

Original article

Adult obesity, farm childhood, and their effect on allergic sensitization

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Background: Obesity as well as a reduced microbial exposure, 2 markers of Western lifestyle, might be associated with an increased risk of allergic sensitization.

Objective: We aimed to analyze the interplay of these markers of Western lifestyle on allergic sensitization.

Methods: A questionnaire survey was completed by rural adults (18-45 years). Clinical assessments included those of sensitization (specific IgE) against inhalant allergens and body mass index (BMI). Subjects were grouped on the basis of their recent BMI (obesity: BMI ≥ 30 kg/m²) and whether they had regular farm contact during the first 3 years of life (farm subjects). Nonobese nonfarm subjects served as the reference group. Overall, 1861 subjects were included in the analyses.

Results: Compared with nonobese nonfarm subjects, nonobese farm subjects showed a decreased odds ratio for sensitization (odds ratio, 0.6; 95% CI, 0.5-0.8). This decrease was not observed in obese subjects (obese nonfarm subjects: 1.2, 0.8-1.9; obese farm subjects: 1.0, 0.6-1.6). Associations were similar for symptoms of allergic rhinitis.

Conclusion: Obesity, as a risk factor for respiratory allergies per se, might diminish or even cancel the protective effect of a farm childhood.

Clinical implications: The high prevalence of respiratory allergies in inner-city societies despite lower levels of hygiene might be explained by obesity. (J Allergy Clin Immunol 2006;117:1016-1023.)

Key words: Leptin, hygiene hypothesis, inhalant allergens, specific IgE

Western lifestyle is characterized by an increased prevalence of obesity and reduced exposure to microbes.¹ In epidemiologic studies, both factors were shown to be associated with a higher prevalence of allergic rhinitis and sensitization.²⁻¹¹

Abbreviations used

BMI: Body mass index

CI: Confidence interval

ETS: Environmental tobacco smoke

OR: Odds ratio

Part of the association between obesity and sensitization has been attributed to the increased production of the proinflammatory hormone leptin, released by adipocytes. Laboratory studies have shown that leptin not only is associated with a T_H1 response¹² but also augments the ovalbumin-induced IgE production in sensitized mice.¹³

According to the hygiene hypothesis, the Western lifestyle is also associated with a reduced burden of exposure to microbial agents like endotoxins, which in turn increases the risk of respiratory allergies via a reduction in T-regulatory cells.^{14,15} This effect has been demonstrated in a number of studies throughout countries by comparing subjects without farm contact during childhood with subjects who had regular farm contact during the first years of life or had prenatal exposure.^{7,8,10,11} However, as recently elucidated, this does not explain why the risk of asthma is increased among inner-city populations in North America with a low degree of "cleanliness."^{1,16} Interestingly, the combined effect of microbial exposure and obesity on respiratory allergies has not yet been studied.

On the basis of these arguments, we aimed to analyze the effect of a farm childhood on the prevalence of sensitization and allergic rhinitis among rural adults with and without obesity.

METHODS

Study subjects

Data of the Lower Saxony Lung Study, a cross-sectional study among rural adults (age 18-45 years) living in 4 towns in northwestern Germany, have been used.^{7,17} All 10,252 inhabitants were invited to answer a mail-in questionnaire. For feasibility reasons, only 7080 of them were a priori randomly selected for additional participation in the medical examination (questionnaire response, 67%; Table I). The study was approved by the Medical Ethical Committee of the Ludwig-Maximilians-University of Munich and the Lower Saxony Medical Board.

Questionnaire

The mail-in questionnaire consisted of validated questions on respiratory health, demographic characteristics, potential confounders, and

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TABLE I. Target population and selection of the population included in the analyses

Target population (n)	All inhabitants of 4 rural towns, age 18-44 y N = 10,252	
Of these:	No (excluded)	Yes (included)
<i>A priori</i> invited to take part in clinical examination (random selection)	3172	7080 (100%)
Questionnaire response	2360	4720 (67%)
Population eligible for the clinical examination*	668	4052
Of these:	No (excluded)	Yes (included)
Participation in clinical examination	1307	2745
Of these:	No (excluded)	Yes (included)
Regular farm animal contact not starting between ages 4 and 18 y	231	2514
Not pregnant or breast-feeding at the time of the examination	92	2422
BMI ≥ 18.5 kg/m ²	34	2388
Missing data on:		
BMI	59	2329
Farm contact during childhood	89	2240
Family history of atopy	218	2022
Other potential confounders	161	
Population included in the analyses (n)		1861

*Subjects with main place of living outside the study area, subjects not able to participate for health reasons, and those not born in the former West Germany were not eligible for the clinical part of the study.

farm contact. The items were mainly taken from the questionnaire of the European Community Respiratory Health Survey¹⁸ and the ALergy and EndotoXin (ALEX) study.¹⁰

Farm contact during the first 3 years of life was defined as present if subjects either answered “yes” to the question, “Did you live on a farm during the first 3 years of your life?” or confirmed that they had visited animal houses regularly during the first 3 years of life.¹⁰

Medical examination

Of those who answered the questionnaire (n = 4720), only subjects whose main place of residence was in the study area, who were physically able to participate, and who were born in the former West Germany were eligible for the medical examinations (n = 4052; Table I). The last criterion was chosen to ensure similar childhood environments. Overall, 2745 (64%) took part in the medical examination. Weight and height of the subjects were measured, and body mass index (BMI) was calculated as weight divided by height squared (kg/m²).

Specific IgE against a panel of ubiquitous allergens (Timothy grass, rye, mugwort, birch, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, cat, and dog) was measured in serum samples (SX-1; Pharmacia CAP system, Freiburg, Germany).

Statistical methods

Subjects who started regular contact to farm animals during childhood but after age 3 years (n = 231), were pregnant or breast-feeding (n = 92), were underweight (BMI < 18.5 kg/m²; n = 34) or had missing data on BMI (n = 59), farm contact during childhood (n = 89), or one of the potential confounders (n = 379; 218 of them only because of missing information on the parental history of allergies) were excluded. Overall, 1861 subjects could be included in the final analyses (Table I).

Three outcome definitions have been used:

- *Symptoms of allergic rhinitis* on the basis of the questionnaire data: Allergic rhinitis was considered present when subjects gave an affirmative response to the question, “Do you have any nasal allergies, including hay fever?”¹⁸
- Specific IgE against a panel of ubiquitous allergens: Subjects with a specific IgE concentration of ≥ 0.35 kU/L (corresponding to RAST class 1 or higher) were regarded as *sensitized*.¹⁸

- *Symptomatic sensitization* was considered if subjects with symptoms of allergic rhinitis also had a specific IgE concentration of ≥ 0.35 kU/L. Subjects who reported symptoms without being sensitized (n = 49) or who had detectable IgE levels but did not indicate symptoms (n = 235) were excluded from this analysis.

The study population was divided into 4 groups:

- Nonobese nonfarm subjects: BMI < 30 kg/m² without farm contact during the first 3 years of life (reference group).
- Obese nonfarm subjects: BMI ≥ 30 kg/m² without farm contact during the first 3 years of life.
- Nonobese farm subjects: BMI < 30 kg/m² and living on a farm or regular visits to animal houses during the first 3 years of life.
- Obese farm subjects: BMI ≥ 30 kg/m² and living on a farm or regular visits to animal houses during the first 3 years of life.

Descriptive data of the 4 groups are presented as absolute and relative frequencies for categorical parameters. χ^2 Tests were used for statistical comparison. For continuous parameters, means with SDs were calculated and compared by using ANOVAs.

The following confounders were *a priori* considered: sex (male, female), age (4 categories), recent or childhood exposure to environmental tobacco smoke (ETS), active smoking (never, exsmoker, and current smoker), level of education (< vs ≥ 12 years of schooling), parental history of allergies, number of siblings ($\leq$ vs >2 siblings), and currently living on a farm.

Locally optimal estimating and smoothing scatter plots functions controlling for these potential confounders were used to visualize the association between BMI and respiratory outcomes. A band width of 0.6 was used for these models.

Finally, the 4 groups were compared using logistic regression models. Results are presented as crude and adjusted ORs with 95% CIs.

RESULTS

No differences were seen for sex and parental allergies (allergic rhinitis, asthma) among the 4 groups under study,

TABLE II. Descriptive data of the study population stratified for farm contact during the first 3 years of life and obesity

Parameter N (%)	Farm subjects		Nonfarm subjects		P_{χ^2}
	BMI <30 kg/m ²	BMI ≥30 kg/m ²	BMI <30 kg/m ²	BMI ≥30 kg/m ²	
N = 1861	793 (100)	127 (100)	818 (100)	123 (100)	
Age (y), mean (SD)	35.0 (7.0)	36.4 (6.3)	32.8 (7.5)	35.2 (7.1)	<.001*
BMI (kg/m ²), mean (SD)	24.5 (2.7)	33.3 (3.7)	24.0 (2.8)	33.1 (3.2)	<.001*
Sex: male	389 (49.1)	67 (52.8)	377 (46.1)	68 (55.3)	.16
Level of schooling <12 y	610 (76.9)	110 (86.6)	582 (71.1)	105 (85.4)	<.001
Parental allergy	253 (31.9)	43 (33.9)	278 (34.0)	38 (30.9)	.78
>2 siblings	507 (63.9)	83 (65.4)	342 (41.8)	68 (55.3)	<.001
Smoking					.003
Exsmoker	170 (21.4)	43 (33.9)	161 (19.7)	27 (22.0)	
Smoker	248 (31.3)	27 (21.3)	290 (35.5)	46 (37.4)	
ETS exposure					
During childhood	430 (54.2)	77 (60.6)	518 (63.3)	83 (67.5)	.001
Now	304 (38.3)	64 (50.4)	342 (41.8)	70 (56.9)	<.001
Living on a farm					
Now	277 (34.9)	49 (38.6)	31 (3.8)	7 (5.7)	<.001
At age 3 y	731 (92.2)	119 (93.7)	0 (0.0)	0 (0.0)	<.001
Regular visits to animal houses at age ≤3 y†	647 (83.4)	105 (84.0)	0 (0.0)	0 (0.0)	<.001
Working on a farm now†	105 (13.6)	25 (20.5)	17 (2.2)	5 (4.2)	<.001

*ANOVA.

†Absolute numbers might differ because of missing data.

whereas age differed slightly but significantly ($P < .001$; Table II). Obese subjects showed a lower level of schooling and were more likely exposed to second-hand smoke compared with nonobese participants. Farm subjects had a higher number of siblings and were less likely to smoke than nonfarm subjects. Recent exposure to farm environments did not differ between obese and nonobese farm subjects. Furthermore, when comparing the groups of either obese or nonobese subjects, BMI was not different between farm and nonfarm subjects.

Locally optimal estimating and smoothing scatter plots smoothers (Fig 1) indicated a higher prevalence of sensitization among nonfarm subjects, but values were significantly different only in the range of normal BMI. With increasing BMI, the differences between farm and nonfarm subjects became smaller, and CIs overlapped. The prevalence of sensitization increased from 17% in nonobese farm subjects, 25% in obese farm subjects, and 31% in nonobese nonfarm subjects to 33% in obese nonfarm subjects ($P_{\chi^2} < .001$; Table III). Unadjusted and adjusted logistic regression models showed a statistically significant lower risk of sensitization for nonobese farm subjects compared with the other 3 groups. In contrast, no significant differences were seen within the other 3 groups. Associations were similar for symptoms of allergic rhinitis and symptomatic sensitization (Table III).

DISCUSSION

The current study confirmed the protective effect of childhood farm contact on allergic sensitization. Taking

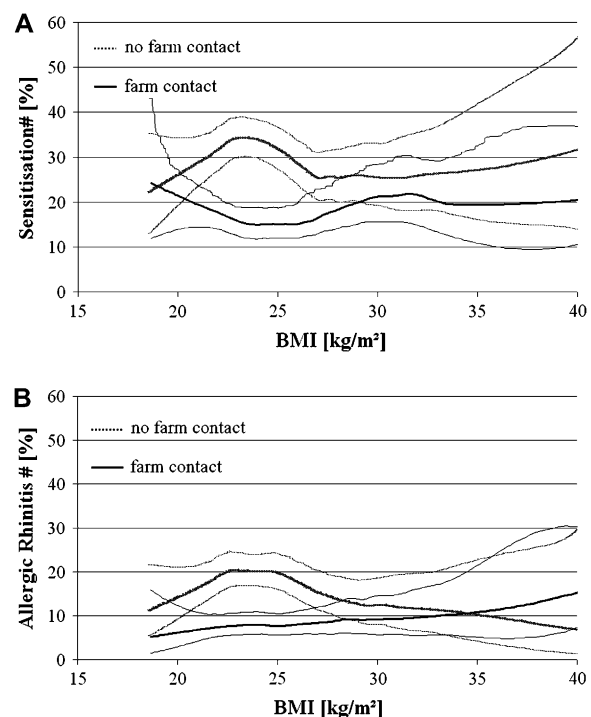


FIG 1. Smoothed plots with 95% CIs of sensitization (A) and allergic rhinitis (B) in relation to BMI stratified for farm contact during the first 3 years of life. Adjusted for age, sex, level of schooling, parental allergy, number of siblings, active smoking, exposure to ETS, and current farm living.

this observation as a point of reference, it provided for the first time evidence that this protection can be diminished or even canceled in obese subjects.

TABLE III. Prevalence, crude and adjusted ORs for the association between farm contact during the first 3 years of life, obesity and health outcomes; ORs with 95% CIs

Farm contact	BMI (kg/m ²)	N	Sensitization [†]	Symptoms of allergic rhinitis	Symptomatic sensitization [‡]
			1820	1843	1518§
No	<30	n (%)	244 (30.7)	152 (19.3)	131 (19.9)
		OR (Reference category)	1	1	1
	≥30	n (%)	39 (32.8)	19 (16.1)	16 (17.2)
		Crude OR (95% CI)	1.1 (0.7-1.7)	0.8 (0.5-1.3)	0.8 (0.5-1.5)
		Adjusted OR (95% CI)*	1.2 (0.8-1.9)	0.9 (0.6-1.6)	0.9 (0.5-1.7)
Yes	<30	n (%)	135 (17.2)	67 (8.6)	46 (6.9)
		Crude OR (95% CI)	0.5 (0.4-0.6)	0.4 (0.3-0.5)	0.3 (0.2-0.4)
		Adjusted OR (95% CI)*	0.6 (0.5-0.8)	0.6 (0.4-0.8)	0.5 (0.3-0.7)
	≥30	n (%)	30 (24.6)	17 (14.3)	13 (13.0)
		Crude OR (95% CI)	0.7 (0.5-1.1)	0.7 (0.4-1.1)	0.6 (0.3-1.1)
		Adjusted OR (95% CI)*	1.0 (0.6-1.6)	0.9 (0.5-1.6)	1.0 (0.5-1.9)

*Adjusted for age, sex, level of schooling, parental allergy, number of siblings, active smoking, exposure to ETS, and current farm living.

[†]Specific IgE against a panel of ubiquitous allergens ≥0.35 kU/L.

[‡]Symptoms of allergic rhinitis and specific IgE against a panel of ubiquitous allergens ≥0.35 kU/L.

[§]Subjects who were sensitized but did not report symptoms (n = 235) and subjects who reported symptoms without being sensitized (n = 49) or had missing data on one of the outcomes (n = 59) were excluded from this analysis.

The strengths of our study were a reasonable response among a large population-based sample of rural subjects, as well as the use of validated questionnaire instruments^{10,18} and objective measures of sensitization and BMI. All assessments were performed following standardized procedures with thorough quality control. A large number of subjects with childhood farm contact could be recruited in this study. Thus, in addition to BMI, we were able to stratify our results according to this type of exposure.

Because of time and financial constraints, only 69% of our population could be invited to take part in the medical examination. Because subjects were a priori selected at random into the medical part of the study, this approach is not considered to have introduced any selection bias. However, only 67% of those invited answered the questionnaire (respondents). To assess potential selection bias, nonrespondents were approached by phone and 433 agreed to answer a 10-item telephone questionnaire. Nonrespondents were more likely to be male than respondents (nonrespondents, 57%; respondents, 49%; $P_{\chi^2} < .01$) and to be born outside the former West Germany (nonrespondents, 19%; respondents, 14%; $P_{\chi^2} < .01$). That females are more likely to participate is a common problem in epidemiologic studies (see example¹⁸). The majority of subjects not born in the former West Germany were subjects from the former Soviet Union. Language barriers might therefore be 1 reason for nonresponse. This nonresponse is not expected to have biased our results because subjects born outside the former West Germany were excluded from our analyses. This was done to minimize confounding by different childhood environments.

With respect to symptoms of allergic rhinitis, respondents (14%) and nonrespondents (14%) did not differ statistically significantly from each other ($P = .8$).

Nevertheless, nonrespondents were more likely to have lived on a farm during the first 3 years of life (46%) compared with respondents (37%; $P_{\chi^2} < .01$). If this overrepresentation of nonfarm subjects were dependent on BMI and the outcome, it might have resulted in selection bias.

Because of the strict criteria chosen, $\frac{1}{5}$ of the study population had to be excluded from the analysis presented in this article. The majority of the subjects excluded had regular childhood farm contact that started after the age of 3 years. Because it is generally assumed that the timing of exposure to farm environments is crucial and has to occur very early in life¹⁰ or even prenatally,⁸ we used the first 3 years of life as a proxy for such early exposures. Inclusion of subjects who started their exposure after the age of 3 years into analyses did not substantially change the results (data not shown).

Because of the limited number of obese subjects, the power was not sufficient to prove formally a statistically significant interaction between farm contact and obesity, although its presence was suggested by the data (Fig 1).

One has to bear in mind the cross-sectional nature of the study. This might have resulted in recall bias because, for example, the information on living on a farm in early childhood was derived from self-reports. Furthermore, selective migration out of the study area might have occurred. Only prospective cohort studies starting in early childhood might overcome these difficulties. Finally, because of financial constraints, we could test only a mixture of ubiquitous inhalant allergens instead of testing each single allergen.

The association between elevated BMI and increased prevalence of sensitization has been demonstrated in a number of epidemiologic studies^{2-6,19} and is supported by experimental animal data.^{12,13} The effect of early childhood, even maternal, exposure to animal farm environments on allergic sensitization has also been confirmed

in many populations (see reviews^{11,20}). Such farm environments are characterized by high levels of various microbial compounds. Surprisingly, the combined effect of farm living and obesity has not been the topic of a study until now. Instead, in 2 recent studies, analyses were adjusted for place of residence (rural vs urban³ or living on a farm during childhood²) when investigating the association between BMI and allergic sensitization.

The knowledge about the underlying pathophysiological mechanisms in the association between obesity and allergic sensitization is still limited. Among the best candidates are the immunomodulatory effects of circulating compounds such as leptin that are linked to body weight and are increased in obese subjects.²¹ In addition, differences in dietary composition might modulate sensitization in obese persons.¹ In the current study, neither information on nutrition nor measurements of leptin levels in serum samples were available; the same was true for body weight during childhood. To have sufficient power to disentangle the interactions among obesity, leptin levels, nutritional behavior, and exposure to farming environments, larger studies especially designed for this question are needed. We hope that the observed association among body weight, early childhood exposure, and the prevalence of allergic sensitization or symptoms of allergic rhinitis will stimulate such research.

In conclusion, our study indicates that the protective effect of early childhood farm contact on allergic sensitization might be diminished by adult obesity. This suggests that either dietary factors or nonspecific systemic inflammation present in obese subjects might counteract or even reverse an acquired protection against the development of allergic sensitization.

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