ORIGINAL ARTICLE

Incidence of Schizophrenia in a Nationwide Cohort of Patients With Type 1 Diabetes Mellitus

Hannu Juvonen, MD; Antti Reunanen, MD, PhD; Jari Haukka, PhD; Maria Muhonen, MD; Jaana Suvisaari, MD, PhD; Ritva Arajärvi, MD, PhD; Timo Partonen, MD, PhD; Jouko Lönnqvist, MD, PhD

Context: Patients with schizophrenia have an increased risk of type 2 diabetes mellitus. However, very few studies have dealt with the association of type 1 diabetes and schizophrenia. Preliminary evidence points to a possible inverse association.

Objective: To investigate the incidence of schizophrenia in a nationwide cohort of patients with type 1 diabetes born in 1950 through 1959 in Finland.

Design: A cohort study of individuals born in 1950 through 1959 with a follow-up of 1969 through 1991.

Setting: Finland.

Patients: All individuals born in 1950 through 1959 with type 1 diabetes were identified through nationwide registers. The incidence of schizophrenia until 1992 among the total 1950-1959 cohort and in individuals with type 1 diabetes was calculated using information from 3 health care registers.

Main Outcome Measure: Incidence of schizophrenia.

Results: The incidence of schizophrenia was 0.21 per 10 000 person-years in the group with type 1 diabetes and 0.56 per 10 000 person-years in the group without type 1 diabetes ($P < .001$).

Conclusion: The incidence of schizophrenia is decreased in patients with type 1 diabetes.

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Comorbidity studies of patients with schizophrenia have found a positive association between schizophrenia and type 2 diabetes mellitus.[1,2] This has been thought to result from numerous factors associated with schizophrenia. The disease itself and its genetic factors, antipsychotic medication, lifestyle changes, and possibly weight gain may play a role.[3-8] There are no conclusive studies, however, on the comorbidity of schizophrenia and type 1 diabetes. Although a Swedish group reported in a research letter that they found no cases of schizophrenia in a cohort of 1154 patients with type 1 diabetes followed up for 4 to 14 years,[9] no further follow-up of this study has been reported. A Danish register study reported a nonsignificant reduction in schizophrenia among patients with type 1 diabetes.[10] A Finnish study based on reimbursed medication for patients with diabetes reported an unexpectedly low use of antipsychotic medication among patients with type 1 diabetes.[11] Interestingly enough, 2 familial case-control studies suggest a positive familial association between the 2 diseases.[10,12]

The autoimmune and viral hypotheses of schizophrenia,[13-15] the varying comorbidity findings for schizophrenia and autoimmune diseases,[10,12,15] the HLA antigen associations of autoimmune disorders[16,17] and schizophrenia,[18,19] and chromosome 6 linkage findings in schizophrenia[20] and autoimmune disorders[21] have led to speculation about links between type 1 diabetes and schizophrenia.[22-24] The links between schizophrenia and other autoimmune disorders, such as rheumatoid arthritis, have been explained by immunological, biochemical, and genetic factors.[25]

The incidence of type 1 diabetes among children in Finland, a north European country with approximately 5 million inhabitants, is the highest in the world and has increased to 3.52 per 10 000 person-years over the last few decades.[26,27] In addition, the prevalence of schizophrenia is somewhat higher in Finland than elsewhere,[28] although the incidence may be declining.[29] There are also interesting nationwide variations: while the incidence

Author Affiliations:
Departments of Mental Health and Alcohol Research (Drs Juvonen, Haukka, Muhonen, Suvisaari, Arajärvi, Partonen, and Lönnqvist) and Health and Functional Capacity (Dr Reunanen), National Public Health Institute, Helsinki, Finland.

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of schizophrenia is highest among those born in eastern Finland and lowest among those born in the west and southwest,[30] the opposite is true for type 1 diabetes.[31] We studied the incidence of schizophrenia in a nationwide cohort of patients with type 1 diabetes born in 1950 through 1959 in Finland.

METHODS

REGISTERS

The unique identification codes of all individuals born in Finland are held in the National Population Register. The nationwide cohort born in 1950 through 1959 consists of 896 175 individuals. This cohort was chosen to allow the best possible reliability and coverage for both type 1 diabetes and schizophrenia.

All Finnish citizens with certain chronic diseases are entitled to full reimbursement of drug costs. Those with schizophrenia and type 1 diabetes are in this category and are centrally registered by the Social Insurance Institution of Finland. Hospital treatments are recorded in the national Hospital Discharge Register, which contains admission and discharge dates and the principal and up to 3 subsidiary diagnoses for each hospital treatment. The Pension Register contains data on all individuals receiving a disability pension along with their respective clinical diagnoses.

PATIENTS WITH TYPE 1 DIABETES

The register of special reimbursement of medicines was used to identify the 5009 individuals with type I diabetes from the nationwide cohort born in Finland in 1950 through 1959. More than 95% of individuals with type 1 diabetes are covered by this register.[11,26]

PATIENTS WITH SCHIZOPHRENIA

The individuals with schizophrenia during the follow-up period of 1969 through 1991 were identified through the 3 aforementioned registers, as in an earlier study.[29] The diagnostic classification used in the registers was the *International Classification of Diseases, Eighth Revision* (*ICD-8*) through 1986 and *DSM-III-R* from 1987 through 1991. The broad diagnostic concept of schizophrenia (*ICD-8* and *DSM-III-R* code 295), including schizoaffective and schizophreniform disorders and also simple schizophrenia and latent schizophrenia in *ICD-8*, which correspond to schizotypal personality disorder in *DSM-III-R*, was applied because this has proved reliable in the registers.[32] Using this definition, we identified in the registers 10 931 patients with schizophrenia born between 1950 and 1959.

Although the specificity and sensitivity of a diagnosis of broad-concept schizophrenia in the registers as described earlier have been studied before, we assessed the specificity separately again. A register-based sample of individuals (n=906) subsequently enrolled in a separate genetic study of schizophrenia was diagnosed by a best-estimate case-note consensus procedure. Two psychiatrists independently made *DSM-IV* diagnoses based on all available case-note information from hospitals and, when needed, from mental health care centers. In cases of disagreement, they reviewed the diagnosis together. If disagreement persisted, a third psychiatrist reviewed the case notes and consensus was reached by all 3. Of the 906 patients in the sample with a diagnosis of schizophrenia in the registers as described earlier, 783 finally received a research diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, or schizotypal personality disorder according to *DSM-IV*. There were 586 patients with different subtypes of schizophrenia, 119 with schizoaffective disorder, and 78 with schizophreniform disorder or schizotypal personality disorder. One hundred twenty-three patients had a research diagnosis outside the broad schizophrenia concept: 35 had affective or delusional psychosis, 6 had organic psychosis, and 67 patients had nonpsychotic disorders, mostly affective type. The information was insufficient for assigning any *DSM-IV* diagnosis in 15 cases. Thus, in the overall sample, which is representative of the nationwide cohort of 1950 through 1959, the proportion of patients with false-positive schizophrenia diagnoses in the registers was 13.6%. Previous studies have shown that the sensitivity of these registers is good and that they can correctly identify more than 90% of patients with schizophrenia.[32]

The psychiatric diagnoses of all patients with both type 1 diabetes and schizophrenia were also assessed separately by the best-estimate case-note consensus procedure according to *DSM-IV*. The reliability of the registers for schizophrenia was considerably lower in the comorbid cases. Of the 49 comorbid cases identified from the registers, only 24 had a research diagnosis of both diseases. There were 11 cases with schizophrenia, 5 with schizoaffective disorder, and 8 with schizophreniform disorder or schizotypal personality disorder in this group of patients with type 1 diabetes. The false positives in these comorbid cases had affective or alcohol-related disorders misdiagnosed as schizophrenia during at least 1 hospital treatment. In addition, there were 2 technical coding errors. In contrast, there were no false positives for type 1 diabetes.

STATISTICAL METHODS

The incidence of schizophrenia and schizophrenia spectrum disorders was calculated from a life table containing the number of persons with schizophrenia and the number of person-years in subpopulations of individuals with and without type 1 diabetes in the 1950-1959 birth cohort.[33] The 95% confidence interval for relative risk was calculated with Poisson regression using diabetes status as an explanatory variable. The diagnosis of schizophrenia was thus register-based in the subpopulation without type 1 diabetes and based on the best-estimate case-note consensus procedure in the subpopulation with type 1 diabetes. Because the estimate of false positives in the former group based on the sample of 906 patients was 13.6%, we performed the calculation assuming the proportion of false positives to be 10% or 20% in the registers.

RESULTS

The incidence of schizophrenia, including schizoaffective disorder, schizophreniform disorder, and schizotypal personality disorder, in the subpopulations with and without type 1 diabetes per 10 000 person-years is presented in **Table 1**.

The incidence of schizophrenia in patients with type 1 diabetes was less than half of that in individuals without type 1 diabetes, and the disparity between men and women persisted in the group with type 1 diabetes. The relative risk of a person with type 1 diabetes having schizophrenia was reduced by 62% (95% confidence interval, 43%-74%) when compared with a person without type 1 diabetes. Among the 24 comorbid patients with both schizophrenia and type 1 diabetes, the mean (SD) age at onset of type 1 diabetes was 14.2 (7.8) years and the mean (SD) age at onset of schizophrenia was 21.8 (4.8) years. Age at onset of schizophrenia was defined as the date of the first hospitalization for the disease.

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Table 1. Incidence of Schizophrenia per 10 000 Person-Years and RR of Schizophrenia in Subjects Without and With Type 1 Diabetes Mellitus[a]

	All		Women		Men	
	Schizophrenia Incidence	RR (95% CI)	Schizophrenia Incidence	RR (95% CI)	Schizophrenia Incidence	RR (95% CI)
Type 1 diabetes						
No	0.56	1 [Reference]	0.49	1 [Reference]	0.63	1 [Reference]
Yes	0.21[b]	0.38 (0.26-0.57)	0.17[c]	0.35 (0.18-0.71)	0.24[b]	0.39 (0.24-0.63)
Assuming 10% false positives						
Type 1 diabetes						
No	0.51	1 [Reference]	0.45	1 [Reference]	0.56	1 [Reference]
Yes	0.21[b]	0.42 (0.28-0.63)	0.17[d]	0.39 (0.20-0.79)	0.24[b]	0.43 (0.26-0.70)
Assuming 20% false positives						
Type 1 diabetes						
No	0.45	1 [Reference]	0.40	1 [Reference]	0.50	1 [Reference]
Yes	0.21[b]	0.48 (0.32-0.71)	0.17[e]	0.44 (0.22-0.88)	0.24[c]	0.48 (0.30-0.79)

Abbreviations: CI, confidence interval; RR, relative risk.
[a] Relative risks and significance of incidence differences are always between populations without and with type 1 diabetes.
[b] $P<.001$.
[c] $P<.005$.
[d] $P<.01$.
[e] $P<.05$.

Table 2. *DSM-IV* Research Diagnoses for All Patients With Register-Identified Schizophrenia With Type 1 Diabetes Mellitus and a Sample of Patients Without Type 1 Diabetes[a]

	No. (%)			
	Schizophrenia	Schizoaffective Disorder	Schizophreniform Disorder or Schizotypal Personality Disorder	Total
Type 1 diabetes	11 (46)	5 (21)	8 (33)	**24** (**100**)
No type 1 diabetes	586 (75)	119 (15)	78 (10)	**783** (**100**)

[a] $\chi^2_2=15.07$; 2-tailed $P<.001$.

The *DSM-IV* research diagnoses for the sample of patients with register-identified schizophrenia without type 1 diabetes and all patients in the birth cohort from 1950 through 1959 with both register-identified schizophrenia and type 1 diabetes are presented in **Table 2**.

In the subpopulation of patients with type 1 diabetes, there was a significant overrepresentation of schizoaffective disorder, schizophreniform disorder, and schizotypal personality disorder.

COMMENT

To our knowledge, this is the first time the comorbidity of schizophrenia and type 1 diabetes has been studied using nationwide registers independently sampled for both diseases. We found a substantially decreased incidence of schizophrenia among patients with type 1 diabetes compared with the population without type 1 diabetes.

However, in register-based studies, the possibility of ascertainment bias must be closely examined. Previous studies on schizophrenia and rheumatoid arthritis comorbidity have highlighted the importance of independent population-based ascertainment of both diseases. The conflicting results of these comorbidity studies may be due to patient populations that could have been biased because they were not population based.[23,25,34,35] In comorbidity studies, the case-finding method must be adapted individually according to the diseases and the prevailing health care system.

The accuracy of register-based schizophrenia diagnoses has been studied in Finland by comparing register diagnoses with those based on clinical interviews or all available case-note information.[32,36] The results show that the schizophrenia diagnoses in the hospital discharge register are sufficiently accurate for research use, especially when a broad concept of schizophrenia (including schizoaffective disorder, schizophreniform disorder, and schizotypal personality disorder) is used.[32,37]

In this study, we separately assessed the proportion of false positives for register-based schizophrenia diagnoses in the nondiabetic and the type 1 diabetes groups. We found the reliability of the registers to be poorer in the comorbid group; the greater proportion of false positives was due to both diagnostic and technical coding errors. This means that register-based comorbidity findings should be interpreted very cautiously; even if registers are reliable in general, it does not guarantee their reliability in patients with more than 1 disease. This is why

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we ascertained all diagnoses in the type 1 diabetic group with the case-note consensus procedure, and the same was done in a representative sample of the group without type 1 diabetes. We avoided overestimating the difference between the nondiabetic and diabetic groups by assuming the proportion of false positives to be 10% or 20% in the nondiabetic group.

According to national population studies, more than 90% of psychotic individuals come into contact with public health care professionals such that they can be identified as index cases in the earlier-mentioned registers.[37] If the probability of individuals with diabetes and schizophrenia being included in the registers as schizophrenia cases was lower than in general, this would inflate the difference between these 2 groups. This is highly improbable because individuals with diabetes have more contacts with health care than those without diabetes. Among patients with diabetes, the psychiatric diagnosis in the registers is often a secondary diagnosis made during a hospital treatment in a somatic ward. These diagnoses proved relatively often to be false positives for schizophrenia.

The characteristics of the register of patients with type 1 diabetes used in this study have been described in detail elsewhere.[26] More than 95% of patients with type 1 diabetes can be identified through this register. It is also unlikely that this register would be less sensitive for patients with an onset of schizophrenia than for patients with no schizophrenia later in life. Patients with type 1 diabetes have an excess of most chronic diseases in the registers because of both real comorbidity and frequent contacts with health care.[11]

The 1950-1959 birth cohort was followed up for schizophrenia during 1969 through 1991 and the age of the cohort at study end was 32 to 41 years. As estimated from Finnish incidence studies, this follow-up included approximately 80% of all schizophrenia cases in this cohort.[29] To exert bias on our results, comorbidity with type 1 diabetes would have to delay the onset of schizophrenia by a substantial number of years, which is highly unlikely. On the contrary, comorbid type 1 diabetes may lower the register-based age at onset of schizophrenia because the comorbid disease increases the probability of the patient being hospitalized.

One possible source of bias would be an excess mortality of those patients with type 1 diabetes who have a liability to schizophrenia. To seriously inflate our results, a substantial part of the mortality of these patients with diabetes should be associated with a liability to schizophrenia before the actual onset of the disease. Mortality in young adults with diabetes is caused mainly (in descending order of importance) by acute diabetic complications, circulatory diseases, late diabetic complications, accidents, and suicides,[38] whereas suicide is the leading cause of death among young adults in the Finnish general population. These mortality data rule out a bias based on different mortality patterns in patients with and without type 1 diabetes.

Type 1 diabetes and schizophrenia are both highly heritable diseases.[39,40] Type I diabetes is an autoimmune disease, and the HLA antigen region accounts for up to 40% to 50% of its genetic susceptibility.[41] There is seasonal variation in the births of patients with type 1 diabetes,[42] and infections are clearly involved in its etiology.[43] Infections during pregnancy, blood group incompatibility, and other pregnancy and neonatal complications may also increase the risk of type 1 diabetes.[44] There are similar but weaker findings concerning schizophrenia. Some HLA antigen alleles have been associated with schizophrenia,[18,45] particularly A9 or its A24 subtype, A10, DQB1*0602, and DRB1*04. Two of these, A24 and DQB1*0602, have also been implicated in type 1 diabetes. Puzzlingly, however, the association has been in the same direction in both diseases: A24 is positively and DQB1*0602 negatively associated with both type 1 diabetes and schizophrenia. However, a recent study suggests that it may not be the actual HLA antigen alleles but excessive matching of HLA antigen alleles between mother and offspring that increases the risk of schizophrenia.[46]

Gestational and childhood infections may increase the risk of developing schizophrenia,[47-49] but the findings are less consistent than in type 1 diabetes.[13,50] Seasonal variation in the births of patients with schizophrenia[51] may support evidence for a role of gestational infections in schizophrenia. Seasonal variations have also led researchers to assess the role of vitamin D in the risk of schizophrenia.[52] Enteroviruses, which are strongly linked to type 1 diabetes,[43] show only weak association with schizophrenia.[53] In contrast, the evidence that obstetric complications and low birth weight increase the risk of schizophrenia is strong.[54]

So what could explain a negative association between 2 disorders with shared features in their etiology? One possibility is a linkage disequilibrium of protective and liability genes for schizophrenia and type 1 diabetes. Several linkage studies of schizophrenia have shown a linkage near the HLA antigen region.[55] One of the strongest candidate genes for schizophrenia, dysbindin,[56] lies fairly close to the HLA antigen region, yet too far for a linkage disequilibrium. The association could be linked to the individual's genetic susceptibility to infections or their consequences (eg, formation of autoantibodies). Another explanation is that early insults (eg, prenatal and childhood infections and obstetric complications) evoke different responses among individuals with a genetic predisposition to type 1 diabetes or schizophrenia, leading to the development of type 1 diabetes in the former and schizophrenia in the latter. Hanson and Gottesman[57] have recently suggested that at least some forms of schizophrenia could result from a genetically mediated central nervous system microvascular inflammatory disease. They hypothesize that the early insults provoke a chronic inflammatory reaction of the central nervous system vascular endothelium leading to schizophrenia and that the negative association between schizophrenia and some autoimmune disorders could be explained by variation in humoral and cellular immune responses. This is possible: it is established that genetic factors modify an individual's susceptibility to microbes and the response to the infection.[58]

The third possible explanation for the lower incidence of schizophrenia among patients with type 1 diabetes is that some factors associated with type 1 diabetes (genetic, endocrinologic, or treatment related [eg, insulin]) could modify the phenotype or clinical pic-

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ture of schizophrenia. A Norwegian congress report supports this hypothesis.[59] Type 1 diabetes was associated with affective symptoms and diagnoses of bipolar and schizoaffective disorders in the preliminary report. The sample was small (N=11), but the results seem to confirm the negative association of type 1 diabetes and schizophrenia. There was also suggestive evidence of an overrepresentation of schizoaffective disorder, schizophreniform disorder, and schizotypal personality disorder in patients with diabetes in our study, which accords with the Norwegian findings.

A previous study appeared to find an excess of type 1 diabetes in the first-degree relatives of patients with schizophrenia.[60] More family studies are needed to confirm these contradictory findings.

The decreased incidence of schizophrenia among patients with type 1 diabetes was substantial. Further studies are needed on systematically ascertained families with both patients with schizophrenia and diabetes. Such families should be studied in detail using clinical assessment and the genetic, immunological, and infectious hypotheses for the etiology of the disease should be tested as well. This study also emphasizes the importance of independent and population-based case finding in epidemiologic comorbidity studies.

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Correspondence: Hannu Juvonen, MD, Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland (hannu.juvonen@ktl.fi).
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