

Decreased prevalence of atopic diseases in children with diabetes

*The EURODIAB Substudy 2 Study Group**

Objective: To test the hypothesis that atopic diseases in early life are associated with a reduced risk (protection) for the development of type 1 diabetes in childhood.

Study design: European centers ($n = 8$) with access to population-based type 1 diabetes registries ($>90\%$ degree of ascertainment) participated in a case control study focusing on early exposures and risk factors for type 1 diabetes. Altogether, data from 1028 members of a case group and 2744 members of a control group corresponding to 85.4% eligible members of the case group and 76.1% of the control group were analyzed. Information in this study was collected regarding atopic diseases (atopic eczema, allergic rhinoconjunctivitis, and asthma).

Results: Atopic disease and asthma particularly are associated with significant reductions in risk of childhood type 1 diabetes. The risk reduction associated with asthma was observed reasonably consistently among the 8 study centers, which represent a wide range of diabetes incidence. Risk reductions associated with all 3 expressions of atopy were particularly marked in children whose type 1 diabetes was diagnosed in the 10- to 14-year age group.

Conclusion: These findings indicate that atopic conditions may be protective against the development of type 1 diabetes and are consistent with the immunologic concept of T_H1 (type 1 diabetes) and T_H2 (atopy) diseases being mutually exclusive. (*J Pediatr* 2000;137:470-4)

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*The participating investigators are listed in the Appendix.

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Type 1 (insulin-dependent) diabetes mellitus is the consequence of a chronic process leading to the destruction of the insulin-producing β cells of the islets of Langerhans in the pancreas. The cause is as yet unclear, but it is generally accepted that both genetic and environmental factors play important roles and the loss of β cells is eventually due to an autoimmune process. Several aspects of the involvement of the immune system are still unknown, but a growing body of evidence suggests that $CD4^+$ T cells (helper T cells) play a key role, and the balance between the 2 subsets of these T cells (T_H1 and T_H2 cells) and the cytokines produced by these cells appear to be vitally important.¹ Type 1

diabetes, autoimmune thyroid diseases, and rheumatoid arthritis are widely considered as T_H1 -mediated organ-specific autoimmune diseases.^{2,3} By contrast, in individuals with atopy, another group of diseases in which the immune system plays an important role, T_H2 activity dominates.⁴ It was also shown in an animal model of diabetes that inducing a shift from T_H1 to T_H2 responses prevents β cell destruction.⁵ It is therefore a plausible hypothesis that atopy may provide some protection against the development of type 1 (insulin-dependent) diabetes mellitus.

As part of a large, multicenter, population-based, case control study focusing on early environmental exposure and risk of the development of type 1 diabetes before the age of 15 years, we collected data on atopic diseases in children with diabetes and in an age-matched control group to test the hypothesis that atopy could protect against diabetes.

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STUDY DESIGN AND METHODS

The 8 participating centers had developed population-based registers of childhood-onset diabetes that had operated since 1989 and were validated by the standards of EURODIAB ACE⁶: Austria, Latvia, Lithuania, Luxembourg, Romania, Bulgaria, Leeds (UK), and Northern Ireland (UK). Altogether, 1204 patients with onset of diabetes before the age of 15 years and 3606

Table I. Data collection

Center	Register years	No. of cases	Response (%)	No. in control group	Response (%)	Selection of control group	Data collection
Austria (Vienna)	1989-1994	117	88.9	477	79.7	Schools*	Q
Bulgaria (West)	1991-1994	176	72.7	562	78.6	Schools and polyclinics*	I
Latvia (one region excluded)	1989-1994	143	98.6	410	79.0	Population register	I
Lithuania (major cities)	1989-1994	124	94.4	369	72.9	Polyclinics*	Q
Luxembourg	1989-1995	59	100.0	188	94.7	Preschools and schools*	I
Romania (Bucharest)	1989-1994	111	73.9	342	81.0	Health service register*	I
United Kingdom (Leeds)	1993-1994	234	88.9	535	76.4	Physician register	I
United Kingdom (Northern Ireland)	1990-1992	240	78.8	723	64.3	Physician register	Q

Q, Questionnaire; I, interviews.
*Two-stage random sampling.

members of a population-based control group selected within age strata compatible with the age distribution of cases were invited to the study. Overall, 85.4% (1028 of 1204) of the patients and 76.1% (2744 of 3606) of the control group participated. Among participants, 98.4% of the case group and 98.1% of the control group answered the questions related to atopy (Table I). The history of atopic diseases was recorded for the case group up to the date of diagnosis and for the control group up to the qualifying date, which was defined as the mid-point of the case recruitment period. For example, a center with case recruitment from January 1, 1990, to December 31, 1992, had the qualifying date of June 30, 1991. Members of the population-based control group were selected from different sources such as population registers, patients of primary care physicians, or school rolls. The study base was temporally and geographically well defined for each country, and the control selection procedure in the individual centers was designed in collaboration with the study coordinators according to local circumstances. To maintain uniform standards among centers, local study leaders received detailed written instructions for selection of members of the control group, for giving patient information and obtaining

consent, and for preparation of an interview schedule or questionnaire. In addition, 2 workshops were organized, and all centers were site-visited by the coordinators.

A set of core variables focusing on perinatal events, infant nutrition, early growth, vaccinations, and infectious, chronic, and atopic diseases was defined. Data were collected by either standardized questionnaires or interviews after appropriate training procedures were performed. Atopic diseases were defined either as the mother's recall of a doctor's diagnosis of atopic eczema or allergic rhinoconjunctivitis or asthma, or according to the following criteria:

- Atopic eczema was a chronic, itching rash with acute exacerbations specifically of the ankles, wrists, folds of the elbows, behind the knees, under the buttocks, or around the neck, ears, or eyes
- Asthma was repeated episodes of wheezing bronchitis especially occurring at night or in association with physical activity
- Allergic rhinoconjunctivitis was repeated episodes of runny nose, sneezing, or running itching eyes but without signs of infection-like fever

The degree of severity of asthma and the other atopic conditions could not

be assessed reliably by the interview or questionnaire.

Core variables were transferred from the interview or questionnaire into a standardized record form for central computerization. Each study center leader obtained permission from the local ethics committee where one existed.

The Mantel-Haenszel approach was used to pool results across centers. This technique derives a separate odds ratio for each center's set of cases and controls. Cornfield's approximation was used to provide 95% CIs for these odds ratios. The Mantel-Haenszel combined odds ratio was then obtained with a weighting based on both the numbers of members of the case and control groups and their exposure rates in each center. In addition to the usual test of significance for the combined odds ratios, a test of heterogeneity was also used to provide a comparison of odds ratios among centers. To adjust for confounders, logistic regression analysis was used. Statistical analysis was performed with the SPSS and STATA packages.

RESULTS

Table II shows the odds ratios and 95% confidence limits for the association between asthma and childhood-

Table II. Exposure rates, odds ratios, and 95% CI for development of diabetes before the age of 15 years with a history of asthma

Individual centers	Exposed/total (%)		OR	95% CI	P value
	Case group (%)	Control group (%)			
Austria	3/99 (3.0)	22/363 (6.1)	0.48	0.15,1.55	.24
Bulgaria	2/128 (1.6)	16/440 (3.6)	0.42	0.00,1.67	.24
Latvia	3/141 (2.1)	8/324 (2.5)	0.86	0.24,3.04	.82
Lithuania	7/116 (6.0)	10/263 (3.8)	1.62	0.62,4.24	.33
Luxembourg	0/56 (0.0)	0/159 (0.0)	—	—	—
Romania	4/82 (4.9)	10/276 (3.6)	1.36	0.44,4.24	.61
United Kingdom, Leeds	56/208 (26.9)	135/409 (33.0)	0.75	0.52,1.08	.12
United Kingdom, Northern Ireland	18/182 (9.9)	79/444 (17.8)	0.51	0.30,0.87	.01
Combined	$\chi^2 = 6.99$	$df = 1$	0.70	0.54,0.91	.008
Test for heterogeneity	$\chi^2 = 6.34$	$df = 6$			.39

*Atopic diseases had to be present before diabetes onset (case group) or qualifying date (control group).

Table III. Exposure rates, odds ratios, and 95% CI for development of diabetes before the age of 15 years with a history of any one of the atopic diseases

Individual centers	Exposed/total (%)		OR	95% CI	P value
	Case group (%)	Control group (%)			
Austria	6/96 (6.3)	51/355 (14.4)	0.40	0.17,0.93	.03
Bulgaria	29/128 (22.7)	65/436 (14.9)	1.67	1.03,2.72	.04
Latvia	29/141 (20.6)	69/323 (21.4)	0.95	0.59,1.55	.85
Lithuania	24/115 (20.9)	37/253 (14.6)	1.54	0.88,2.71	.14
Luxembourg	1/43 (2.3)	9/139 (6.5)	0.34	0.00,2.19	.30
Romania	8/82 (9.8)	36/276 (13.0)	0.72	0.33,1.59	.43
United Kingdom, Leeds	89/208 (42.8)	206/409 (50.4)	0.74	0.53,1.03	.07
United Kingdom, Northern Ireland	34/176 (19.3)	135/429 (31.5)	0.52	0.34,0.80	.002
Combined	$\chi^2 = 4.64$	$df = 1$	0.82	0.68,0.98	.03
Test for heterogeneity	$\chi^2 = 21.29$	$df = 7$			.003
Combined*	$\chi^2 = 9.27$	$df = 1$	0.73	0.60,0.90	.002
Test for heterogeneity*	$\chi^2 = 12.46$	$df = 6$			.052

*Bulgaria excluded.

onset insulin-dependent diabetes mellitus by center. The Mantel-Haenszel combined odds ratio was significantly decreased ($P = .008$) for asthma, with no evidence of heterogeneity among centers (Table II). The combined odds ratios for atopic eczema was not decreased, and there was heterogeneity among centers. This heterogeneity was mainly due to the high odds ratio in the Bulgarian center. Except for this center, the odds ratios were decreased in most other centers. The combined odds ratio (Bulgaria excluded) was decreased

without significant heterogeneity (odds ratio 0.78; 95% CI 0.61, 1.00). The combined odds ratio for allergic rhinoconjunctivitis was not significantly decreased, but the individual odds ratios were <1 in 6 of the 8 centers.

If any of the 3 atopic diseases was considered, the combined odds ratio was found to be significantly decreased (odds ratio 0.82; 95% CI 0.68, 0.98, $P = .03$) with evidence of heterogeneity among centers (Table III). Again, this heterogeneity was mainly due to the Bulgarian results. The amount of het-

erogeneity was considerably reduced when Bulgaria was omitted.

Logistic regression analysis was also performed to adjust for possible confounders: low birth weight (<2500 g), advanced maternal age (>25 years), and short duration of breast-feeding (≤ 2 months). The odds ratios after adjustment is done for these potential confounders (shown in the final line of Table IV) are similar to the pooled odds ratios.

To test whether the "protective" effect of atopic diseases was different for

Table IV. Odds ratios for atopic disease by age group with adjustments for low birth weight (<2500 g), advanced maternal age (>25 years), and short duration of breast-feeding (≤2 months)

Age groups	Asthma			Eczema			Allergic rhino-conjunctivitis			Any one of the atopic diseases		
			P value			P value			P value			P value
0-4 years	0.87	(0.46,1.65)	.67	1.06	(0.63,1.79)	.82	1.20	(0.37,3.88)	.77	0.91	(0.58,1.43)	.67
5-9 years	0.61	(0.37,1.00)	.051	1.16	(0.79,1.70)	.46	1.08	(0.63,1.85)	.78	0.97	(0.70,1.32)	.83
10-14 years	0.61	(0.37,1.00)	.048	0.63	(0.40,0.99)	.04	0.52	(0.30,0.91)	.02	0.59	(0.42,0.83)	.002
All ages	0.66	(0.49,0.90)	.008	0.92	(0.71,1.18)	.49	0.80	(0.55,1.14)	.21	0.79	(0.64,0.97)	.02

diabetes onset in different age groups, odds ratios were calculated for the 3 age groups (0 to 4 years, 5 to 9 years, and 10 to 14 years). All 3 expressions of atopic diseases were most markedly associated with type 1 diabetes in the 10- to 14-year age group. Table IV shows these age group comparisons with adjustments for confounders.

DISCUSSION

This multicenter case control study showed a decreased prevalence of atopic diseases, particularly asthma, in children with diabetes, suggesting that the occurrence of atopic diseases may protect against the development of type 1 diabetes. This protective effect was not observed in the 2 younger age groups (0 to 4 years and 5 to 9 years), but all 3 expressions of atopic diseases were markedly inversely related to type 1 diabetes diagnosed between 10 and 14 years of age. This age-dependent effect is not easily explainable. It is plausible that as a result of long periods of remissions and the wide range in the severity of symptoms, only children aged 10 to 14 years had lived enough to provide a true childhood prevalence of atopic diseases and thus to demonstrate the postulated "protection."

It is important to note that the prevalence of atopic disease in our control groups was similar to that found in a large international study.^{7,8}

The decreased prevalence of any atopic disease in children with diabetes

was observed in most centers. The heterogeneity in the analysis of any atopic disease appeared to be attributable mainly to the aberrant Bulgarian eczema finding. The reasons for this result are not clear. The diagnostic criteria and data collection procedures were uniform in all participating centers. One speculative explanation could be that eczema may have different causes in different countries, and in Bulgaria 1 or possibly more of these causes is associated with diabetes. It could also be due to some genetic factors such as founder effects, although this seems unlikely in the case of Bulgaria.

The association between diabetes and atopic disease could be confounded by variables such as low birth weight, short duration of breast-feeding, and advanced maternal age, factors that have been shown to decrease the risk of type 1 diabetes.^{9,10} Adjustment for these confounders had negligible effect on the odds ratio. It could be argued that parents of children with diabetes regularly seen by a physician might remember exposures such as atopic diseases more accurately than parents of members of the control group (recall bias, disease-dependent bias). This type of bias, however, would tend to underestimate the effect rather than exaggerate it.

A similar inverse relationship between the presence of atopic disease and type 1 diabetes has been reported in 1971 by Hermansson et al.¹¹ In a more recent study only 4% (4 of 101) of the patients with diabetes and 11% (10 of 90) of the subjects in the control

group had clinical symptoms of allergic rhinitis and asthma ($P < .05$), and patients with diabetes also had reduced bronchial reactivity as determined by a bronchial inhalation challenge and exercise testing.¹² In contrast, Strömberg et al¹³ found a similar prevalence of atopic disease in children in diabetic and control groups. It is important to note that all these studies were clinic-based and not population-based, and only a small number of members in the case and control groups were studied. Our study is the first population-based, large multicenter study to demonstrate that atopic diseases may be protective against the development of type 1 diabetes in children. Our results are consistent with a recent British study that reported that children with diabetes had fewer symptoms of asthma compared with the background population in the ISAAC study.¹⁴

Our finding is similar to a recent observation of decreased prevalence of atopic conditions in rheumatoid arthritis, another T_H1 -mediated organ-specific autoimmune disease.¹⁵ According to the accepted immunologic paradigm, type 1 diabetes is thought to be a T_H1 -lymphocyte-mediated disease,¹ whereas atopy is clearly a T_H2 disease.⁴ In view of the current concept of the negative interaction between T_H1 and T_H2 subsets, the simplest explanation of our findings would be that children who are strong T_H2 -like reactors (with susceptibility to atopic diseases) are constitutionally less likely to have T_H1 -mediated features such as

development of type 1 diabetes. It is also possible that the early information input of the immune system (eg, less T_H1 -inducing signal and more T_H2 -inducing signal) leads to the promotion of the T_H2 cell lineage in children with atopic diseases.¹⁶ Although this may be an oversimplification, the recent observation of an inverse association between tuberculin responses (a marker of T_H1 -mediated acquired immunity) and atopic diseases further supports this speculation.¹⁷

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APPENDIX

The EURODIAB Substudy 2 Study Group

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