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Autoimmune diseases, bipolar disorder, and non-affective psychosis

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Abstract

Objective—Clinic-based studies of immune function, as well as comorbidity of autoimmune diseases, bipolar disorder, and schizophrenia, suggest a possible autoimmune etiology. Studies of non-affective psychosis and schizophrenia suggest common etiologies. The objective was to determine the degree to which 30 different autoimmune diseases are antecedent risk factors for bipolar disorder, schizophrenia, and non-affective psychosis.

Methods—A cohort of 3.57 million births in Denmark was linked to the Psychiatric Case Register and the National Hospital Register. There were 20,317 cases of schizophrenia, 39,076 cases of non-affective psychosis, and 9,920 cases of bipolar disorder.

Results—As in prior studies, there were a range of autoimmune diseases which predicted raised risk of schizophrenia in individuals who had a history of autoimmune diseases, and also raised risk in persons whose first-degree relatives had an onset of autoimmune disease prior to onset of schizophrenia in the case. These relationships also existed for the broader category of non-affective psychosis. Only pernicious anemia in the family was associated with raised risk for bipolar disorder (relative risk: 1.7), suggesting a small role for genetic linkage. A history of Guillain-Barré syndrome, Crohn's disease, and autoimmune hepatitis in the individual was associated with raised risk of bipolar disorder.

Conclusions—The familial relationship of schizophrenia to a range of autoimmune diseases extends to non-affective psychosis, but not to bipolar disorder. The data suggest that autoimmune processes precede onset of schizophrenia, but also non-affective psychosis and bipolar disorder.

Keywords

autoimmune disease; bipolar disorder; epidemiology; non-affective psychosis; register; schizophrenia

This paper extends earlier work on autoimmune diseases and schizophrenia (1) to bipolar disorder and disorders with features similar to schizophrenia, sometimes termed *non-affective psychosis.* This new analysis, with more than twice as many observations, allows comparison of bipolar disorder to schizophrenia, as well as facilitating more precise study of the temporal relationship of autoimmune disease and the first diagnosis of bipolar disorder,

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schizophrenia, and non-affective psychosis. The presentation of these disorders in parallel fashion facilitates assessment of the value of the nosologic distinctions between them.

The autoimmune diseases which have been studied most thoroughly in their relationship to bipolar disorder are the autoimmune thyroid diseases and multiple sclerosis (MS). The relationship between affective psychosis and thyroid disorder was noticed as early as 1888 (2). The metabolic slowing related to thyroid hormone deficiency could possibly be related to symptoms of depression (e.g., 3), but there is also a consistent association with psychosis, including a particular association, not always confirmed, with rapid-cycling bipolar disorder (4–6). The serotonin and thyroid systems are connected (7), and there are putative but unproven associations between antithyroid antibodies and mood disorders (8,9). The effect of lithium on thyroid function was noticed years ago (10), but the observation may result in part from a constitutional factor which predisposes to bipolar disorder (11,12).

The relationship of affective disorders to MS has been studied for decades (e.g., 13). To some extent, MS presents with affective symptoms, but there is comorbidity of the diagnosed cases as well as symptom overlap (14,15). Three small family studies suggest a genetic relationship between the two disorders (16–18). As with bipolar disorder, the relationship is clouded by the possibility that treatment for MS is connected to affective state (19).

The literature on autoimmune diseases and schizophrenia has been reviewed previously (1). It is particularly rich for celiac disease (20), autoimmune thyroid disease (21), and rheumatoid arthritis (22). In our earlier work we showed that thyrotoxicosis, celiac disease, autoimmune hemolytic anemia, and Sjogren's syndrome were more common in the family members of persons diagnosed with schizophrenia, prior to the diagnosis of schizophrenia in the case, and were more common in the cases of schizophrenia themselves as well, prior to the diagnosis of schizophrenia (1). A later study from Sweden showed that the risk of both schizophrenia and non-affective psychosis was raised by about 50% after the diagnosis of celiac disease, although the relationship was statistically significant only for the broader category of non-affective psychosis (23).

Materials and methods

The Danish Civil Registration System (CRS) was established in 1968 to register all people living in Denmark (24). Among many other variables, it includes an individual's CRS number, gender, date of birth, vital status, and CRS number of parents. The CRS number is used as a personal identifier in all national registers, enabling accurate linkage between registers. Our study population included all persons born in Denmark between 1 January 1945 and 31 December 1996 who were alive at their 10th birthday or 1 January 1977, whichever came last (3.57 million people).

The study population was linked to the Danish Psychiatric Central Register (25), which was computerized in 1969, to obtain information on date of first diagnosis of bipolar disorder, schizophrenia, or non-affective psychosis. The Danish Psychiatric Central Register contains data on all admissions to Danish psychiatric inpatient facilities and, from 1995 on, information on outpatient visits to psychiatric departments. From 1969 to 1993, the diagnostic system used was the Danish modification of the International Classification of Diseases, 8th revision (ICD-8) (26), and from 1994 on, the ICD, 10th revision (ICD-10) (27). Cohort members were classified with bipolar disorder (ICD-8: 296.19, 296.39; ICD-10: F30-F31), schizophrenia (ICD-8: 295 except 295.79; ICD-10: F20), or non-affective psychosis, including schizophrenia, schizophrenia-related personality disorders, schizoaffective disorder, delusional disorder, and schizophreniform disorder (ICD-8: 295,

297, 298.39, 301.83; ICD-10: F20-F29) if the individual had been admitted to a psychiatric hospital or been in outpatient care with that diagnosis. Date of onset was defined as first day of first contact (in- or outpatient) with each of these three categories of diagnosis. Individuals with multiple diagnoses on successive contacts could enter the cohorts for each of the three categories of diagnosis.

There were 9,920 cases of bipolar disorder, of whom 56% were females; 15% were aged 14–24, 55% were aged 25–44, and 29% aged over 45. There were 20,317 cases of schizophrenia, of whom 38% were females: 34% were aged 14–24, 57% were aged 25–44, and 9% over 45. There were 39,076 cases of non-affective psychosis, of whom 45% were females: 33% were aged 14–24, 56% were aged 25–44, and 11% were over 45.

Information about autoimmune diseases in cohort members and their mothers, fathers, and siblings was obtained from the Danish National Hospital Register, which contains information on all discharges from Danish hospitals since 1977; outpatients have been included in the register since 1995 (28). Diagnostic information in the National Hospital Register is based on the Danish version of the ICD-8 from 1977 to 1993, and the ICD-10 from 1994 to 2006. All treatments in Danish hospitals are free of charge for all residents. Cohort members and their parents and siblings were classified as having a positive history of one or more of 30 autoimmune diseases (Table 1) if they had been admitted or had been in outpatient care with the relevant diagnosis. The time of onset was defined as the first day of the first contact with the autoimmune diagnosis in question. Each person can have a history of more than one autoimmune disease. In these analyses some of the diagnostic categories have been narrowed compared to our previous work, focusing as tightly as possible on the autoimmune categories [compare Table 1 in this paper to Table 1 in Eaton et al. (1)]. The category of *'any of 30 autoimmune diseases'* is included to help judge whether the pattern is general or specific to one or a limited number of autoimmune diseases.

A total of 3,571,730 persons were followed from their 10th birthday or 1 January 1977 (whichever came last) until onset of the disorders of interest, death, emigration from Denmark, or 31 December 2006 (whichever came first), amounting to 77 million person-years from 1977 to 2006. However, when type 1 diabetes was the exposure, the follow-up started at the 10th birthday or 1 January 1986, as the diagnosis of type 1 diabetes was not introduced as a separate diagnosis until 1986. In the analysis of family history presented in Table 1, the cohort is limited to 2,901,158 persons born in Denmark between 1945 and 1996, with known identity of the mother and followed during 58 million person-years from 1977 to 2006. Persons born before 1968 have a link to their mother if they were residing on the same address when the CRS started in 1968 (24).

The incidence rate ratio (in this paper referred to as *relative risk*) was estimated by log-linear Poisson regression (29) with the GENMOD procedure in SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA). All relative risks were adjusted for calendar year, age, and interaction with sex. In models with family history of autoimmune diseases as the exposure of interest, the age of the mother and father at the time of the child's birth was also adjusted. These factors are adjusted in the models presented because they may possibly affect the risk for schizophrenia and other psychoses and be associated with the occurrence of autoimmune diseases. Age, calendar year, and history of autoimmune diseases in parents or siblings were also treated as time-dependent variables, whereas all other variables (sex and mother's and father's age at the time of the child's birth) were treated as variables independent of time. Calendar year was categorized in one-year periods. Age, as well as age of the parent at the child's birth, was categorized to ensure adequate numbers of cases in the separate categories: in one category for the range 10–14 years, in one-year intervals from the 15th to the 20th birthday, in two-year intervals from the 20th to the 30th birthday, and in five-year

intervals thereafter. Maternal age at the time of the child's birth was categorized with the following cutoff points: 12, 25, 30, 35, and 40 years; paternal age had cutoff points of 12, 25, 30, 35, 40, 45, or unknown father. The p-values and 95% confidence intervals (CI) were based on likelihood ratio tests (30). The parameters shown are presented in bold when the 95% CI does not include 1.0. The adjusted score test (31) suggested that the regression models were not subject to overdispersion.

For study of the relative risk for the psychiatric disorders associated with prior autoimmune diseases in the individual, time since an autoimmune disease was included as a time-dependent variable (30), which during follow-up was measured as the number of years since first contact with a diagnosis of the autoimmune disease. This variable was collapsed into two categories: 0–4 complete years (*concurrent*) and ≥ 5 complete years (*delayed*). These categories are arbitrary but yield a reasonable distribution of cases in each category. Since registration started in 1977, persons born between 1945 and 1967 could have had an autoimmune diagnosis before 1977, and for these persons our registered number of years since onset is biased toward being too small.

The study was approved by the Danish Data Protection Agency.

Results

The effects of autoimmune diseases in parents and siblings were studied in the population of persons with known identity of the mother: that is, a cohort of 2,901,158 persons born in Denmark between 1945 and 1996 were followed during 58 million person-years from 1977 to 2006. There are statistically significant and positive associations for the familial relationships for type 1 diabetes, MS, iridocyclitis, autoimmune hepatitis, psoriasis, dermatopolymyositis, and Sjogren's syndrome to schizophrenia (Table 1, with autoimmune diseases presented in the order of occurrence in the ICD). The large sample size facilitates even a moderately small relative risk to be statistically significant; e.g., the largest relative risk is only 2.1 for dermatopolymyositis. For bipolar disorder only pernicious anemia has a significant raised risk: 1.7. Even with this many years of follow-up, the relative risks are based on small numbers. For example, there were 23 cases of bipolar disorder with family history of pernicious anemia, and 6,447 cases of bipolar disorder with no history of pernicious anemia (relative risk of 1.7); 475 cases of schizophrenia with family history of type 1 diabetes, and 16,247 cases of schizophrenia without a history of type 1 diabetes (relative risk of 1.3). There is no increase in risk of bipolar disorder associated with autoimmune diseases in general (relative risk of 1.0), and a slight but statistically significant increase in risk of schizophrenia associated with autoimmune diseases in general (relative risk of 1.2).

The effect of a history of an autoimmune disease in an individual was studied in the population of persons born in Denmark between 1945 and 1996 (3,571,730 persons) who were followed during 77 million person-years from 1977 to 2006. One possible explanation for co-occurrence of the psychiatric with the autoimmune diseases is that the diagnosis of an autoimmune disease may lead to diagnosis of the psychiatric disorder through increased medical attention. In this situation, the psychiatric diagnosis would closely follow the autoimmune diagnosis in time. It is also possible that the psychiatric and autoimmune diseases share an etiology which leads to diagnosis of both disorders close in time, and there might be differential delays in diagnosis which might lead one or the other disorder to be antecedent, giving a possibly false impression of cause. The ascertainment bias is a less likely explanation for a comorbidity in which the autoimmune disease precedes the psychiatric disorder by several years. For that reason we divide the effect of history of each autoimmune disease into whatever effect might exist in the first 4 complete years (labelled

concurrent in Table 2) and the effect which might exist after ≥ 5 years following onset of the autoimmune disease (labelled *delayed* in Table 2).

As suggested in the literature, thyrotoxicosis and MS predict bipolar disorder, but the effect is only significant during the first 4 complete years after onset of the autoimmune disease. This pattern of raised risk for bipolar disorder only in the concurrent period exists also for ulcerative colitis, psoriasis, and rheumatoid arthritis. The pattern of risk of bipolar disorder is raised also for individuals who have had Guillain-Barré syndrome or autoimmune hepatitis at least five years prior to onset, but there are not enough cases to determine whether the risk might be raised in the concurrent period as well. For those with Crohn's disease, the risk of bipolar disorder is raised in both the concurrent and delayed time periods. There is statistically significant increased risk for both the concurrent and delayed periods for the occurrence of any of the autoimmune diseases (relative risks of 1.7 for concurrent and 1.2 for delayed; see Table 2).

There is a raised risk of concurrent or delayed diagnosis for schizophrenia for five autoimmune diseases for which there is also a familial association—type 1 diabetes, iridocyclitis, autoimmune hepatitis, psoriasis, and Sjogren's syndrome—suggesting a shared genetic etiology for these diseases with schizophrenia. For thyrotoxicosis, there appears to be a shared etiology not linked to family background. There is a positive association of Crohn's disease and Guillain-Barré syndrome and schizophrenia, with a delay of more than five years in the two diagnoses. The overall effect of autoimmune diseases in general is a raised risk of 1.4 for concurrent and 1.3 for delayed periods (Table 2).

Results for non-affective psychosis (Table 3) closely parallel those for schizophrenia (Tables 1 and 2). For all disorders with sufficient sample size to analyze, the relationship of the autoimmune disease to schizophrenia in the parents or siblings is similar in strength and direction to that for the more inclusive category of non-affective psychosis. For all but one of the seven (autoimmune hepatitis), the effect is equal to or stronger in the group with schizophrenia than in the more inclusive group with non-affective psychosis. Similarly for comorbidity of autoimmune diseases in the cases (right column of Table 3), the pattern of coefficients is very similar to that in Table 2. The exception is scleroderma, which did not have a statistically significant relationship to schizophrenia by itself, but which predicted onset of non-affective psychosis soon after the autoimmune disease (relative risk of 2.9). The results for familial relationship of any autoimmune disease and non-affective psychosis are slightly weaker than for schizophrenia (relative risk of 1.1) but there is a slightly stronger increase in risk when the individual has a history of any autoimmune diseases (relative risks of 1.5 and 1.4 for concurrent and delayed periods, respectively).

Discussion

These results continue to suggest a general relationship between autoimmune diseases and schizophrenia. The contrast with bipolar disorder is striking in that, with the exception of a relative risk of 1.7 for pernicious anemia (Table 1), there are no significant familial associations at all with autoimmune diseases, and for any autoimmune disease, no increase in risk at all. The contrast with schizophrenia strengthens the credibility of the findings for schizophrenia, as well as reinforcing the nosologic distinction between the two disorders. The results also are consistent with prior research in failing to demonstrate substantially different risk patterns between schizophrenia and non-affective psychosis.

These new analyses replicate our earlier work (1) in finding statistically significant and positive associations for the familial relationships for type 1 diabetes, psoriasis, dermatopolymyositis, and Sjogren's syndrome to schizophrenia. The earlier positive familial

associations for pernicious anemia, autoimmune hemolytic anemia, thyrotoxicosis, thyroiditis, celiac disease, and rheumatoid arthritis are in the same positive direction but not statistically significant, possibly because of the more precise categorizations of the autoimmune diseases. For MS, iridocyclitis, and autoimmune hepatitis, there are significant familial associations not found in the earlier study, possibly due to the larger sample in the current work. The replication is only partly independent since nearly half of the cases of schizophrenia in this study were also included in the previous study. These results also replicate prior work in showing enhanced relative risks for schizophrenia in persons with a prior diagnosis of thyrotoxicosis, autoimmune hepatitis, and celiac disease (although the relative risk of 1.8 for celiac disease is not statistically significant in this analysis). For thyrotoxicosis and celiac disease there is partial confirmation in the relationships with concurrent autoimmune diagnosis and non-affective psychosis.

The positive association of bipolar disorder with ulcerative colitis, psoriasis, and rheumatoid arthritis are the strongest candidates for explanation by ascertainment bias, since there is no literature suggesting common etiology and since the association is only through diagnoses which occur in close temporal association, but this noncausal explanation is vitiated by the association with Crohn's disease, which is moderately strong and significant in both the concurrent and delayed time periods. The delayed association with Guillain-Barré syndrome is puzzling, as it is for schizophrenia.

The strongest results in the analyses of comorbidities in cases of both schizophrenia and bipolar disorder are for Guillain-Barré syndrome and autoimmune hepatitis. Autoimmune hepatitis may represent a misdiagnosis of the autoimmune nature of the hepatitis connected to intravenous drug use in cases. The results for Guillain-Barré syndrome suggest an etiologic pathway related to infectious agents (32–34) which have been linked in prior research to schizophrenia (35).

There are important limitations to the methods. The diagnosis is that of the treating clinician, not a strict research diagnosis. It is possible that the diagnostic practices in Denmark are different from those in other countries, which might limit the generalizability of the results; however, any differences would also have to apply differentially to those with and without psychoses in order to affect the conclusions. It is impossible to rule out the bias that might arise from increased medical attention due to one disorder leading to diagnosis of the comorbid disorder. Even with this large population, the diseases are rare enough that it is difficult to analyze data according to sex or by age of onset. The results on familial association are compromised because the parents and siblings may not have lived through the age of onset for the autoimmune diseases.

The pattern of results is strongest, and includes the most prior autoimmune diseases, for the situation in which the autoimmune diagnosis occurred within the five years prior to diagnosis of the three categories of psychosis (*concurrent*). Here the contrast between schizophrenia and bipolar disorder is not strong (36). For schizophrenia, there were 11 diseases in which the relative risk could be ascertained, and in 9 of these 10 the relative risk was 1.0 or larger (Table 2); for bipolar disorder: 8/8 with relative risks 1.0 or larger (Table 2); and for non-affective psychosis: 16 relative risks of 1.0 or larger out of 17 diseases in which it could be estimated (Table 3). As noted above, the high number of patients diagnosed with psychoses could in part be due to the fact that they are already in contact with medical services. Also, we cannot be sure that the time of first psychosis diagnosis or the time of the first autoimmune diagnosis is close to the onset of the respective disorders, so that the temporal order and relationship of the disorders is uncertain. However, the results suggest the possibility that the onset of psychosis—including bipolar disorder—in some cases arises in connection with a contemporary inflammatory process associated with these

autoimmune diseases. Infection has been considered as a potential factor in the neurodevelopmental process for decades (37,38). More recently, there has been interest in infection, inflammation, and autoimmune processes as part of the process initiating or being involved in episodes in adults (39–41). Also of possible relevance to both the individual and familial association between psychosis and autoimmune diseases, genetic markers in the HLA region have repeatedly been associated with schizophrenia in linkage (42,43) and association studies (44–46). Some of the identical immune-related markers in schizophrenia (47) have also been found in bipolar disorder (48). This has led some to recommend future research on monitoring of immune markers during the course of illness (49), and we further surmise that an autoimmune process may operate prior to onset of psychosis.

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Table 1

Adjusted relative risks of bipolar disorder and schizophrenia according to history of 30 autoimmune diseases in parents or siblings

			Bipolar disorder (n = 6,470)		Schizophrenia (n = 16,722)	
Autoimmune disease in parent or sibling	**ICD-8**	**ICD-10**	**No. cases**	**Relative risk[a]**	**No. cases**	**Relative risk[a]**
Pernicious anemia	281.0	D51.0	23	**1.7**	26	1.1
Autoimmune hemolytic anemia	283.90–91	D59.1	1	–	9	1.6
Idiopathic thrombocytopenic purpura	446.49	D69.3	7	1.3	8	0.8
Thyrotoxicosis	242.00	E05.0	82	1.1	142	1.1
Autoimmune thyroiditis	245.03	E06.3	12	1.4	23	1.3
Type 1 diabetes	249	E10	203	1.0	475	**1.3**
Primary adrenocortical insufficiency	255.1	E27.1	7	1.5	14	1.4
Multiple sclerosis	340	G35	50	1.0	141	**1.3**
Guillain-Barré syndrome	354	G61.0	19	0.9	45	1.1
Iridocyclitis	364	H20	22	0.7	89	**1.4**
Crohn’s disease	563.01	K50	45	1.1	81	0.9
Ulcerative colitis	563.19	K51	86	1.0	208	1.2
Autoimmune hepatitis	571.93	K73	13	1.0	45	**1.7**
Primary biliary cirrhosis	571.90	K74.3	4	–	9	1.2
Celiac disease	269.00	K90.0	12	1.4	22	1.2
Pemphigus	694 (×694.05)	L10	0	–	6	2.2
Pemphigoid	694.05	L12	3	–	6	1.7
Psoriasis vulgaris	696.09–10, 696.19	L40 (×L40.4)	65	1.0	158	**1.2**
Alopecia areata	704.00	L63	3	–	14	1.6
Vitiligo	709.01	L80.9	4	–	4	–
Seropositive rheumatoid arthritis	712.19, 712.39, 712.59	M05–M06	135	1.0	273	1.1
Juvenile arthritis	712.09	M08	11	1.7	24	1.3
Wegener’s granulomatosis	446.29	M31.3	5	1.3	9	1.4
Dermatopolymyositis	716	M33	5	1.0	20	**2.1**
Polymyalgia rheumatica	446.30–31, 446.39	M31.5–6, M35.3	58	1.0	61	0.8
Myasthenia gravis	733.09	G70.0	8	1.7	10	1.1
Scleroderma	734.0	M34	5	0.7	8	0.6

			Bipolar disorder (n = 6,470)		Schizophrenia (n = 16,722)	
Autoimmune disease in parent or sibling	**ICD-8**	**ICD-10**	**No. cases**	**Relative risk[a]**	**No. cases**	**Relative risk[a]**
Systemic lupus erythematosis	734.19	M32.1, M32.9	15	1.1	29	1.0
Sjogren's syndrome	734.90	M35.0	12	0.9	33	**1.5**
Ankylosing spondylitis	712.49	M45.9	16	1.0	36	1.1
Any of 30 autoimmune diseases	–	–	796	1.0	1,205	**1.2**

ICD-8 = International Classification of Diseases, 8th revision; ICD-10 = ICD, 10th revision.

[a]Relative risks were adjusted for age and its interaction with sex, calendar year, and ages of the mother and father at the time of the child's birth. Persons with no parent or sibling having a diagnosis of the autoimmune disease in question were chosen as reference category. **Boldface** indicates that the 95% confidence interval did not include 1.0. Relative risks were not estimated when there were < 5 exposed cases.

Table 2

Adjusted relative risks of bipolar disorder and schizophrenia according to time since first contact with each autoimmune disease

	Bipolar disorder (n = 9,920)			Schizophrenia (n = 20,317)		
		Relative risk[a]			Relative risk[a]	
Autoimmune disease[b]	**No. cases[c]**	**Concurrent[d]**	**Delayed[e]**	**No. cases[c]**	**Concurrent[d]**	**Delayed[e]**
Thyrotoxicosis	28/16	**1.9**	1.5	28/18	**1.9**	**2.1**
Thyroiditis	1/0	–	–	3/1	–	–
Type 1 diabetes	28/39	1.3	1.1	59/49	**1.7**	1.0
Primary adrenocortical insufficiency	2/2	–	–	1/2	–	–
Multiple sclerosis	18/12	**2.0**	1.0	11/8	1.0	0.8
Guillain-Barré syndrome	3/8	–	**2.4**	4/10	–	**2.2**
Iridocyclitis	11/11	1.8	1.8	17/10	**1.8**	1.3
Crohn's disease	16/22	**1.9**	**1.8**	11/28	0.7	**1.7**
Ulcerative colitis	31/23	**1.8**	1.0	28/35	1.0	1.2
Autoimmune hepatitis	0/7	–	**3.0**	12/15	**5.4**	**5.6**
Celiac disease	3/0	–	–	4/5	–	1.8
Psoriasis vulgaris	22/13	**2.3**	0.9	28/23	**2.0**	1.4
Seropositive rheumatoid arthritis	26/13	**1.8**	0.8	12/12	0.8	0.8
Juvenile arthritis	1/3	–	–	2/12	–	1.4
Polymyalgia rheumatica	4/1	–	–	0/1	–	–
Scleroderma	0/1	–	–	1/2	–	–
Systemic lupus erythematosis	3/4	–	–	5/2	2.0	–
Sjogren's syndrome	2/2	–	–	6/1	**3.8**	–
Ankylosing spondylitis	1/4	–	–	4/4	–	–
Any of 30 autoimmune diseases	182/176	**1.7**	**1.2**	228/238	**1.4**	**1.3**

[a] Relative risks were adjusted for age and its interaction with sex and calendar year. Persons without a history of the autoimmune disease in question were chosen as reference category. **Boldface** indicates that the 95% confidence interval did not include 1.0.

[b] Only autoimmune diseases with ≥ 5 cases of bipolar disorder or ≥ 5 cases of non-affective psychosis in either the period of 4 complete years after diagnosis of the autoimmune disease (concurrent) or in the subsequent period (delayed) after onset of the autoimmune disease were included.

[c] Number of cases in the concurrent period/number of cases in the delayed period.

[d] Relative risk the first 4 complete years following date of onset of the autoimmune disease.

[e] Relative risk ≥ 5 years after date of onset of the autoimmune disease.

Table 3

Adjusted relative risks of non-affective psychosis according to history of autoimmune diseases in parents or siblings, and according to time since first diagnosis of each autoimmune disease in the probands

	Autoimmune disease in siblings or parents[a,b]		Time since autoimmune disease in proband[b,c]		
Autoimmune disease	**No. cases**	**Relative risk**	**No. cases[d]**	**Concurrent[e]**	**Delayed[f]**
Pernicious anemia	48	1.1	3/1	–	–
Autoimmune hemolytic anemia	10	1.0	2/2	–	–
Idiopathic thrombocytopenic purpura	15	0.8	4/3	–	–
Thyrotoxicosis	266	1.1	59/26	**2.1**	1.5
Thyroiditis	42	1.4	7/4	1.8	–
Type 1 diabetes	785	**1.2**	109/104	**1.7**	1.2
Primary adrenocortical insufficiency	25	1.4	1/5	–	1.9
Multiple sclerosis	226	**1.2**	35/28	**1.6**	1.3
Guillain-Barré syndrome	96	**1.3**	10/11	**2.3**	1.3
Iridocyclitis	153	**1.3**	25/18	1.5	1.2
Crohn's disease	159	1.0	29/46	1.0	**1.5**
Ulcerative colitis	357	1.1	68/64	1.3	1.1
Autoimmune hepatitis	83	**1.8**	24/29	**5.7**	**5.6**
Primary biliary cirrhosis	20	1.4	0/1	–	–
Celiac disease	39	1.2	12/7	**2.8**	1.3
Pemphigus	11	**2.2**	0/1	–	–
Pemphigoid	10	1.6	1/0	–	–
Psoriasis vulgaris	274	**1.2**	46/50	**1.8**	**1.6**
Alopecia areata	18	1.1	4/3	–	–
Vitiligo	9	0.8	4/2	–	–
Seropositive rheumatoid arthritis	472	1.0	28/35	0.9	1.2
Juvenile arthritis	43	1.2	4/19	–	1.2
Wegener's granulomatosis	15	1.3	4/2	–	–
Dermatopolymyositis	27	**1.6**	1/2	–	–
Polymyalgia rheumatica	129	1.0	5/2	2.6	–
Myasthenia gravis	16	1.0	4/2	–	–

	Autoimmune disease in siblings or parents[a,b]		Time since autoimmune disease in proband[b,c]		
Autoimmune disease	**No. cases**	**Relative risk**	**No. cases[d]**	**Concurrent[e]**	**Delayed[f]**
Scleroderma	22	0.9	6/3	**2.9**	–
Systemic lupus erythematosis	54	1.1	9/11	1.8	1.7
Sjogren's syndrome	51	1.3	8/2	**2.5**	–
Ankylosing spondylitis	61	1.0	9/13	1.1	1.5
Any of 30 autoimmune diseases	2,097	**1.1**	467/479	**1.5**	**1.4**

The number of persons with non-affective psychosis was 30,561 among 2,901,158 population in the two left columns on association in the family, in which the link to the mother was possible, and 39,067 among 3,571,730 population in the three rightmost columns on association in the probands.

[a] Relative risks were adjusted for age and its interaction with sex, calendar year, and ages of the mother and father at the time of the child's birth. Persons with no parent or sibling having a diagnosis of the autoimmune disease in question were chosen as reference category.

[b] Relative risks whose 95% confidence interval excludes 1.0 are in **boldface**. Relative risks were not estimated when there were < 5 exposed cases.

[c] Relative risks were adjusted for age and its interaction with sex and calendar year. Persons without a history of the autoimmune disease in question were chosen as reference category.

[d] Number of concurrent cases/number of delayed cases.

[e] Relative risk in the first 4 complete years following onset of the autoimmune disease.

[f] Relative risk ≥ 5 years after onset of the autoimmune disease.