Original Article

Exposure to Farming Environments in Early Life and Type 1 Diabetes

A Case-Control Study

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It has been hypothesized that a stimulation of regulatory cytokines by microbial compounds reduces autoimmune as well as atopic diseases. Farm-related contact to microbial compounds protects from allergies, but no data on the association between farm contact and type 1 diabetes is available. The aim of this study was to test this association. A case-control study was conducted in five children's hospitals. Regular contact to farm animals and potential confounders were assessed using a postal questionnaire. Eligible subjects were all prevalent cases with type 1 diabetes registered in the hospitals and hospital-based control subjects (response rate 91%). Included were children aged 6–16 years living in rural areas with German nationality (242 case and 224 control subjects). Regular contact to stables (adjusted odds ratio 1.2 [95% CI 0.5–2.7]) was not associated with type 1 diabetes. In addition, regular contact to specific farm animals was not associated with case status. There was a tendency for an inverse relationship between allergic rhinitis and type 1 diabetes (0.6 [0.3–1.1]; *P* = 0.11). There was no evidence that early exposure to farm animals largely decreases the risk in children for developing type 1 diabetes. *Diabetes* 54: 3212–3216, 2005

Because the concordance rate for monozygotic twins is only ~50%, environmental factors may play an important role in the etiology of type 1 diabetes (1,2). This is supported by the recent increase in the incidence of type 1 diabetes in industrialized countries (3,4) and a marked geographical variation (5). Furthermore, the risk of type 1 diabetes in immigrants becomes similar to the country to which they migrate (6).

These observations are in line with the so-called "hygiene hypothesis," suggesting that the development of autoimmune and atopic diseases is facilitated by a decreasing level of microbial exposure in early life (7). It is thought that a lack of stimulation of regulatory cytokines by infectious organisms (like bacteria, viruses, and parasites) leads to an increase in diseases associated with T helper 1 cell response (like type 1 diabetes) as well as T helper 2 cell response (like respiratory allergies) (8,9).

Consistent with the hygiene hypothesis, subjects living in rural areas and having contact to farm animals in the 1st year of life have consistently been shown to have a lower prevalence of respiratory allergies (10–15). The burden of microbial compounds (endotoxins, β-glucans) found in these environments may be responsible for this inverse association (12,16–18).

On the other hand, there is conflicting evidence as to whether the prevalence of type 1 diabetes is lower (19–25) or higher (26–29) in children living in rural areas. However, in these studies, contact with farm animals in infancy has not been measured. We therefore conducted a case-control study in rural areas of southern Germany to assess the potential association between exposure to farming environments and the development of type 1 diabetes in children.

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RESEARCH DESIGN AND METHODS

The study was done at five pediatric diabetes referral centers in southern Bavaria (Munich, Regensburg, Rosenheim, Landshut, and Neuburg/Donau). Except for the center located in Munich, which included urban and rural subjects, these clinics mainly take care of patients from rural areas. While they are thought to cover most of the patients with type 1 diabetes in the area, no data exist on the completeness of coverage.

Control subjects were in- and outpatients visiting the department of surgery of the same hospitals between May and June 2004. To minimize selection bias, eligible control subjects were patients with a relatively wide range of diagnoses (fractures, sprains, cuts, burns, enuresis, phimosis, or appendicitis).

Inclusion criteria for case and control subjects were *1*) age between 6 and 16 years (reference day 1 May 2004) and *2*) living in rural areas (<100,000 inhabitants) of the study region. Overall, 319 prevalent case and 299 control subjects met the inclusion criteria. Twenty-nine of these subjects (8 case and 21 control subjects) were not eligible (moved outside the study area, not able to answer the questionnaire because of language problems, or invalid address data). In addition, only subjects with German nationality were considered. This was done because in Germany nationality reflects ethnicity rather than place of birth, and the number included (8 case and 5 control subjects) was too small to perform stratified analyses. The study was approved by the ethical committee of the Ludwig-Maximilians University, Munich.

The parents of case and control subjects were contacted between May and July 2004 using a postal questionnaire. Up to two reminders were sent within 3 weeks to all nonresponders. In addition, control subjects not responding

TABLE 1
Selected descriptive characteristics of the study population (2004)

	Case subjects	Control subjects	P_t-test
n	242	224	
Age (years)	11.2 ± 2.8; 11.5 (6–16)	10.0 ± 2.8; 10.0 (6–16)	<0.001
Age at diagnosis (years)	6.7 ± 3.4; 4.0 (1–14)	—	—
			$P_{\chi^2\ \text{test}}$
Sex: female	107 (44.2)	95 (42.4)	0.70
Birth weight <2,500 g	30 (12.4)	30 (13.4)	0.76
Allergic rhinitis	30 (12.4)	33 (14.7)	0.46
Family history			
Older siblings	117 (48.3)	118 (52.7)	0.35
Younger siblings	116 (47.9)	115 (51.3)	0.46
Parents with type 1 diabetes	17 (7.0)	2 (0.9)	0.001
Day care attendance			
Age 0–2 years	50 (20.7)	71 (31.7)	0.02
Age 3–5 years	152 (62.8)	125 (55.8)	
Never*	40 (16.5)	28 (12.5)	
Nutrition			
Breast feeding <7 months	158 (65.2)	140 (62.5)	0.55
Nutritional supplements other than breast feeding <3 months	123 (50.8)	89 (39.7)	0.02
Raw milk consumption during 1st year of life	6 (2.5)	7 (3.1)	0.67
BMI (kg/m^2)			
≤16.3 (1st quartile)	41 (16.9)	78 (34.8)	<0.001
≤18.1 (2nd quartile)	63 (26.0)	59 (26.3)	
≤20.5 (3rd quartile)	59 (24.4)	55 (24.6)	
>20.5 (4th quartile)	79 (32.6)	32 (14.3)	
Place of living			
Rural town	78 (32.2)	61 (27.2)	0.24
Village	164 (67.8)	163 (72.8)	
Regular contact to pets (ever)†			
Dogs	114 (47.1)	120 (53.6)	0.16
Cats	145 (59.9)	145 (64.7)	0.28
Rabbits	98 (40.5)	87 (38.8)	0.72
Others	63 (26.0)	54 (24.1)	0.63
Farm living			
Living on a farm during 1st year of life	28 (11.6)	20 (8.9)	0.35
Living on a farm now	25 (10.3)	15 (6.7)	0.17
Regular contact to stables during†			
1st year of life	38 (15.7)	36 (16.1)	0.91
2nd to 6th year of life	57 (23.6)	60 (26.8)	0.42
Now	56 (23.1)	51 (22.8)	0.92
Regular contact with farm animals† (ever)			
Cattle	30 (12.4)	37 (16.5)	0.21
Pigs	12 (5.0)	17 (7.6)	0.24
Sheep or goat	18 (7.4)	19 (8.5)	0.68
Poultry	38 (15.7)	34 (15.2)	0.88
Horses	39 (16.1)	35 (15.6)	0.89

Data are means ± SD; median (range) or n (%). *"Never" includes day care attendance starting after age 5 years. †"Regular" defined as at least once a week.

within 5 weeks after the first mailing (n = 55; 18% of the control subjects) were contacted by phone. Because the response rate among case subjects was already >90% after the second reminder, they were not contacted by phone.

Questionnaire. The parental questionnaire contained 23 items taken mainly from preexisting validated questionnaire instruments (International Study of Asthma and Allergies in Childhood [30], Allergies and Endotoxin [ALEX] Study [18], and BABY-DIAB [31]). In addition to standard sociodemographic factors (age, sex, nationality, height, and weight), potential risk factors for type 1 diabetes were assessed (e.g., parents or grandparents with type 1 diabetes, infant nutrition, day care attendance). With respect to living in rural areas, the following parameters were assessed: current place of residency (rural town or village), consumption of raw farm milk ("which type of cow's milk, if any, did your child mainly consume during the 1st year of life: cow milk from supermarkets, uncooked raw cow milk directly from the farm, cooked cow milk directly from the farm, or no cow milk at all"), regular contact to stables and the type of farm animals kept in these stables (cattle, pigs, goats, sheep, horses, and poultry) ("has/had your child had regular [at least once a week] contact to the following animals"), and the timing of these exposures to farm animals (1st year of life, 2nd to 6th year of life, or at the time of the study) (18).

Additionally, prevalence of respiratory allergies was assessed (30). No other markers of atopy (atopic dermatitis or atopic asthma) were included in the questionnaire. Case subjects were also asked about the age at onset of the type 1 diabetes. The questionnaire was pilot tested with 20 parents visiting the outpatient clinic of the University Children's Hospital in Munich.

Statistical analyses. The analyses were restricted to case and control subjects with complete data in the parameters used for the multivariate models (242 case and 224 control subjects).

We used cross-tabulation to visualize bivariate distributions of categorical predictors and outcomes. Differences between the categories were tested using the two-sided χ^2 test. A P value <0.05 was considered statistically significant. Multiple logistic regression models were developed to assess the association between farm contact (living on a farm, regular contact to farm animals in stables, and consumption of raw farm milk) and type 1 diabetes, adjusting for the following potential confounders: medical center, age on 1 May 2004, sex, day care attendance, place of residence (rural town or village),

TABLE 2
Results of the multiple logistic regression models for the associations between predictors under study and type 1 diabetes

	n	Adjusted for age and sex	Fully adjusted*
Parents with type 1 diabetes	19	9.3 (2.1–41.5)	9.3 (1.9-44.2)
Kindergarten attendance			
Never†	68	1	1
3–6 years	277	0.78 (0.45-1.3)	1.0 (0.57–1.9)
0–2 years	121	0.51 (0.28–0.96)	0.60 (0.30–1.2)
Other nutrition than breast milk <3 months	212	1.6 (1.1–2.4)	1.7 (1.1–2.6)
BMI (kg/m^2)			
≤16.3 (1st quartile)	119	1	1
≤18.1 (2nd quartile)	122	1.8 (1.1–3.1)	1.9 (1.1–3.3)
≤20.5 (3rd quartile)	114	1.5 (0.8–2.7)	1.6 (0.8–3.2)
>20.5 (4th quartile)	111	3.2 (1.6–6.2)	3.6 (1.7-7.5)
Rhinitis	63	0.72 (0.42–1.2)	0.61 (0.33–1.1)
Raw milk consumption during the 1st year of life	13	0.62 (0.20–1.9)	0.88 (0.26–3.0)
Regular contact to stables during‡			
1st year of life	74	0.95 (0.57–1.6)	1.2 (0.5–2.7)
2nd to 6th year of life	117	0.84 (0.55–1.3)	0.81 (0.41–1.6)

Data are odds ratio (95% CI). *Adjusted for age, sex, center, and mutually adjusted for all other variables listed in the table. †"Never" includes day care attendance starting after age 5 years. ‡"Regular" defined as at least once a week.

period of exclusive breast feeding, parental history of type 1 diabetes, and BMI. The fully adjusted odds ratios (ORs) were compared with those only adjusted for age and sex.

RESULTS

Descriptive statistics

The overall response rate was 91.1% among case subjects and 90.5% among control subjects. At diagnosis, case subjects were on average (means ± SD) 6.7 ± 3.4 years old. In the crude analyses, case subjects were older, were more likely to have parents with type 1 diabetes, had a higher BMI, and were introduced to other nutrition than breast milk earlier than control subjects (Table 1). No statistically significant differences between case and control subjects were found with respect to sex, number of siblings, prevalence of rhinitis, and low birth weight. The relative frequency of regular contact to pets was equally distributed among case and control subjects.

With respect to farm-related factors (living on a farm, regular contact to farm animals in stables, and consumption of raw farm milk), no statistically significant differences were seen between case and control subjects. Case and control subjects also did not differ with respect to type of farm animals they encountered.

Multiple logistic regression models

Table 2 presents the results of the logistic regression models after adjustment for age and sex as well as of the fully adjusted models. As in the bivariate models, no association was seen between regular contact to farm stables or raw milk consumption and case status.

Including type of farm animal contact in the models, no statistically significant association could be shown between contact to cattle (OR 0.63 [95% CI 0.32–1.24]; P = 0.18), pig (0.52 [0.20–1.38]; P = 0.19), sheep or goat (0.99 [0.41–2.40]; P = 0.99), poultry (1.47 [0.77–2.80]; P = 0.24), or horse (1.05 [0.54–2.04]; P = 0.88) and type 1 diabetes. With respect to pets, case status was inversely related to regular contact to dogs (0.67 [0.44–1.04]; P = 0.07). No association was seen with respect to contact to cats (0.86 [0.55–1.35]; P = 0.51), rabbits (1.19 [0.76–1.87]; P = 0.44), or other pets (1.10 [0.62–1.96]; P = 0.75).

In the multivariate model, rhinitis was inversely related to case status; however, the association did not reach the level of statistical significance (0.61 [95% CI 0.33–1.10]; P = 0.11, Table 2). As in the bivariate models, parents with type 1 diabetes and early nutrition other than breast milk were predictors of case status.

DISCUSSION

In the population of rural children included in our study, no association between living on a farm, regular contact to farm animals in stables, or consumption of raw farm milk and type 1 diabetes was found.

More than 90% of the parents responded to the postal questionnaire. Therefore, a major selection bias cannot be anticipated. In addition, a large number of subjects living in rural areas could be included in our analyses. The number of these subjects with regular contact to animal houses was high: 120 of the participants had regular contact to farm animals before the age of 6 years. Nevertheless, a lack of statistical power to detect weak effects cannot be ruled out.

A detailed questionnaire instrument with mainly standardized questions was used (18,30–31). However, the case subjects included in our study were not newly diagnosed, and, therefore, recall bias might have taken place. This approach had to be done, as the number of incident cases of type 1 diabetes in the study area is <50 per year. As the parents of the case subjects were most likely not aware of a potential association between farm factors and diabetes, no major bias is expected to result from this selection of case subjects. In addition, recall bias is expected to result in an overestimation of the association under study (e.g., 32).

Nondifferential misclassification of exposure might have taken place due to the fact that the exposure assessment was done retrospectively and no objective markers of microbial exposure like endotoxins could be measured. However, it has been shown that subjects who report contact to stables and farm animals have a higher exposure to endotoxins (17,18).

As in any case-control study, the major problem is the selection of an appropriate control group that adequately reflects the underlying study base (33). To increase efficiency, we excluded all children who did not live in rural areas from our study population (n = 234). Using this approach, control subjects were considered to be equally likely exposed as the case subjects. In all centers, the department of surgery provided the control patients. In four of five centers, neither other units of surgery nor other referral centers for type 1 diabetes exist in the area. Therefore, case and control subjects are thought to be equally likely to be treated in the same hospital had they been diagnosed with type 1 diabetes (33). Restricting our analyses to these four hospitals did not change the risk estimates (data not shown).

Our study confirmed some of the known environmental risk factors for type 1 diabetes, like early nutrition other than breast milk and high BMI after adjusting for potential confounders (34–36). A not significantly reduced risk for type 1 diabetes was found for those with early day care attendance and atopic diseases. These results are in accordance with some recent studies (37,38).

To increase the response rate, our questionnaire only included potential risk factors that might confound the association between farming-related risk factors and type 1 diabetes. Therefore, no information on other risk factors like maternal age at birth or socioeconomic status is available.

We could not confirm all results of a recent case-control study from the U.K. (34) where older siblings and regular contact to pets were associated with a reduced risk of type 1 diabetes. In our study, only regular contact to dogs was inversely but not significantly related to case status ($P = 0.07$). However, the British study included urban and rural citizens and did not take farm contact into account. Overall, our study implies that one of the major factors protecting from allergies in children might not be strongly associated with type 1 diabetes. However, more studies are warranted to confirm these findings.

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APPENDIX

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