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The combined effects of family size and farm exposure on childhood hay fever and atopy

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Abstract

Background: Exposure to farming environments and siblings is associated with reduced risks of childhood hay fever and atopy. We explored the independence and interaction of these protective effects in the GABRIELA study.
Methods: Questionnaire surveys on farming, asthma, and allergies were conducted in four central European areas among 79,888 6–12-yr-old children. Aeroallergen-specific serum IgE was measured in a stratified sample of 8,023 children. Multiple logistic regression was used to compare gradients in allergy prevalence by sibship size across three categories of exposure to farming environments.
Results: The prevalence of hay fever ranged from 2% (95% confidence interval 1.6%; 2.7%) among farmers' children with more than two siblings to 12% (11.2%; 13.0%) among children with no farm exposure and no siblings. Farming families were larger on average. More siblings and exposure to farming environments independently conferred protection from hay fever and atopy. There was no substantial effect modification between family size and exposure to farming environments. The odds ratios for hay fever per additional sibling were 0.79 among unexposed non-farm children, 0.77 among farm-exposed non-farm children, and 0.72 among children from farming families (2df interaction test: $p = 0.41$).
Conclusion: The inverse association of exposure to farming environments with hay fever is found in all sizes of family, with no substantial tendency to saturation or synergism. This suggests that different biological mechanisms may underlie these two protective factors. Combinations of a large family and exposure to farming environments markedly reduce the prevalence of hay fever and indicate the strength of its environmental determinants.

A higher number of siblings, specifically older siblings, and exposure to farming environments have been shown to reduce the risk of childhood hay fever and atopy (1, 2). It is known that families living on a farm are larger in size.

We have checked all publications included in a recent meta-analysis of the 'farm-effect' on asthma (3) and updated that systematic search for hay fever. While most studies adjusted for family size or birth order, there seems to be no publication which aimed specifically at disentangling the 'farm-effect' and the 'sibling-effect' on childhood hay fever or atopy. To our knowledge, there are only two articles that displayed data on both effects from mutually adjusted models (4, 5).

Both studies, independently conducted in Austria and in Finland, reported data from 710 children. They found a statistically significant protective effect of parents working on a farm. One reported a non-significant protective effect of number of older siblings without a clear dose-response relationship (4). The other found a non-significant protective effect of number of siblings; however, the definition of this variable and the reference category are not described in the manuscript (5). Neither of them reports a test for interaction between both variables.

The effects of family size and exposure to farming environments on hay fever are both remarkably strong, indicating great potential for preventive action if their underlying mechanisms were known (2, 6). However, the question remains whether they act independently or follow patterns of saturation or even synergism. We sought to answer this with data from the large population-based GABRIELA study.

Methods

Study population

The GABRIELA study was conducted in rural areas of southern Germany (Bavaria and Baden-Württemberg), Switzerland, Austria, and Poland. The study design has been described in detail previously (7).

Within the GABRIELA study, the 'farm-effect' is weaker in Poland than in the other four German-speaking centers. To reduce heterogeneity across centers, the Polish data were excluded.

In winter 2006/2007, 79,888 (60.4%) elementary school children aged from 6 to 12 participated in Phase 1 in the German-speaking centers. Family size, exposure to farming environments, and symptoms as well as doctor's diagnosis of hay fever were assessed with a short self-administered parental questionnaire. Three exclusive exposure strata were defined: (i) farm children, that is, children living on a farm run by the family; (ii) exposed non-farm children, that is, children not living on a farm but regularly exposed to stables, barns (at least once a week over 6 months) or unprocessed cow's milk consumed directly from a farm ever in life; and (iii) unexposed non-farm children. For Phase 2 in spring/summer 2007, random samples stratified for exposure (n = 9,668) were selected. Of those, 8,023 participants provided blood samples for specific serum immunoglobulin E (IgE) measurements. The ethics committees of the respective universities as well as the data protection authorities approved the study.

Outcome variables

Doctor-diagnosed hay fever was an affirmative response to the question 'Has a doctor ever diagnosed your child with hay fever?'. Hay fever symptoms were reported sneezing or a runny, blocked, or itchy nose all together with itchy or watery eyes in the past 12 months. Serum IgE antibodies against individually tested allergens (*D. pteronyssinus*, cat dander, rye, timothy, mugwort, and common silver birch) were measured in one laboratory at the Robert-Koch-Institute, Berlin, Germany (UNICAP 1000™; Phadia AB, Uppsala, Sweden).

Atopy was defined as allergen-specific serum IgE of at least 0.7 kU/l against one or more of *D. pteronyssinus*, cat dander, rye, timothy, mugwort, or common silver birch. Further analyses were conducted using a cutoff of 0.35 kU/l or 3.5 kU/l.

Explanatory variables

For exposure to farming environments, the definition used for the stratified sampling was used as a categorical variable with unexposed non-farm children as the reference. The total number of siblings was assessed in the self-administered Phase 1 questionnaire and modeled as a categorical variable with no siblings as the reference. For only 5% of the participants, more than three siblings were reported and because of these sparse data they were grouped in a category of three or more siblings.

The birth dates of all siblings who were in elementary school at the time of Phase 1 were queried. Children belonging to the same family were identified by the combination of birth dates. The 79,888 participants clustered in 66,304 families, of which 12,518 (18.9%) had more than one participating child. For n = 7,530 families with more than one participating child, all siblings (n = 15,595) participated and were in elementary school during Phase 1. For this subset, birth order of all siblings in the family was known and analyzed.

Putative confounding variables

Study centers were Austria, Switzerland, Bavaria (Germany), and Baden-Württemberg (Germany). Age was entered into models as a continuous variable as the exact age at Phase 1. Familial allergies were present if either asthma or hay fever or atopic eczema were reported for either parent or a sibling and absent otherwise. Parental education was high if either parent was qualified for university entrance according to the country specific schooling systems and low otherwise. Parental smoking was present if either parent reported current smoking and absent otherwise. If all information was missing for one of these indicators of familial exposures, the respective variable was coded as missing, and the observation was excluded from the multivariate analyses.

Statistical analyses

Associations were modeled as odds ratios with 95% confidence intervals using multivariate logistic regression with weighted stratified techniques where appropriate. Multiplicative interaction was tested for by introduction of interaction terms in these models. The interaction term with both number of siblings and exposure to farming environments, as categorical variables is tested on six degrees of freedom. To conduct a more powerful test, we also tested the gradient of number of siblings (effect per additional sibling) across the three categories of exposure to farming environments. This interaction term is tested on two degrees of freedom.

To account for the family clustering in analyses of birth order, odds ratios with 95% confidence intervals were estimated by generalized estimating equations (GEE) using an independent correlation structure. Using an unstructured correlation structure did not meaningfully alter the displayed results.

All models were adjusted for study center, sex, age, familial allergies, parental education, and parental smoking. The sample size was reduced to 74,724 (94%) due to missing information for these covariates. For the subset with information on atopy, the effective sample size in multivariate models was 7,563 (94%). All computations were performed with SAS V9.2, The SAS Institute, Cary, NC, USA.

Results

Farm children have more siblings than their rural peers (Table 1). Previously published characteristics, in particular the lower prevalence of doctor-diagnosed hay fever and atopy among farm children compared with the unexposed reference, are also displayed in Table 1.

Table 2 shows that the prevalence of doctor-diagnosed hay fever and atopy decline with an increasing number of siblings or an increasing level of exposure to farming environments. The prevalence of doctor-diagnosed hay fever was 12% among children with no farm exposure and no siblings and 2% among farm children with more than two siblings. For the prevalence of atopy, these figures were 45% and 20%, respectively. A similar pattern was observed for hay fever symptoms (data not shown).

Using a categorical definition of the number of siblings and exposure to farming environments in multivariate logistic regression models, there was no substantial effect modification between the two for their effect on doctor-diagnosed hay fever ($p_{int} = 0.63$), hay fever symptoms ($p_{int} = 0.10$), or atopy ($p_{int} = 0.38$). In addition, there was no clear tendency toward synergy or saturation: the interaction odds ratio estimates had a mixed pattern for doctor-diagnosed hay fever and hay fever symptoms but were all above one for atopy; the latter indicating synergy of the effects on a multiplicative scale.

Figure 1 shows the adjusted dose-response relationship on a log scale for both effects on doctor-diagnosed hay fever. For atopy, these associations are depicted in Fig. 2. The pattern is very similar; however, both effects are of smaller magnitude compared with the effects on doctor-diagnosed hay fever, and the precision of their estimation is less due to the smaller sample size. Again, the analysis of hay fever symptoms resembled the pattern for doctor-diagnosed hay fever. However, the effects tended to be less strong (data not shown).

Modeling a trend per additional sibling, the odds of hay fever were reduced by a similar amount in each category of exposure to farming environments: OR (95%CI) per sibling 0.79 (0.76; 0.83) among unexposed non-farm children, 0.77 (0.72; 0.83) among exposed non-farm children, and 0.72 (0.62; 0.83) among farm children. (2df interaction test: $p_{int} = 0.41$). For atopy, these odds ratios were 0.80 (0.71; 0.90), 0.94 (0.84; 1.05), and 0.85 (0.76; 0.95), respectively, with a statistically non-significant interaction ($p = 0.11$). Using the more specific, clinically more relevant cutoff of 3.5 kU/l also suggested an attenuated effect per sibling only among the exposed non-farm children (OR 0.80, 0.89, and 0.82, respectively, $p_{int} = 0.46$). Only when atopy was defined at the more sensitive but less specific cutoff of 0.35 kU/l, the interaction term became statistically significant ($p_{int} = 0.02$, tested on 2df), and the effect per additional sibling was attenuated among the exposed non-farm and the farm children. This attenuation could be an indication for saturation: the protective effect through family size does not further add to the protection conferred by exposure to farming environments.

In the subset of n = 15,595 participants for which birth order was available, the odds ratio for doctor-diagnosed hay fever was 0.82 (0.71; 0.94) per older sibling adjusting for total number of siblings [OR per additional sibling 0.79 (0.68; 0.92)] and exposure to farming environments as well as the other confounders.

Table 1 Characteristics of the study population in total and across levels of exposure to farming environments

	Total (n = 79,888) n (%)	Farm (n = 9,611) n (%)	Exposed non-farm (n = 18,182) n (%)	Unexposed non-farm (n = 52,095) n (%)
Female sex	39576 (49.7)	4804 (50.0)	9317 (51.3)	25455 (49.1)
Age [mean (SD)]	8.8 (1.5)	8.9 (1.6)	8.9 (1.6)	8.7 (1.5)
Familial allergies	36778 (46.5)	3267 (34.2)	8272 (45.8)	25239 (49.0)
Parental smoking	46505 (58.8)	3897 (40.8)	10423 (57.7)	32185 (62.5)
High parental education	16996 (22.3)	887 (9.8)	3872 (22.2)	12237 (24.6)
Number of siblings				
0	6900 (8.7)	365 (3.8)	1441 (8.0)	5094 (9.9)
1	38047 (48.2)	2994 (31.3)	7981 (44.3)	27072 (52.7)
2	22453 (28.4)	3525 (36.9)	5625 (31.2)	13303 (25.9)
≥3	11565 (14.6)	2678 (28.0)	2976 (16.5)	5911 (11.5)
[Mean (SD)]	1.6 (1.1)	2.0 (1.2)	1.6 (1.1)	1.5 (1.1)
Hay fever symptoms	8173 (10.3)	402 (4.2)	1618 (9.0)	6153 (11.9)
Doctor-diagnosed hay fever	6940 (8.8)	291 (3.0)	1263 (7.0)	5386 (10.4)
Atopy*	2491 (35.6)	669 (22.7)	858 (32.0)	964 (39.8)

*Data were derived from phase 2 and are displayed with unweighted n and weighted%. The total study population for atopy included 8,023 children; of those, there were 2,977 farm children, 2,660 exposed non-farm children, and 2,386 unexposed non-farm children. Atopy was defined as allergen-specific serum IgE of at least 0.7 kU/l against one or more of *D. pteronyssinus*, cat dander, rye, timothy, mugwort, or common silver birch.

Table 2 Prevalence* of doctor-diagnosed hay fever and of atopy† stratified by exposure to farming environments and number of siblings

	Doctor-diagnosed hay fever			Atopy†		
Number of siblings	Farm	Exposed non-farm	Unexposed non-farm	Farm	Exposed non-farm	Unexposed non-farm
0	4.1 (2.1;6.2)	8.9 (7.5;10.4)	12.1 (11.2;13.0)	27.5 (17.7;37.3)	28.2 (21.3;35.1)	45.1 (38.1;52.1)
1	3.8 (3.1;4.5)	7.7 (7.1;8.2)	11.2 (10.9;11.6)	25.0 (22.2;27.8)	33.2 (30.5;36.0)	41.8 (39.1;44.6)
2	2.9 (2.3;3.5)	6.1 (5.5;6.7)	9.2 (8.7;9.7)	22.4 (20.0;24.9)	32.1 (29.1;35.2)	40.0 (36.2;43.8)
≥3	2.2 (1.6;2.7)	5.9 (5.0;6.7)	8.1 (7.4;8.8)	19.6 (17.0;22.2)	31.1 (26.9;35.4)	30.9 (25.3;36.4)

*Prevalence in% with 95% confidence intervals.
†Atopy was defined as allergen-specific serum IgE of at least 0.7 kU/l against one or more of *D. pteronyssinus*, cat dander, rye, timothy, mugwort, or common silver birch and measured in a subset of n = 8,023 participants.

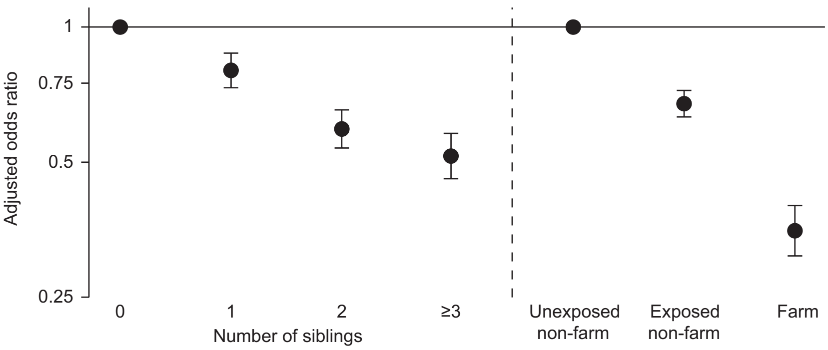

Figure 1 Mutually adjusted odds ratios (in addition adjusted for study center, sex, age, familial allergies, parental education, and parental smoking) with 95% confidence intervals for the effect of number of siblings and exposure to farming environments on doctor-diagnosed hay fever (n = 74,724).

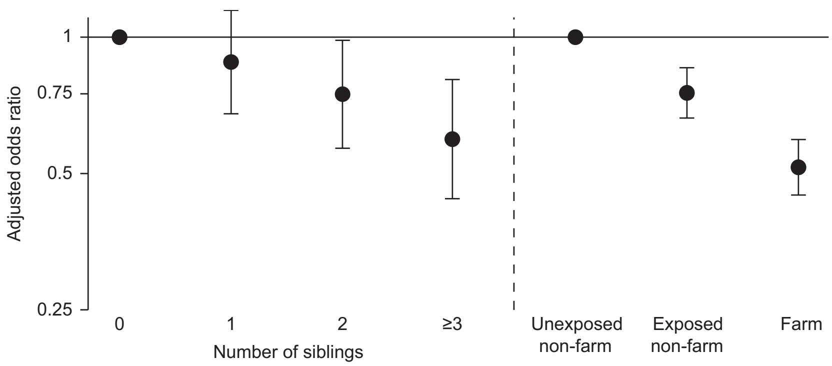

Figure 2 Mutually adjusted odds ratios (in addition adjusted for study center, sex, age, familial allergies, parental education, and parental smoking) with 95% confidence intervals for the effect of number of siblings and exposure to farming environments on atopy (atopy was defined as allergen-specific serum IgE of at least 0.7 kU/l against one or more of *D. pteronyssinus*, cat dander, rye, timothy, mugwort, or common silver birch and measured in a subset of n = 8,023 participants) (n = 7,563).

Discussion

The inverse association of farming with hay fever and atopy is found in all sizes of family, with no clear tendency to total saturation or synergism. This suggests that different mechanisms may underlie these two protective factors. Combinations of family size and farm exposure markedly reduce prevalence of allergic disease and indicate the strength of environmental determinants. The lowest prevalence of doctor-diagnosed hay fever (2.2%) is found among farm children with three or more siblings. This prevalence is only 25% of the prevalence in the total population (8.8%), which translates into a population attributable fraction of 75% for having fewer than three siblings and/or not being brought up on a farm.

The GABRIELA study is one of the largest population-based studies conducted on the effect of exposure to farming environments on allergic disease. This allowed a thorough analysis of the total number of siblings with enough data for high precision in the typically sparse cells of only children living on a farm and children with a high number of siblings among the unexposed non-farm children.

Precision and power may be an issue for the analyses of atopy in our study. A statistically significant interaction suggesting saturation between the effects of farming and family size was only detected when the most inclusive definition of atopy (which led to the largest number of atopics) was employed in a simplified model assuming a linear trend per additional sibling. However, the more specific definitions at cutoffs of 0.7 and 3.5 kU/l did not only result in non-significant test for interaction but also resulted in inconclusive patterns of effects with an attenuation of the effect of family size only among the middle category of farm exposure. This suggests that our study does not necessarily lack the power to detect interaction between both effects for atopy, but that using an inclusive, less specific atopy definition may obscure true patterns due to false positives.

The GABRIELA study was conducted in rural areas only. It is conceivable that the prevalence of 12% among the unexposed non-farm only children is even higher in urban children. Furthermore, the prevalence of 2% among farm children with three or more siblings might be even lower if we counted older siblings rather than total number of siblings. This is substantiated by the effect of birth order that we detected in addition to the effect of total number of siblings. The population attributable fraction for both exposures combined might thus be even higher than 75% if birth order was considered, or a comparison to urban rather than rural populations was drawn.

However, birth order could only be analyzed in a subset of the study population for which all siblings participated in the study and were in elementary school. The latter restricts to families with rather short birth intervals, because elementary school education is 4 yrs in all study areas but Switzerland, where it is 6 yrs. In particular, the families with a large number of siblings will have a shorter birth interval. Furthermore, family structure and birth order were assessed by comparison of reported birth dates which could lead to some errors. Nonetheless, a subset of the families identified via birth date combinations was validated against an identification algorithm by housing address which showed minimal misclassification.

Our analyses on the total number of siblings in the full study population did not specifically account for the familial clustering which may lead to an underestimation of the variance. However, only 19% of the participating families contributed data for more than one family member. Moreover, we adjusted for variables that act on a family level such as familial allergies, parental education, and parental smoking. In fact, due to our definition, the exposure to farming environments was assigned on a family level for farm children, whereas it could be different for siblings within a family for exposed farm children. The definition of the former includes the family running a farm, while for the latter, the regular exposure to barns or stables or the consumption of farm milk was reported on an individual level. Compared with a GEE accounting for the familial clustering, the logistic regression analyses gave almost similar results adjusting for the family-based covariates.

Birth order is only one more specific aspect of the effect of family size which might be a proxy for early infections or – possibly more likely – in utero programming, endocrine effects, or maternal immunity (6, 8, 9). Similarly, the exposure to farming environments as we defined it in our study could be a proxy for microbial exposure and xenogeneic pressure which modulate innate and adaptive immune responses (2, 10). This is substantiated by previous findings also in the GABRIELA study (11, 12).

In our large study, there is no clear evidence of synergy or saturation of the effects of these two proxies. This implies that both effects – and thus their true underlying specific exposures – act through different mechanisms. Our data suggest that even in rural areas about 75% of doctor-diagnosed hay fever may be accounted for by lack of exposure to these poorly understood protective factors associated with siblings and farming environments. Therefore, there is substantial potential for preventive actions if these specific protective factors can be identified.

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