found among farm children compared with nonfarm children in phases I and II (Table I), with the exposed nonfarm children having intermediate prevalences. After adjusting for confounding variables, the adjusted odds ratios (aORs) for asthma, hay fever, and atopic sensitization with farming status (farm vs nonfarm) were as follows: 0.68 (95% CI, 0.59-0.78; $P < .001$), 0.43 (95% CI, 0.36-0.52; $P < .001$), and 0.54 (95% CI, 0.48-0.61; $P < .001$), respectively. For atopic dermatitis, the farm effect only amounted to an aOR of 0.80 (95% CI,