The Effect of Day Care Exposure on the Risk of Developing Type 1 Diabetes

A meta-analysis of case-control studies

OBJECTIVE — Exposure to infections in infancy or childhood may be important in the pathogenesis of type 1 diabetes, but a protective role has also been suggested. We tested the hypothesis that increased early contact with infectious agents, measured by day care exposure, would decrease the risk of type 1 diabetes in childhood.

RESEARCH DESIGN AND METHODS — We conducted a systematic review of case-control studies. Meta-analysis was performed to combine results, assess for heterogeneity, and explore variation in study design.

RESULTS — Several generally well-designed case-control studies show a statistically significant protective effect of day care on type 1 diabetes. However, meta-analysis revealed too much heterogeneity to accept the overall synthesis results and none of the studies used prerecorded data. Day care does seem to have a protective effect in the subgroup of children who will be diagnosed with type 1 diabetes before the age of 5 years (odds ratio = 0.6, 95% CI 0.5–0.8); however, this result is based on only two studies.

CONCLUSIONS — Recall bias is one alternate explanation for these data; confirmation using prerecorded data is required. Such data could be prospectively measured in cohort studies of children at risk. We also suggest that information about day care attendance be measured in randomized trials of agents for the prevention of type 1 diabetes, as day care exposure could potentially modify the effect of the preventive agent.

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Type 1 diabetes is one of the most common chronic diseases beginning in childhood (1,2), and successful primary prevention therefore would be highly desirable. However, a deeper understanding of its etiology may be necessary before this can be achieved. To date, the autoimmune pathophysiology of type 1 diabetes has been established, and a strong polygenetic component to its etiology has been identified (3). Nonetheless, there is a strong noninherited component (4) that may include either causal or protective environmental factors (5). Exposure to infections during infancy or childhood is of special interest because of the discovery of very early development of autoimmunity (6) and clinical disease (2). Day care attendance is a good proxy for exposure to infections, as it captures the presence of asymptomatic or minor infections that would not otherwise be reported, recorded, or later recalled (7). Although randomized controlled trials of the effects of day care exposure in children in the general population have been done (8), the data on health outcomes are too limited to analyze (9). We therefore tested the hypothesis that increased early contact with infectious agents, measured by day care exposure, would decrease the risk of type 1 diabetes in childhood by performing a meta-analysis of case-control studies on this point.

RESEARCH DESIGN AND METHODS

Search methods
Two investigators (B.K. and S.P.T.) searched for relevant studies. Using MEDLINE Advanced 1966–1999 (WebSPirs 4.0), we executed the following search strategy: (“explode Diabetes Mellitus, Insulin-Dependent/all subheadings”) and (“explode ‘Socioeconomic Factors/all subheadings’ or “day care” textword or “crowding” textword). Both investigators then independently screened the MEDLINE citations to identify potentially eligible studies using a preconstructed paper form with two basic criteria: 1) studies of humans with type 1 diabetes, and 2) potentially contains data on the risk of developing the disease due to day care attendance. A supplementary PubMed search of MEDLINE and PREMEDLINE on 15 June 2000 combined the search terms “day care” (medical subject heading [MESH] term or textword) and “diabetes” (MESH term or textword). In addition, an OLDMEDLINE search (Internet Grateful Med, 1960–1965 editions) combined the search terms “day care” (keyword term or textwords) and “diabetes” (keyword term or textword). The same strategy was used for EMBASE Pediatrics (WebSPirs 4.0, 1990 to March 2000) editions. Titles obtained from these supplementary searches were then independently reviewed to assess the possibility that each study contained case-control data on day care and type 1 diabetes. The reference lists and PubMed “related articles” of eligible studies were assessed in the same manner. No language restrictions were used.

Review methods
We each separately reviewed the potentially eligible manuscripts using a more detailed paper form. This form contained...
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of cases</th>
<th>Cases</th>
<th>Case-finding system</th>
<th>Source of control subjects</th>
<th>Matched control subjects; ratio; factors</th>
<th>Defined exposure Method</th>
<th>Different accuracy for case and control subjects</th>
<th>Selection of control subjects potentially related to exposure</th>
<th>Potential for recall bias</th>
<th>OR 95% CI</th>
<th>Ages and years (y)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siemiatycki et al., 1989</td>
<td>Incident</td>
<td>0–17 y, Sep 83–Feb 86</td>
<td>Region; metro Montreal, 1981 census</td>
<td>Adequate Friends (majority); others hospitalised</td>
<td>Yes; 2:1; sex, age, socio-economic status</td>
<td>Attended nursery or day care before age 5 years</td>
<td>Interview</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>1.5</td>
<td>1.0–2.3</td>
</tr>
<tr>
<td>Blom et al., 1989</td>
<td>Incident</td>
<td>0–14 y, Sep 85–Aug 86</td>
<td>Region; Sweden</td>
<td>Adequate Residents; random population register</td>
<td>Yes; 2:1; sex, age, county</td>
<td>Organised outside home care before age 7 years</td>
<td>Self-admin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>0.6</td>
<td>0.4–0.7</td>
</tr>
<tr>
<td>Verge et al., 1994</td>
<td>Incident</td>
<td>5–14 y, Jan 90–Jul 91</td>
<td>Region; New South Wales, Australia</td>
<td>Adequate Residents; random student selection</td>
<td>No; 2:1</td>
<td>Attended day care before age 3 years</td>
<td>Self admin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>1.6</td>
<td>0.9–2.6</td>
</tr>
<tr>
<td>Tal et al., 1998</td>
<td>Incident</td>
<td>0–30 y, Jan 84–Dec 93</td>
<td>Region; Taipei City</td>
<td>Adequate Friends; classmate, colleague</td>
<td>Yes; 2:1; sex, age, socio-economic status</td>
<td>One or more years of kindergarten</td>
<td>Interview</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>0.5</td>
<td>0.3–1.0</td>
</tr>
<tr>
<td>McKinney et al., 2000</td>
<td>Incident</td>
<td>0–15 y, Jan 93–Dec 94</td>
<td>Region; former Yorkshire RHA</td>
<td>Adequate Residents; random health service register</td>
<td>Yes; 2:1; sex, age, local authority</td>
<td>Any regular social mixing situation before age 1 year</td>
<td>Interview</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>0.7</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>EURO-DIAB Austria, 2000</td>
<td>Incident</td>
<td>5–15 y, Jan 89–Dec 94</td>
<td>Region; Vienna</td>
<td>Adequate Residents; random student selection</td>
<td>No; 3:1</td>
<td>Regular 3–1 days per week for at least 1 year before school age</td>
<td>Self admin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>0.4</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>EURO-DIAB Latvia, 2000</td>
<td>Incident</td>
<td>5–15 y, Jan 89–Dec 94</td>
<td>Region; Latvia, except one region</td>
<td>Adequate Residents; random population register</td>
<td>No; 3:1</td>
<td>Regular 3–1 days per week for at least 1 year before school age</td>
<td>Interview</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>0.4</td>
<td>0.3–0.7</td>
</tr>
<tr>
<td>EURO-DIAB Lithuania, 2000</td>
<td>Incident</td>
<td>5–15 y, Jan 89–Dec 94</td>
<td>Region; Lithuania</td>
<td>Adequate Residents; random population health clinic register</td>
<td>No; 3:1</td>
<td>Regular 3–1 days per week for at least 1 year before school age</td>
<td>Self-admin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>0.6</td>
<td>0.3–1.1</td>
</tr>
<tr>
<td>EURO-DIAB Luxembourg, 2000</td>
<td>Incident</td>
<td>5–15 y, Jan 89–Dec 95</td>
<td>Region; Luxembourg</td>
<td>Adequate Residents; random student selection</td>
<td>No; 3:1</td>
<td>Regular 3–1 days per week for at least 1 year before school age</td>
<td>Interview</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>1.5</td>
<td>0.6–3.6</td>
</tr>
<tr>
<td>EURO-DIAB Romania, 2000</td>
<td>Incident</td>
<td>5–15 y, Jan 89–Dec 94</td>
<td>Region; Bucharest</td>
<td>Adequate Residents; random health service register</td>
<td>No; 3:1</td>
<td>Regular 3–1 days per week for at least 1 year before school age</td>
<td>Interview</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>0.3</td>
<td>0.2–0.6</td>
</tr>
<tr>
<td>EURO-DIAB UK-NI, 2000</td>
<td>Incident</td>
<td>5–15 y, Jan 90–Dec 92</td>
<td>Region; N. Ireland</td>
<td>Adequate Residents; random population health clinic register</td>
<td>No; 3:1</td>
<td>Regular 3–1 days per week for at least 1 year before school age</td>
<td>Self-admin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>0.7</td>
<td>0.5–1.1</td>
</tr>
</tbody>
</table>
sections to confirm study eligibility according to three criteria: case-control study (study design) of day care attendance (exposure) and type 1 diabetes (outcome). It was also used to assess important study design features of case-control studies (10–12) and to extract data on results. Specifically, we assessed each study to confirm that the identified cases were typical for type 1 diabetes and to determine whether incident or prevalent cases were used. We examined studies for the adequacy of their case-finding system if the study source population was defined by geographic region; we examined studies with source population defined by catchment area for whether the control group was restricted to residents of a defined area. Finally, we assessed each study for information about its control group selection (13) and comparable accuracy of information. We then extracted the definition of exposure and the numbers of exposed and unexposed subjects within the case and control groups, along with information about the use of matching and whether matching was incorporated into the analysis.

### Statistical methods

We performed the meta-analysis with Review Manager 4.1 beta 2/Meta-View 4.1 software (The Cochrane Collaboration). Because not all studies used matching or analyzed appropriately for matched data or presented the matched results in sufficient detail for meta-analysis, we treated all studies as unmatched case-control studies for purposes of the meta-analysis. As a result, the effect size may be underestimated (14); overestimation can occur only if the matched studies are in the opposite direction of the overall summary. We examined the results of fixed-effect (Mantel-Haenszel) and random-effect (Dersimonian and Laird) models. Sensitivity analysis was performed for differences in study design and in case or exposure definitions. Finally, a post hoc analysis based on differences in the rate of participation in the control group was performed. For all comparisons, we assessed statistical heterogeneity, which is a measure of whether the variation in study results is greater than would be expected by chance alone. Statistical heterogeneity was deemed acceptable if the test $P$ value for homogeneity was >0.1. All results are expressed as the computed pooled odds ratios [ORs] and 95% CIs.

### RESULTS

#### Search results

The primary MEDLINE search identified 326 records. Examination of these records yielded 49 potentially eligible manuscripts for further review; 4 of these met the eligibility criteria (15–18). The supplementary PubMed search yielded 40 records, including 2 recent manuscripts, that met the eligibility criteria (19,20). No additional eligible studies were discovered using OLDMEDLINE (0 records) or EMBASE Pediatrics (11 records). No additional studies were found from the reference lists of the eligible manuscripts (245 titles, with 7 manu-
scripts further examined) or PubMed related articles (815 titles, 15 abstracts, and 6 manuscripts further examined).

Review results
The 6 manuscripts that met the eligibility criteria included 11 primary studies, each obtaining cases from a defined geographic region (Table 1 and Fig. 1). Of these 11 studies, 9 included randomly sampled population-based control subjects and all met other design standards, such as an adequate case-finding system and identical methods of data collection for case subjects and control subjects within each study (Table 1). However, no study used prerecorded data on exposure.

Statistical results
Only the results of the random-effect models are shown; the fixed-effect model gave similar results. The overall calculated summary statistics (OR = 0.69, P = 0.01, Fig. 1) were deemed potentially misleading due to statistical heterogeneity (test for homogeneity $\chi^2 = 42.71$, df = 10, $P = 0.00$), possibly a result of important effect-modification because of the variability in the ages of subjects and the definitions of exposure among studies. Sensitivity analysis revealed continued heterogeneity when analyzed by whether the method of data collection was interview or self-administered questionnaire (not shown), by whether or not the participation rate of control subjects exceeded 80% (not shown), and by whether or not exposure was before or after the age of 3 years (Fig. 2). However, both of the studies that included children diagnosed with type 1 diabetes before the age of 5 years showed a strongly protective and statistically significant effect (OR = 0.6, 95% CI 0.5–0.8), with acceptable statistical test heterogeneity ($\chi^2 = 1.25$, df = 1, $P = 0.26$) (Fig. 3).

CONCLUSIONS — Although several generally well-designed case-control studies show a statistically significant protective effect of day care on type 1 diabetes, meta-analysis reveals too much heterogeneity to accept the overall synthesis results. The exception was the subgroup of two studies restricted to children under 5 years of age at diagnosis, a minority of people diagnosed with the disease. Due to the retrospective nature of meta-analysis, we were not able to study potential effect-modifiers of this protective association in those younger than 5 years of age.

When meta-analysis of observational data is performed, consideration of study bias is critical (12). We considered that socioeconomic status may bias the results of the studies, because it potentially could be associated with both day care usage and differential participation of control subjects and case subjects, potentially act-
ing through mobility out of study region (21), lack of telephone, or willingness to participate. However, we saw no effect on heterogeneity in the subgroup analysis based on the participation rate of control subjects. It is also essential to consider potential biases that may systematically affect the results of all included studies (22). Here, the potential for recall bias (23) is one such factor, as none of the studies used prerecorded data. For example, bias would be introduced if parents of children newly diagnosed with diabetes underreported day care exposure compared with parents of control children.

We conclude that confirmation of the suggested protective effect of day care is needed using data on day care exposure collected before the diagnosis of type 1 diabetes is made. Such data would have to be prerecorded for other purposes in case-control studies but could be prospectively measured in cohort studies of children at genetic risk for type 1 diabetes. We also suggest that information about day care attendance be measured in randomized trials of agents for the prevention of type 1 diabetes, as day care exposure could potentially modify the effect of the preventive agent.

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References


