

Original Article

Association between infectious diseases and type 1 diabetes: a case-crossover study

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Background: To investigate the role of infectious diseases in the development of type 1 diabetes, this study estimated the relative risks of type 1 diabetes immediately after infectious diseases.

Research design and methods: A case-crossover design was employed. Information on infectious diseases during 407 d before the onset of type 1 diabetes was collected from medical records and parents' interviews for 260 patients in Chinese type 1 diabetes registry. The frequency of infectious diseases in 42 d before the onset of type 1 diabetes was compared with either the usual frequency of infectious diseases over the past year or the actual frequency of infectious diseases in a comparable 42-d control period.

Results: Forty-eight (18%) patients were reported to have infectious diseases during this period based on medical records and interviews with parents. The relative risk of type 1 diabetes onset was markedly elevated to 10.1 (5.6, 17.9) immediately after infectious diseases, suggesting the role of infections as a precipitator. The relative risk decreased gradually before and after 42 d and was similar between male and female patients.

Conclusion: The results showed that infectious diseases are associated with a large and transient increase in the risk of type 1 diabetes during 42 d after the infection.

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Type 1 diabetes is one of the most important chronic diseases of children in the United States. The incidence of the disease exceeds that of cancer, rheumatoid arthritis, cystic fibrosis, multiple sclerosis, and essentially all non-communicable diseases of youth (1).

Type 1 diabetes is associated with a 7- to 11-fold increased mortality (2). The disease is a potent determinant of subsequent blindness, a major risk factor for renal disease, and one of the most potent determinants of premature coronary death (3–5). The incidence of type 1 diabetes appears to be increasing rapidly in the US, and world wide, reasons for which are not known (6).

It is well established that susceptibility to type 1 diabetes is partly inherited, but environmental factors also have an important role based on the geographic, temporal variation of type 1 diabetes incidence and the result of twin study (7). Infection is one of the

most likely candidates that is involved in the development of type 1 diabetes. There is, however, surprisingly little direct evidence for infections causing diabetes on a population basis. Infection may be involved at two stages in the development of type 1 diabetes, first, as initiating factors which start the diabetogenic process and second, as precipitating factors which non-specifically precipitate clinical diabetes (8). Research has demonstrated that exposure to infections during the gestational period, the neonatal period, and the early childhood might be associated with the initiation of the immune process leading to beta cell destruction and glucose intolerance years later (9–11). Other studies suggested that infection could also act as precipitating factors, promoting an already ongoing autoimmune destructive process and leading to clinical diabetes (9, 12). Evidence for congenital rubella and diabetes is very strong, but

evidence for infections precipitating diabetes is not as convincing

If outbreaks of infectious illness non-specifically precipitate type 1 diabetes, the traditional case-control study would not be suitable for investigating events immediately preceding the onset of type 1 diabetes. The development of the case-crossover method by Maclure (13–16) offers an opportunity to investigate potential triggering factors. The design was originally employed to investigate events that might precipitate myocardial infarction (MI). As such, all subjects who entered the study were cases of MI. The frequency of potential triggering events during a 2-h hazard period before the onset of MI was contrasted to either the usual frequency or the frequency during a comparable 2-h control period. The 2-h hazard period was decided upon to detect the biologic events that might precipitate MI. Case-crossover methods are being used more and more in epidemiology to examine precipitating factors for such diverse endpoints as injuries, traffic accidents, and MI. To our knowledge, this is the first time it has been used in diabetes.

In this article, a similar approach has been employed with type 1 diabetes but with a much longer hazard period. We started with a hazard period of 42 d based on the suggestions in Gamble’s paper (8) and then extended to the periods of 28, 35, 49 and 56 d. The rationale is that if events occur during the hazard period that occur in a greater frequency than the control period, then these events are most likely to be the triggering events. Each patient contributes information in both hazard and control periods, thus serving as a case and a self-matched control. The main advantages are avoidance of control-selection bias and perfect control for confounding by chronic risk factors.

China is a particularly suitable place to investigate the association between type 1 diabetes and infectious diseases for two reasons: first, its low incidence rate of type 1 diabetes; second, its large variation in the incidence rate of type 1 diabetes. The attributable risk for a single factor will be greater in the low-risk area compared with that in the high risk one (17). The

geographic and temporal variations of incidence rate also facilitate the investigation of triggering factors of type 1 diabetes (18, 19).

In this article, we have used a case-crossover design to quantify the relative risk of type 1 diabetes after infectious diseases as compared with periods of no infections, the timing of the effect, and the effect in subgroups. The data were obtained from the type 1 diabetes registry in China, medical records of patients, and interviews with parents. Two approaches were used to collect the control data: the usual frequency and the control period approach. The benefits and disadvantages of different approaches were discussed.

Research design and method

Research design

The case-crossover design was employed to assess the effect of exposure to infections on the risk of type 1 diabetes during a brief ‘hazard period’. With this method, control information for each patient is based on his or her previous exposure to infections.

In this article, the ‘hazard period’ was initially defined as 42 d immediately before the onset of type 1 diabetes. This cut-point was chosen based on the slope of the epidemic curve (8). Several other lengths of ‘hazard period’, for example, 28, 35, 49, and 56, were investigated and compared, and the ‘hazard period’ that gave the highest relative risk was the most likely to be the average induction time.

The frequency of infectious diseases in the hazard period was compared with two types of control data obtained from the patients (Fig. 1): the usual frequency of infectious diseases over the past year and the actual frequency of infectious diseases in the comparable 42-d control period 1 yr before the onset of type 1 diabetes. The later approach explains why we collected data about infectious diseases during 407 d before the onset of type 1 diabetes. Detailed description of the design can be found at <http://www.pitt.edu/~super1/lecture/lec0821/index.htm>.

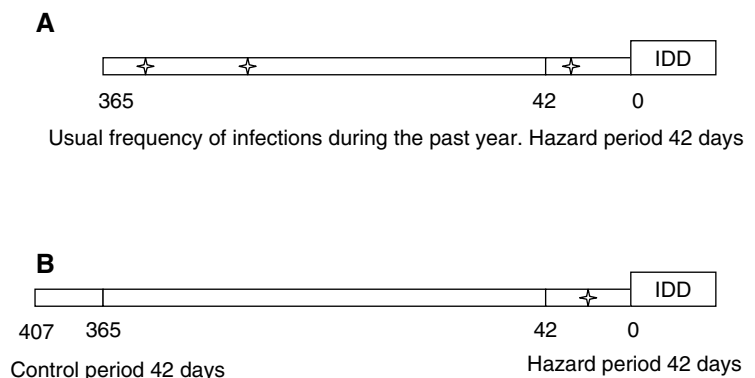


Fig. 1. Schematic representation of two different approaches to collect control data in case-crossover studies. (A) Usual frequency approach; (B) control period.

Study population

The Chinese type 1 diabetes registry was established in 1991 as part of the World Health Organization (WHO) DiaMond Project. There were five centers participating in this study, which included a total of 260 patients registered between 1 January 1998 and 31 December 2001. The five centers were all population based (Shenyang, Dalian, Beijing, Shanghai and Nanjing) and were chosen because these cities had well-equipped medical institutions and well-developed disease monitoring systems, which ensured the accurate and prompt report of infectious diseases.

The definition of a type 1 diabetes case was according to WHO DiaMond criteria (WHO multinational project, 1991), that is, individuals were diagnosed by a physician, placed on daily insulin injection before their 15th birthday, residents in the defined areas of registration at the time of the first insulin administration, and age 0–14 yrs at the time of diagnosis.

Case ascertainment was ensured by collecting data from at least two independent sources. As a primary source, cases were identified from the medical records in the hospital by a member of the local center. The secondary source was the student physical examination records from the school health program. Other sources included the records of approval of the birth of a second child from the Family Planning Committee, the insurance company's payment voucher for the hospitalization of a type 1 diabetes child, the Child-Woman Care Network records, and the records from anti-epidemic stations.

Ascertainment was >93% (18). Data accuracy was assessed in two manners. The first was to randomly select 10% of the cases for re-examination at each center. The second was to look for discrepancies of data elements from the primary and secondary sources of ascertainment.

Information on infectious diseases

The information on infectious diseases was obtained from three sources: records from the pediatrician's office, interviews with the patient's family members, and the records from the local center for Infectious Disease Control and Prevention. Data were obtained on the date and type of infectious diseases occurred within 407 d before the onset of type 1 diabetes for each patient. Information on infectious diseases was collected by 28 February 2002.

The study coordinator from each center received a training course on the methods of this study and the epidemiology of diabetes. Then each center created a local method of operation based on the DiaMond MOO. This was originally overviewed by the project coordinator in China. It was then translated into English and received approval from the Institutional

Review Board (IRB) at the University of Pittsburgh. The study protocol was approved by the IRB of each center, and informed consent was obtained from each patient.

Statistical analysis

The analysis of case-crossover study depends upon the approaches to collect control data.

The Mantel–Haenszel method for follow-up studies with sparse data in each stratum (13) was applied when the control data were collected based on each individual's usual frequency of infectious diseases over the year preceding his/her type 1 diabetes. The amount of person-time exposed to infectious diseases was estimated by multiplying the reported usual frequency of exposure by the pre-defined induction time t_0 (e.g., 42 d).

The unexposed person-time was calculated by subtracting the exposed person-time from the total number of days in a year. The 48 subjects in this study produced 48 strata following this approach. The Mantel–Haenszel method for stratified data was used to estimate the pooled relative risk of having type 1 diabetes during a period of infections compared with that during period of no infections. The relative risk for 28, 35, 49, and 56 d was also estimated and compared. The relative risk and 95% confidence interval were calculated by using STATXACT 5.0 (Cytel Software, Cambridge, MA, USA).

The conditional logistic regression model (20) was applied when the control data were collected from a comparable 42-day control period. The pairs were made up of two intervals for each patient, the hazard period and the control period. Information for the model came from two types of patients, the first being exposed in the hazard period but not the control period, the second being exposed in the control period but not the hazard period. Standard conditional logistic regression model was applied, with the logit of type 1 diabetes being dependent variable and the binary variable of infections as the independent variable. The

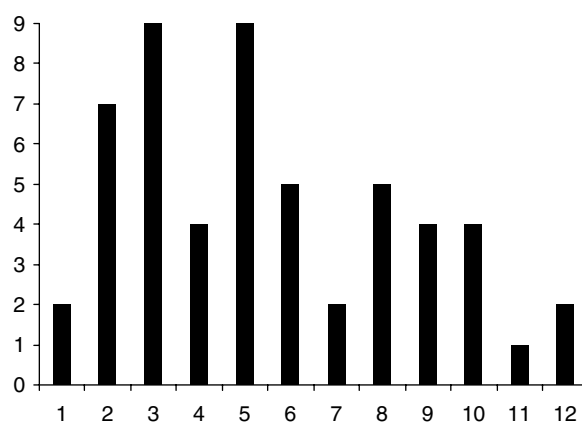


Fig. 2. Frequency of infectious diseases by month.

relative risk and 95% confidence interval were estimated using SAS for windows version 8.0 (SAS Institute Inc, Cary, NC, USA).

Results

Study population

Among the 260 patients, 48 (18%) patients reported that they had infectious diseases during 407 d before the onset of type 1 diabetes. Because patients who had no exposure to infectious diseases did not contribute information to the assessment of the relative risk of triggering type 1 diabetes onset, all analyses of risk were based on the data from the 48 patients who had history of infectious diseases during the 407 d. The frequency of infectious diseases in these 48 patients was displayed by month in Figure 2. Of the 48 patients, 21 (44%) were male, 27 (56%) were female, and the average age was 9.3 (SD = 4.3). Six (13%) out of 48 patients had a family history of type 1 diabetes. Most of the patients (47, 98%) were from the Han ethnic group and only one patient was from the Hui ethnic group.

Records from the pediatricians' offices (source 1) provided the information of infectious diseases for 36 patients. Interviews with the patients' parents (source 2) provided the information of infectious diseases for 46 patients. Among them, 36 patients had exactly the information provided by the pediatricians' offices, and the rest of the 10 patients had some records of infections that were not provided by the pediatricians' offices. The records from the local Center for Infectious Disease Control and Prevention (source 3) provided information for 11 patients. The records of 9 patients were consistent with source 1 and source 2. The records of 2 patients did not appear in the other two sources. The relative risk from different sources was not significantly different from each other in preliminary analysis. Therefore, all subsequent analyses were based on the combined information from all three sources.

Results from the Mantel–Haenszel method

Data on the usual frequency of infectious diseases showed that 43 patients had infections once a year.

Among them, 27 patients had infections within 42 d before the onset of type 1 diabetes. Five patients had infections twice a year and two of them had one infection within 42 d before type 1 diabetes (Table 1). Using the Mantel–Haenszel method, the relative risk of onset of type 1 diabetes within 42 d after infectious diseases was 10.1 (95% CI = 5.6–17.9). When different lengths of hazard period were applied, the relative risk for the 28, 35, 42, 49, and 56 d periods are 8.3, 9.8, 10.1, 9.2, 9.4, respectively. The induction time was likely around 42 d. Thus, all subsequent analyses were based on the 42 d hazard period.

Results from the conditional logistic regression model

Of the 48 patients, 29 patients reported exposure to infectious diseases during the 42-d hazard period but not the control period. There was only one patient exposed to infectious diseases during the control period and not in the hazard period. The remaining 18 patients did not report exposure to infectious diseases at either the hazard or control period.

No patients were exposed to infectious diseases during both periods. The relative risk of type 1 diabetes in 42 d after infectious diseases was estimated as 29.0 [95% confidence interval (CI) = 4.0–213.0] using the conditional logistic regression.

Results on sub-group analysis

There were 14 different types of infectious diseases occurring during the 407 d (Table 2). Upper respiratory system infection and colds were the two most frequent types reported, with frequencies of 20 (38%) and 10 (19%), respectively. The relative risks of type 1 diabetes in 42 d after upper respiratory system infections and colds were 30.8 and 7.7, respectively, by using the Mantel–Haenszel estimator (Table 3).

The relative risk of type 1 diabetes was similar between males (9.1) and females (10.8). When classified by the age of diabetes onset, the relative risk of type 1 diabetes was higher among subjects with early onset diabetes (age < 10, RR = 16.2) in contrast to late onset diabetes (age > 10, RR = 6.5). Subjects who were diagnosed during warm seasons (May–October) showed a higher relative risk (13.6 vs. 7.1) in contrast

Table 1. Summary of patients by usual frequency of infections per year and occurrence of infections within 42 d

Number of subjects	Usual frequency of infections	Had infections within 42 d before type 1 diabetes	Exposed person-time per year	Unexposed person-time per year
27	1	Yes	42	323
16	1	No	42	323
2	2	Yes	84	281
3	2	No	84	281

Table 2. Type and frequency of infectious diseases among study population

Type of infections	Frequency	Percent	Cumulative percent
Upper respiratory system infection	20	38	38
Cold	10	19	57
Bronchitis	6	11	68
Chicken pox	3	6	74
Pneumonia	2	4	78
Parotitis	2	4	82
Influenza	2	4	86
Fever	2	2	88
Urinary system infections	1	2	90
Oral infections	1	2	92
Skin infections	1	2	94
Cough	1	2	96
Tuberculosis	1	2	98
Diarrhea	1	2	100

to those who were diagnosed during cold seasons (November–April) (Table 3).

Discussion

The case-crossover design has been successfully applied to investigate events that might precipitate MI and many other disorders (13–16). It is the first time to our knowledge that this method has been used to examine factors that might precipitate type 1 diabetes. For the patients in our study, an episode of infectious disease was associated with a transient risk of type 1 diabetes in the subsequent 42 d that was 10 times higher than the risk during periods of no infections. Despite strong evidence by Yoon and others that infectious diseases could trigger type 1 diabetes, there was very little evidence on a population basis that they did cause diabetes. This is one of the strongest evidences that infectious agents precipitated diabetes on a population basis. These findings are unlikely to be accounted for by recall bias or confounding, since the major source of information was medical records and the case-crossover design employed in this study eliminated the effect of confounding by factors that differed among patients.

Since the case-crossover design uses self-matching, all characteristics of an individual that remain constant over time do not vary within strata (21). Thus, there can be no confounding by these characteristics and there is the freedom from between-person confounding. However, there can be within-person confounding. This problem arises when multiple transient exposures are correlated in time within an individual (14, 15).

Within-person confounding can be modeled in case-crossover studies as long as data regarding the temporal correlation between multiple exposures are collected. For example, exposure to chemical poisons may coincide with the exposure of infections.

This can be easily adjusted using conditional logistic regression with a term entered for chemical poisons (20). Although it is possible that there was some confounding by other transient exposures that coincided with infection, it is unlikely to account for such a strong association that we observed.

A factor potentially limiting our study is recall bias (22, 23). It may be argued that people tend to recall more disease events happening immediately before the onset of type 1 diabetes than that occurring longer before. Our study design helped to minimize this bias by using medical records as the major source to collect

Table 3. Relative risk of type 1 diabetes in 42 d after infections for various subgroups using the Mantel–Haenszel method

Sub-groups	Number of patients	Number of patients had infections within 42 d	Relative risk	95% confidence interval	
By type of infections	Upper respiratory system infection	20	16	30.8	25.2–39.9
	Cold	10	5	7.7	3.6–15.3
By age	<10	24	17	16.2	6.7–39.3
	≥10	24	12	6.5	3.0–14.5
By gender	Male	21	12	9.1	3.8–21.8
	Female	27	17	10.8	5.0–23.6
By weather	November–April	21	11	7.1	3.0–16.5
	May–September	27	18	13.6	6.1–30.7
All patient		48	29	10.1	5.6–17.9

information on infectious diseases. Records from pediatrician's offices (source 1) provided the information of infectious diseases for 36 patients, supplemented by interviews with the parents (additional 10 patients) and the records from the local Center for Infectious Disease Control and Prevention (additional 2 patients). Furthermore, infectious diseases are relatively rare events and are easily remembered by parents. The data from interviewing the parents serve as a good supplementary part for the overall information, because they can provide information on mild to moderate infections, which may not show up in medical records. Thus, it is unlikely the strong association that we observed may have been attributed to recall bias.

The consistency of the relative risks estimated from two types of control data also confirms the validity of the findings. Both the usual frequency and the control period approach showed that an episode of infectious disease was associated with an elevated transient risk of type 1 diabetes in the subsequent 42 d. However, the precision of relative risk estimators in case-crossover studies varies greatly depending upon the strategy used in control sampling. In the pair-matched control period approach, the 95% CI was 17 times wider than that estimated by the usual frequency approach. This is in part due to the fact that the data from 18 patients, who did not report infectious diseases at either hazard or control period, were excluded from the analysis using the control period approach, whereas all 48 patients were included in the analysis using the usual frequency approach. This suggests that the study efficiency is greatly increased as the length of the control period is increased and more information is provided for each stratum. The benefit of the usual frequency approach is that more subjects and more relevant information can be included in the analyses, and the results are more precise (24). However, it is difficult to control for covariates in either method. Data collected from the control period approach can be analyzed by conditional logistic regression, which is easier to control for various covariates. But the disadvantage is that a portion of the subjects and a portion of the information were excluded from the analyses. Thus, the precision is lower (24, 25).

With regard to the frequency by which type 1 diabetes is triggered by infections, it is important to distinguish absolute risk from relative risk (14–16). A limitation of case-crossover design used in this study is similar to one in case-control studies, the absolute risk of type 1 diabetes onset cannot be directly estimated from the data. However, an estimate of the baseline risk can be made with the use of other data sources. For example, on the basis of the Chinese type 1 diabetes registry data (18), the baseline risk of type 1 diabetes for a Chinese child aged 0–14 is

0.51 per 100 000. Thus, during the 42 d after infections, his/her risk of developing type 1 diabetes would be increased by 10 times, but the absolute risk is still as low as 5.1 per 100 000. The large relative risk suggested a major role of infections in precipitation of type 1 diabetes. Despite the large relative risk, only 18% participants reported an infection, which could suggest that infection only acts as one of the precipitating factors of type 1 diabetes. It is also possible that many of the infections were missed due to minimal symptoms or difficulty of recall.

Among all the types of infections that were present in this study, upper respiratory system infection was the most frequent one and 16 out of 20 cases occurred within 42 d before the onset of type 1 diabetes, which made the relative risk as high as 30.8. The second most frequent infection was a cold, with a relative risk of 7.7, which was slightly lower than the overall relative risk for infections in general. One major difference between upper respiratory system infection and the common cold is the etiology. Upper respiratory system infection, including pharyngitis, croup and sinusitis, is usually caused by adenovirus or parainfluenza virus, whereas the major pathogens of the common cold are rhinovirus and coronavirus. Therefore, it is most likely that certain types of virus play a more important role in precipitating type 1 diabetes. Studies indicated that coxsackievirus and rotavirus might accelerate or exacerbate islet autoimmunity (26, 27) and that the timing of infection, rather than its presence or absence, might have etiological implications for the development of type 1 diabetes (26). These findings suggested that we could apply the case-crossover design to investigate the role of specific virus infection in the etiology of type 1 diabetes.

Subgroup analyses were also conducted by gender, by age, and by season. There is not much difference in the relative risk between boys and girls, whereas children who have early onset diabetes (<10 yrs) and whose diabetes was diagnosed in warm season (May–October) have a higher relative risk of developing type 1 diabetes within 42 d of infection. These results suggested that children who develop diabetes at different ages and seasons may have different precipitating factors. Other researches also indicated that infections might modify the autoimmune process in an age-dependent manner and depending upon the timing and number of exposures (11, 28, 29). Because of the small number of cases exposed to infection, we were unable to evaluate whether the risk of having type 1 diabetes differed among other subsets of patients. For example, we could not verify whether the risk of sustaining an infection-associated type 1 diabetes differs for patients with different ethnic groups, family histories or frequencies of infections.

In this study, we demonstrated that infectious diseases could substantially increase the risk of type 1

diabetes in children aged 0–14 in China. The study design and the sources of information decreased the chances of confounding and bias and provide an appropriate method to investigate precipitating factors of type 1 diabetes. Further studies are needed to investigate the type and number of infections on the risk of type 1 diabetes in different age groups.

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