A Meta-Analysis of the Association Between Childhood Type 1 Diabetes and Atopic Disease

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OBJECTIVE — To review the published literature and perform a meta-analysis summarizing the evidence in support of an inverse association between type 1 diabetes and the atopic disorders: asthma, eczema, and allergic rhinitis in children.

RESEARCH DESIGN AND METHODS — MEDLINE, Web of Science, and PubMed were searched to identify relevant studies. These were assessed on quality criteria, and odds ratios (ORs) and 95% CIs were calculated for each study from the reported prevalences of atopy in children with diabetes and in control children. Meta-analysis was then used to derive a combined OR and test for heterogeneity in findings between studies.

RESULTS — Twenty-five studies were identified. Heterogeneity in the findings from different studies was evident but was considerably reduced when the asthma and rhinitis analyses were restricted to those studies judged to be of adequate design. The meta-analysis revealed an inverse association between asthma and type 1 diabetes, but the finding only attained significance when analysis was restricted to the studies of adequate design (OR 0.82, 95% CI 0.68–0.99). In this subset an association of similar magnitude was observed between eczema and type 1 diabetes (0.82, 0.62–1.10) although this failed to attain statistical significance, and heterogeneity between studies was still present. There was little evidence of an association between rhinitis and type 1 diabetes (0.97, 0.82–1.16) in this subset of studies.

CONCLUSIONS — Our analysis suggests that there is a small but significant reduction in the prevalence of asthma in children with type 1 diabetes, but the findings for the other atopic diseases are less conclusive.

Diabetes Care 26:2568–2574, 2003

Type 1 diabetes results from an abnormal T-cell–mediated autoimmune response, thought to be primarily of the T helper type 1 (Th1) cells. By contrast, T helper type 2 (Th2) cells predominate in allergic diseases. A review of the role of infections in susceptibility to both autoimmune and allergic diseases (1) noted the increasing rates of both disorders in recent decades in developed countries (2,3) and suggested that there is a positive association between allergic and autoimmune diseases in individual patients. This issue has previously been addressed by others who have sought to clarify the nature of any association at the patient level. Some studies have reported an inverse relationship, but the findings have been conflicting, possibly because of poor design or inadequate size and consequent lack of power. In the latter situation a meta-analysis is valuable in synthesizing the available evidence (4). We therefore assessed the evidence for an association between type 1 diabetes and atopic disorders in children by conducting a systematic review of published epidemiological studies.

RESEARCH DESIGN AND METHODS

Search

The search used MEDLINE through OVID ONLINE using this strategy: ("explode 'Diabetes Mellitus, Insulin Dependent'/all subheadings") and (("explode 'Asthma' or 'asthma' textword") or ("explode 'Eczema' or 'eczema' textword") or ("explode 'Rhinitis' or 'rhinitis' textword") or ("'atopy' textword")). A similar strategy was used in searches on Web of Science and PubMed. Finally, to identify epidemiological studies that potentially could have investigated atopy as one of a number of risk factors, a more general search was conducted on MEDLINE using this broader strategy: ("explode 'Diabetes Mellitus, Insulin Dependent'/all subheadings") and (("explode 'Case-Control'") or ("explode 'Cohort'") or ("explode 'Risk Factor'")). On each database the search was limited to studies on humans published before March 2003. Abstracts were screened independently by two investigators (C.R.C. and C.C.P.) to establish if the studies were likely to provide relevant data based on the following inclusion criteria: *1*) they identified comparable groups with and without type 1 diabetes, *2*) they ascertained the prevalence of one or more manifestation of atopic disease in these two groups whether at diabetes diagnosis or subsequently, and *3*) they recorded data that were primarily related to the childhood period. Studies that made use of comparative data on atopic diseases gleaned from other publications were not excluded from consideration at this stage. Citations identified from the more general MEDLINE search were initially screened

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Received for publication 17 April 2003 and accepted in revised form 16 June 2003.

Abbreviations: Th1, T helper type 1; Th2, T helper type 2.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of studies that have investigated the association between atopic diseases and type 1 diabetes*

Study			Case Subjects				Control Subjects		Exposure					
First author, year (reference)	Design	Country	Source	Age at onset	Age at study	No.*	Source (matching variables)	No.*	Method	Asthma	Eczema	Rhinitis	Any atopy	Prior†
Hermansson, 1971 (9)	C-C¶	Sweden	Västerbotten county register	<16 yr	?	128 (?)	Västerbotten county population register	310 (?)	Medical records and examination	—	—	—	Diagnosis	No
Villa, 1988 (28)	C-C¶	Italy	?	?	7–18 yr	101 (?)	School population	90 (?)	Questionnaire	—	—	—	Symptoms	No
Siemiatycki, 1989 (27)	C-C¶	Canada	Montreal registry	<18 yr	<15 yr	161 (100)	Friends (age, sex, district)	321 (100)	Telephone interview	← Unspecified →				Yes
Blom, 1991 (24)	C-C	Sweden	Swedish registry	<15 yr	<15 yr	264 (67)	Swedish population register (age, sex, county)	388 (49)	Questionnaire	On medication‖	—	—	—	Yes
Strömberg, 1995 (10)	C-C¶	Sweden	Norrkoping hospital	?	7–18 yr	61 (100)	School friends (age, sex)	72 (92)	Questionnaire	← Unspecified →				No
Douek, 1999, 2000 (11,12)	C-C	United Kingdom	Oxford registry	<15 yr	12–14 yr	157 (76)	ISAAC atopy study (age)	2,324 (86)	Questionnaire	← Symptoms‖ →			—	No
Vargas, 1999 (18)	C-C¶	Puerto Rico	Puerto Rico registry	<15 yr	13–22 yr	102 (?)	Puerto Rican high school	80 (?)	Questionnaire	Diagnosis or symptoms	—	—	—	No
Stene, 2000 (31)	C-C	Norway	Vest-Agder registry	<15 yr	<15 yr	85 (94)	Vest-Agdar population register	1,071 (73)	Questionnaire	← Unspecified →			—	Yes
EURODIAB, 2000 (13)	C-C	Austria	Vienna registry	<15 yr	<15 yr‡	99 (85)	School lists (age)	363 (76)	Questionnaire	← Diagnosis or symptoms →				Yes
	C-C	Bulgaria	W. Bulgarian registry	<15 yr	<15 yr‡	128 (73)	School, policlinic lists (age)	440 (78)	Interview					
	C-C	Latvia	Latvian registry	<15 yr	<15 yr‡	141 (99)	Latvian population register (age)	324 (79)	Interview					
	C-C	Lithuania	Lithuanian registry	<15 yr	<15 yr‡	116 (94)	Policlinic lists (age)	263 (71)	Questionnaire					
	C-C	Luxembourg	Luxembourg registry	<15 yr	<15 yr‡	56 (95)	Preschool, school lists (age)	159 (85)	Interview					
	C-C	Romania	Bucharest registry	<15 yr	<15 yr‡	82 (74)	Health service register (age)	276 (81)	Interview					
	C-C	United Kingdom	Leeds registry	<15 yr	<15 yr‡	208 (89)	General practice list (age)	409 (76)	Interview					
	C-C	United Kingdom	N. Ireland registry	<15 yr	<15 yr‡	182 (76)	General practice list (age)	444 (61)	Questionnaire					
Huang, 2001 (22)	C-C¶	United States	Diabetes website	<18 yr	?	403 (?)	U.S. health surveys	10,904 (?)	Questionnaire	← Unspecified →			—	No
Oleson, 2001 (21)	C-C	Denmark	Danish registry	<16 yr	3–15 yr	817 (89)	Danish birth register (age)	7,683 (79)	Questionnaire	← Diagnosis →			—	No
Kero, 2001 (14)	Cohort	Finland	Hospital discharge & social support register	<8 yr	<8 yr	181	Finnish birth register (age)	59,684	Record linkage	ICD code or benefit register	—	—	—	No
Sebastiani, 2001 (26)	C-C	Italy	Rome county registry	<15 yr	11 yr§	150 (93)	Rome county school population (age, sex)	750 (94)	Questionnaire	← Unspecified →			—	No
Simpson, 2002 (30)	Cross-sectional	United Kingdom	General practice database	<15 yr	<15 yr	89	Registered general practice patients	49,051	Consultation in practice database	← Code for diagnosis (ICD) or symptoms →				No
Meerwaldt, 2002 (15)	C-C	Netherlands	Dutch Pediatricians	<13 yr	7–12 yr	188 (?)	ISAAC atopy study (age)	781 (?)	Questionnaire	← Symptoms‖ →			—	No
Matilla, 2002 (16)	C-C	Finland	Finish registry	<15 yr	10–27 yr	361 (42)	Finnish population register (age, sex)	483 (59)	Questionnaire	Diagnosis	—	—	—	No
Wright, 2003 (23)	C-C¶	United Kingdom	5 North Trent hospitals	?	11 yr§	226 (?)	ISAAC atopy study	5472 (?)	Questionnaire	On medication	—	—	—	No
Rosenbauer, 2003 (33)	C-C	Germany	German registry	<5 yr	<6 yr	760 (71)	German population register (age, sex, area)	1886 (43)	Questionnaire	← Unspecified →				Yes

*Number included in the analysis (percentage response rate for asthma exposure); †exposure referring to period prior to diabetes; ‡age at which atopic exposure was determined; §mean age; ‖exposure referring to the year prior to questionnaire; ¶study design failed to satisfy quality criteria. C-C, case-control; ISAAC, the International Study of Asthma and Allergies in Childhood.

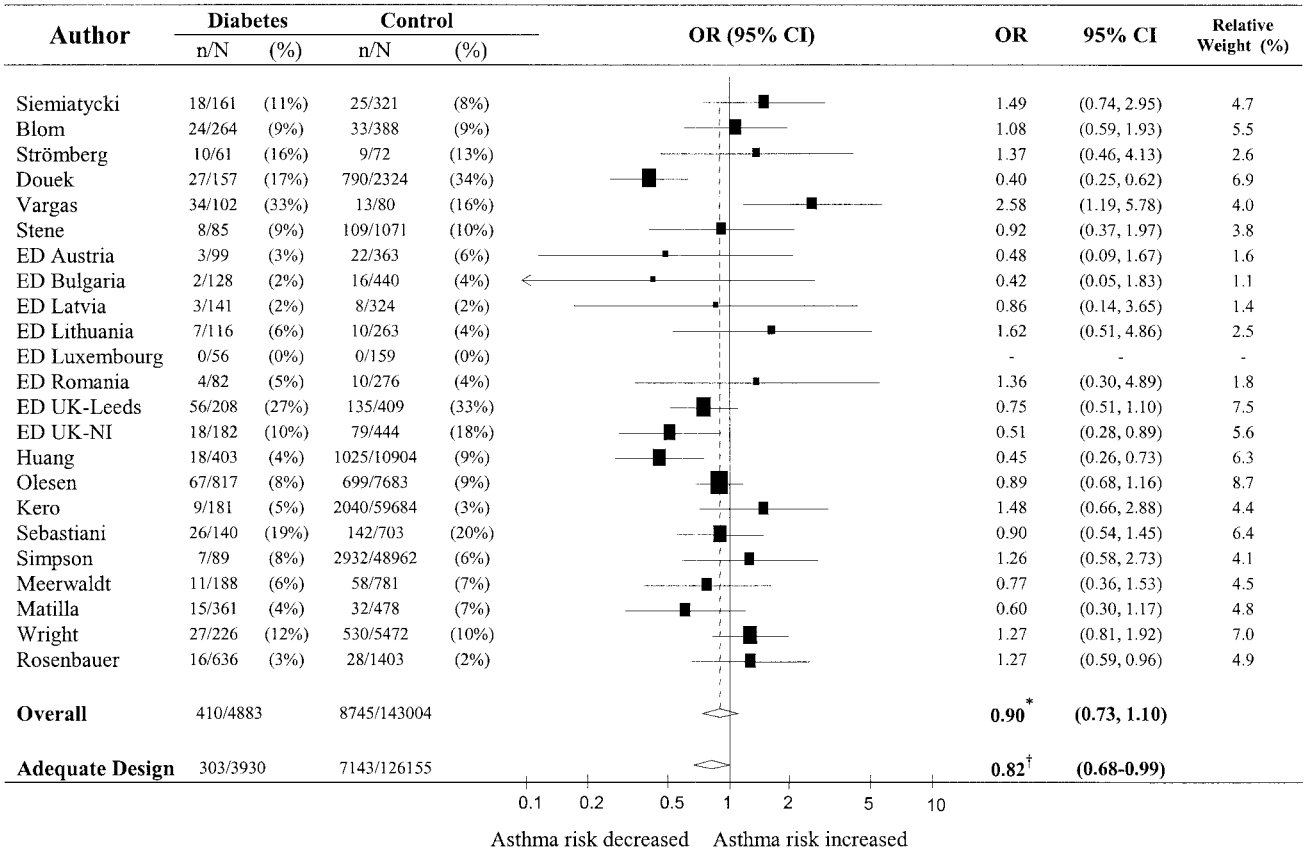

Figure 1—*Meta-analysis of studies of asthma and type 1 diabetes using the random-effects model, ordered by date of publication. ED, EURODIAB; n, number of subjects with asthma; N, total number of subjects in diabetes and control groups. *Test for overall effect:* $z = -1.06$, $P = 0.29$; *test for heterogeneity* $\chi^2 = 43.6$, $df = 21$, $P = 0.003$. *†Test for overall effect:* $z = -2.07$, $P = 0.04$; *test for heterogeneity* $\chi^2 = 23.0$, $df = 16$, $P = 0.11$.

to remove obviously irrelevant studies. The reference lists of all pertinent articles were also examined. Finally, proceedings of recent relevant conferences were reviewed.

Most studies identified were of the case-control design, with case definition based on childhood-onset type 1 diabetes and atopic diseases considered as potential risk factors. No studies were found when these roles were reversed, reflecting the much lower prevalence of diabetes. The atopic manifestations considered were asthma, eczema, allergic rhinitis, or any atopy (defined as any of these three diseases).

Eligible studies were assessed independently by two reviewers using a structured form to abstract information about the study (country and year of publication), study subjects (source, area, and age at diagnosis), and atopy exposures (method of ascertainment and definitions used). Studies were also assessed for quality, and a subgroup was identified that was considered of adequate design, based on three criteria: *1*) representative case ascertainment, e.g., through a population-based registry, *2*) population-based control selection, and *3*) identical ascertainment of atopy exposure in the diabetic and control groups. Information about atopy prevalence was then extracted. Authors were contacted to clarify ambiguities or incompleteness in the published results and in one instance to request information restricted to the age-group <15 years of age.

Statistical methods

Odds ratios (ORs) and exact 95% CIs were calculated for each atopic exposure and for combined atopy where possible. If no exposure occurred in the diabetic or control group, a correction of one-half was added to both the exposed and unexposed groups to provide an estimate of the OR (5), and the Woolf approximation was used to calculate 95% CIs. In one cross-sectional study the Mantel-Haenszel method was used to adjust the OR for age in 5-year age-groups. Tests for heterogeneity between studies were conducted and random-effect models used to calculate pooled ORs (6). Random-effect models were deemed more appropriate than fixed-effect models because they provide a more conservative OR estimate, representing the mean association in the populations, and it was anticipated that there would be heterogeneity because of the observational nature of these studies. Study-specific weights in the random-effects model were calculated and scaled to percentages. Publication/selection bias was investigated by checking for asymmetry in funnel plots of the logarithm of the study ORs against their SEs (7,8). A subset analysis was conducted on studies that met the three quality criteria. Another analysis was further restricted to studies in which atopy exposure was ascertained before diabetes diagnosis. Exploratory investigations of heterogeneity were also conducted by subdividing studies by geo-

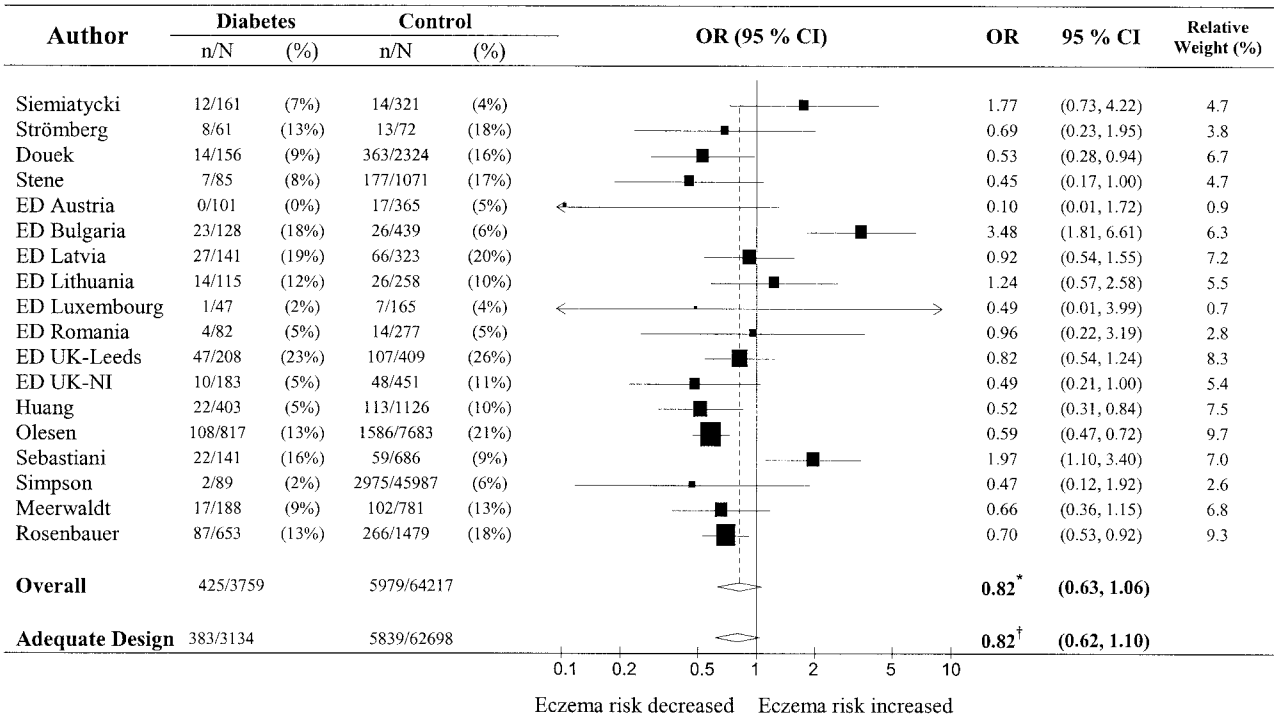

Figure 2—*Meta-analysis of studies of eczema and type 1 diabetes using the random-effects model, ordered by date of publication. ED, EURODIAB; n, number of subjects with eczema; N, total number of subjects in diabetes and control groups. *Test for overall effect: z = −1.52,* P *= 0.13; test for heterogeneity* $\chi^2 = 53.2$, *df = 17,* P *< 0.001. †Test for overall effect: z = −1.33,* P *= 0.18; test for heterogeneity* $\chi^2 = 47.5$, *df = 14,* P *< 0.001.*

graphic region, incidence level, and atopy ascertainment features (e.g., doctors' diagnosis). As the meta-analysis was conducted from summary figures rather than individual case records, the ORs could not be adjusted for confounders. Most studies incorporated some form of matching diabetic and control subjects for age; a few reported ORs adjusted for other confounders. Statistical analyses were performed using STATA 7.0 (Stata, College Station, TX).

RESULTS — The searches identified eight eligible articles using MEDLINE (9–16), a further six through Web of Science (17–22), and another from PubMed (23). The more general MEDLINE search identified four further articles (24–27). Review of reference lists revealed three additional publications (28–30), and two more abstracts (31,32) were discovered in conference proceedings.

Six of these articles were excluded from further consideration. One was excluded (25) because more detailed information was available in a previous report (13), and three meeting abstracts (19,20,29) were excluded in favor of the subsequent article (15). After contact with the authors, two further abstracts were excluded; one (32) because information specific to the childhood age range was obtained from an associated study (30) and another (17) because more detailed information was available from an article in press (33).

The 19 remaining publications, 14 articles, 3 abstracts, and 2 letters, corresponded to 25 studies since 2 publications referred to different atopic conditions recorded in a single study (11,12) and 1 publication reported results from 8 studies (13). Of these, 23 contained data on asthma, 18 on eczema, 18 on rhinitis, and 13 on a combined atopy exposure. The study characteristics are summarized in Table 1. Seven studies were judged to have inadequate study design, three featured nonrepresentative case ascertainment (10,22,28), three non–population-based control subjects (10,18,27), and three ascertained atopy differently in diabetic and control groups (9,22,23).

Results from all studies for asthma, eczema, and rhinitis are summarized in Figs. 1, 2, and 3, respectively. Analyses including all studies suggested weak inverse associations between diabetes and each atopic exposure, although none attained statistical significance ($P < 0.05$): asthma (OR 0.90, 95% CI 0.73–1.10), eczema (0.82, 0.63–1.06), rhinitis (0.88, 0.68–1.12), and any atopy (0.80, 0.64–1.01). Funnel plots (Fig. 4) did not reveal any obvious departures from symmetry, which is suggestive of publication/selection biases. Although the rhinitis plot suggested a deficit of smaller nonsignificant studies, the pooled OR was close to 1 so the omission of the studies should not result in bias. There was evidence of statistically significant heterogeneity between the studies: asthma ($P = 0.003$), eczema ($P < 0.001$), rhinitis ($P = 0.002$), and any atopy ($P = 0.04$). This was confirmed by failure of the funnel plots to demonstrate the expected funnel shape, indicating that even the largest studies showed differences that could not be explained by chance and suggesting that bias and confounding could be present. The meta-analyses were therefore repeated and restricted to studies with an adequate design. The resulting pooled ORs were statistically significant for asthma (0.82, 0.68–0.99) but not for eczema (0.82, 0.62–1.10), rhinitis (0.97, 0.82–1.16), or any atopy (0.84, 0.65–

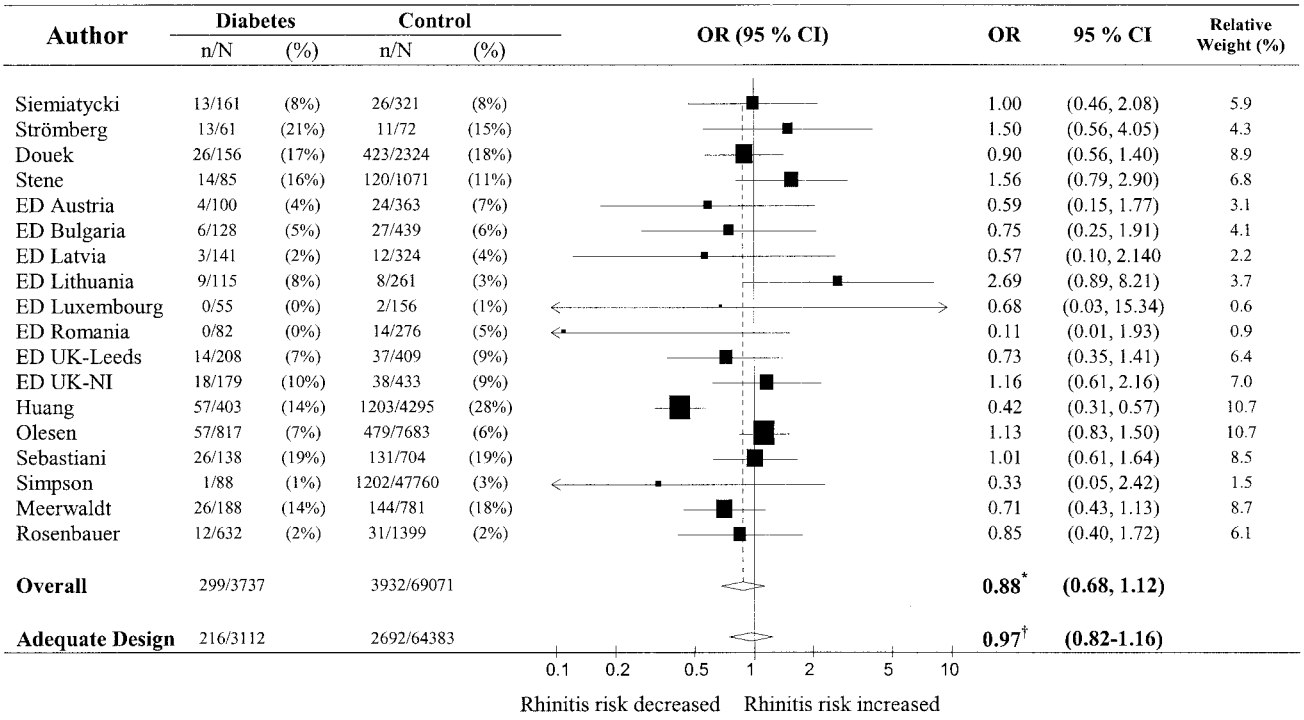

Figure 3—*Meta-analysis of studies of rhinitis and type 1 diabetes using the random-effects model, ordered by date of publication. ED, EURODIAB; n, number of subjects with rhinitis; N, total number of subjects in diabetes and control groups. *Test for overall effect: z = −1.02,* P *= 0.31; test for heterogeneity* $\chi^2 = 39.2$, *df = 17,* P *= 0.002. †Test for overall effect: z = −0.30,* P *= 0.77; test for heterogeneity* $\chi^2 = 14.4$, *df = 14,* P *= 0.42.*

1.08). There was less evidence of heterogeneity for asthma ($P = 0.11$) and rhinitis ($P = 0.42$), but the findings for eczema ($P < 0.001$) and any atopy ($P = 0.03$) were still significant. Heterogeneity for eczema was dramatically reduced ($P = 0.52$) only after further removing two outlying centers with significant positive associations, which resulted in a significant OR (0.66, 0.58–0.75). Funnel plots conformed more closely to the expected shape when restricted to the adequate studies.

Analyses of the adequately designed studies with the additional restriction that exposure was measured before diabetes diagnosis gave findings that were not markedly altered: asthma (OR 0.83, 95% CI 0.66–1.05), eczema (0.87, 0.59–1.29), rhinitis (0.99, 0.72–1.37), and any atopy (0.84, 0.64–1.10). None of the other exploratory subdivisions revealed a markedly more homogenous grouping and therefore did not identify sources of heterogeneity.

CONCLUSIONS — Our synthesis of adequately designed studies showed a small but significant reduction in the frequency of asthma among children with diabetes. Although the associations with eczema, rhinitis, or any atopy did not attain significance, the results for eczema and any atopy were nevertheless consistent with a small reduction similar in magnitude to that for asthma. Failure to detect any association with rhinitis may reflect the difficulty of ascertaining this form of atopy reliably by questionnaire.

The heterogeneity between the ORs, even for the adequately designed studies, could indicate true effect differences between populations, but possible sources of bias must also be considered (34). The limitations of a meta-analysis based solely on summary statistics make it difficult to rule out biases from confounding factors. In six studies, attempts were made to control for various confounding factors (13,14,16,21,27,33), but few had any appreciable impact. It is difficult to predict what effect confounding by such variables as birth weight, breast feeding, family size, and maternal age might have, but the evidence from these studies would suggest that it may be small.

In the predominantly retrospective studies of this review, it is possible that recall of atopy could differ between the parents of diabetic and control children, but it is unclear in which direction any bias might operate. Subsequent to a diagnosis of diabetes, children have more frequent contact with health services that could result in greater likelihood that atopic conditions would be diagnosed. Alternatively the burden of coping with diabetes could lead to atopic conditions being relegated in importance in parents' minds and therefore underreported. Only the latter bias could explain our finding of an inverse relationship between diabetes and asthma.

Another potential source of bias was the generally lower response rates in control compared with case subjects. If there was an increased likelihood of response for children with atopy, this could lead to an overestimation of atopy prevalence in control subjects. Although we cannot rule out this effect, it is primarily a concern in studies where atopy was the main focus of investigation. In one such study (21) a comparison of early and late responders showed no difference in atopy status. Cohort studies of young children at high risk for diabetes should be less affected by these sources of bias and may help to resolve the issue, although an early report from one such study (35) was inconclusive.

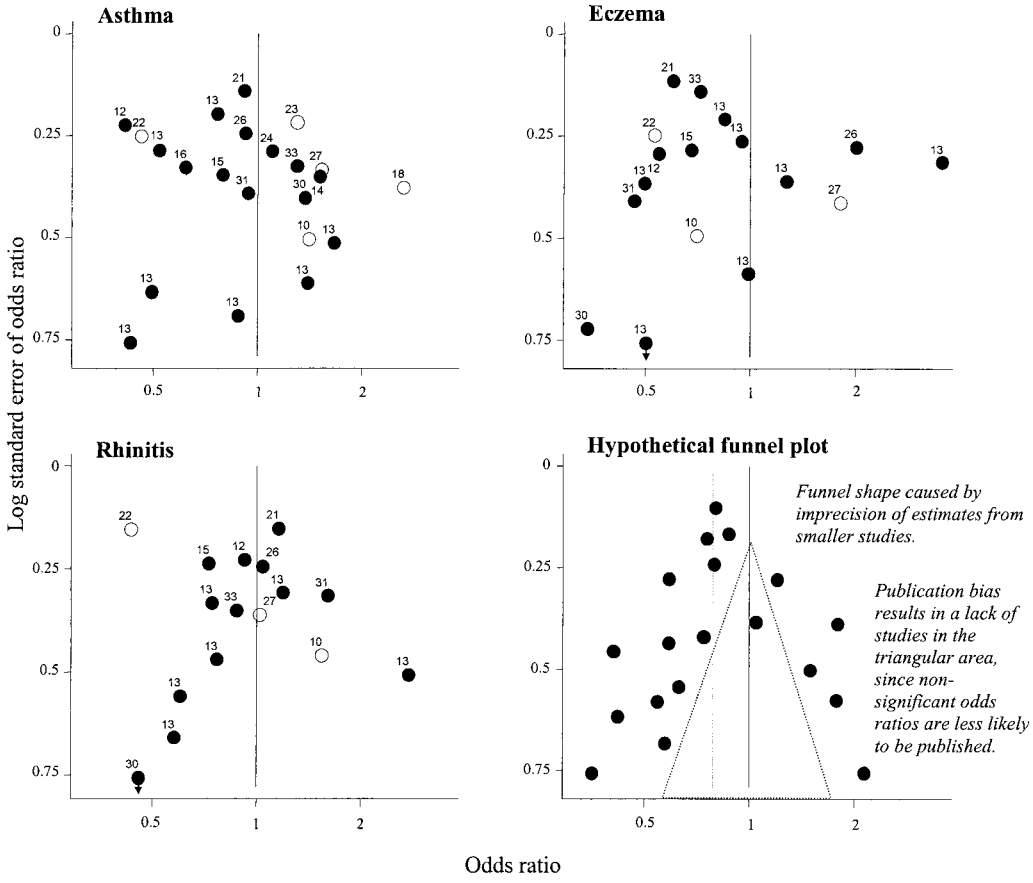

Figure 4—*Funnel plots of observational studies of atopy exposures and diabetes. Studies of adequate (●) and inadequate (○) design are labeled by reference number.*

The hygiene hypothesis argues that early environmental stimulation by infections is necessary to achieve a mature and balanced repertoire of immune responses (36). Epidemiological studies provide evidence that frequent exposure to infections early in life is protective for both diabetes (25,37,38) and asthma (39,40). The protective mechanisms induced by infection are unknown but thought to be related to the production of regulatory T-cells. Complex interactions between various components of the immune system control the production of Th1 cells, which are traditionally associated with autoimmune disease, and Th2 cells, which are traditionally associated with allergic disease (41,42). Such interactions could explain an inverse relationship between autoimmune and allergic disease such that the hygiene hypothesis is consistent with an inverse association between atopic diseases and type 1 diabetes at the individual level, despite their simultaneously increasing incidence in the population. Such inverse associations have been reported for other autoimmune disorders (43,44). However, the conclusion that the hygiene hypothesis provides the explanation for these inverse associations could be premature because there may be other shared environmental or genetic risk factors that predispose to one disease and protect against another.

The focus of this review has been on the association between type 1 diabetes and atopy in childhood, and there is evidence to suggest that the findings may have differed if the analysis had been based on older age-groups (30,45).

In summary, our analysis suggests that children with type 1 diabetes have a slight but significant reduction in the risk of asthma, although findings for the other atopic diseases are less conclusive. Some early reports may inadvertently have exaggerated the strength of the association between atopic conditions and type 1 diabetes.

Acknowledgments— C.R.C. received a Northern Ireland Department of Education and Learning grant.

Thanks to those who kindly supplemented their published data.

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