# Subsequent Risks of Parkinson Disease in Patients with Autoimmune and Related Disorders: A Nationwide Epidemiological Study from Sweden.

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# SUBSEQUENT RISKS OF PARKINSON DISEASE IN PATIENTS WITH AUTOIMMUNE AND RELATED DISORDERS: A NATION-WIDE EPIDEMIOLOGICAL STUDY FROM SWEDEN

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**ABSTRACT**

OBJECTIVES: To investigate associations between autoimmune disorders and Parkinson disease (PD), and to study whether the risk is associated with follow-up time and age.

METHODS: Standardized incidence ratios (SIRs) were calculated for PD in patients with autoimmune disorders by comparing them to subjects without autoimmune disorders.

RESULTS: Among 310 522 patients with a total of 33 conditions of autoimmune disorders, 932 patients developed subsequent PD, giving an overall SIR of 1.33 and 1.19 for PD diagnosed later than 1 year after follow-up. Six types of autoimmune disorders showed an increased risk. These conditions included: amyotrophic lateral sclerosis, Graves/hyperthyroidism, hashimoto/hypothyroidism, multiple sclerosis, pernicious anemia, and polymyalgia rheumatica. The risks depended on the age at hospitalization for PD.

CONCLUSIONS: A 33% overall excess risk of PD was noted among patients with an autoimmune disorder, the risk was increased during the first ten years of follow-up after hospitalization of autoimmune disorders.

Key words: autoimmune disorders, subsequent PD, population-based, follow-up study

## INTRODUCTION

Parkinson disease (PD) is the most common neurodegenerative condition affecting movement in later life. The etiology of PD is still largely unknown. Genetic susceptibility has been proven to play a role in the development of PD [1]. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis [2]. Psychiatric disorders [3], socioeconomic status and occupational exposure [4] have been reported in association with PD. The association between PD and autoimmune disorders has been examined in a few previous studies based on the hypothesis that neurodegeneration, mitochondrial dysfunction and oxidative stress, may act in part by causing an accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons [5-8]. For example, amyotrophic lateral sclerosis [6], multiple sclerosis [7], and pernicious anemia [9] have been associated with PD. A population-based case-control study from Denmark observed, however, no overall association between a diagnosis of autoimmune disease and risk for subsequent PD [10]. PD has also been suggested as an autoimmune disease because of signs of neuroinflammation and peripheral immune infiltration [11].

In the present study we used nation-wide Swedish data resources on 33 medically diagnosed types of autoimmune disorders and PD, to analyze risks of PD in patients with autoimmune disorders. There was also a specific aim to further analyze the association between follow-up time and age with PD. The present report is based on 310 000 patients with hospitalization for autoimmune disorders who were also diagnosed with PD.

## MATERIAL AND METHODS

Data used in this study were retrieved from the MigMed database [4, 12], located at the Center for Primary Health Care Research at the Lund University. We used the main diagnoses for autoimmune and related disorders recorded in the register. PD was defined according to the International Classification of Diseases (ICD) (7th, 8th, 9th and 10th revisions); codes included: ICD-7: code 350, ICD-8: code 342.0, ICD-9: code 332, and ICD-10: codes G20 and G21. Additional linkages were carried out to national census data to obtain individual socioeconomic status, occupation, geographical region of residence; the national Registry of Causes of Death (to identify date of death), and the Migration Registry (to identify date of emigration). All linkages were performed by the use of an individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for each person in order to provide anonymity.

*Individual-level variables*

Individual variables were gender, age, geographic region of residence, socioeconomic status, and comorbidities.

Gender: males or females.

Age was divided into 5-year categories, and the groups were merged as necessary.

Geographic region of residence was included as an individual variable to adjust for possible differences in hospital admissions for PD between different geographic regions in Sweden. It was categorised as 1) large city (city with a population of >200,000 (i.e., Stockholm, Gothenburg, or Malmo), 2) Southern Sweden (both rural and urban), and 3) Northern Sweden (both rural and urban). Sweden is divided into 25 counties. The border between Northern and Southern Sweden has traditionally been defined by the Dalälven River. Therefore, in the present study, all counties north of that river were defined as being part of Northern Sweden. All three of

Sweden's "large cities" are located south of the Dalälven River; they were excluded from the Southern Sweden category.

Occupation was used as a proxy for socioeconomic status. Occupational data were retrieved from national census records in the MigMed Database. We classified each individual's occupation into one of six categories: 1) farmer, 2) self-employed, 3) professional, 4) blue collar worker, 5) manual worker, and 6) other. Individuals without paid employment were included in the "other" category. For individuals aged <20 years, parental occupation was used.

Comorbidity was defined as the first diagnosis at follow up from 1964-2007: 1) Chronic obstructive pulmonary disease (COPD); ICD-7: 500, 501, 502, ICD-8: 490-493, ICD-9: 490-496, and ICD-10: J40-J49, and 2) Alcoholism and alcohol related liver disease; ICD-7: 307, 322, 581, ICD-8: 291,303,571, ICD-9: 291, 303, and ICD-10: F10 and K70.

*Predictor variable*

The predictor variable was hospitalisation for an autoimmune disorder according to ICD-7, ICD-8, ICD-9 and ICD-10 (supplementary Table 1).

Statistical analysis

Person-years were calculated from start of follow-up on 1 January 1964 until hospitalization for the last autoimmune disorder, death, emigration or closing date on 31 December 2007. Standardized incidence ratios (SIRs) were calculated as the ratio of observed (O) to expected (E) number of cases using the indirect standardisation method [13]. The expected numbers were calculated as the hospitalization rates for all individuals without a history of autoimmune and related disorders, and the rates were standardized by gender, age, period (5 years group), socioeconomic status, geographic region of residence, and comorbidities.

$$SIR = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*},$$

where $O = \sum o_j$ denotes the total observed number of cases in the study group; $E^*$ expected number) is calculated by applying stratum-specific standard incidence rates ($\lambda_j^*$) obtained from the reference group to the stratum-specific person-years ($n_j$) of risk for the study group; $o_j$ represents the observed cases that the cohort subjects contribute to the jth stratum; and J represents the strata defined by the cross-classification of the different adjustment variables; gender-, age-, time period-, socioeconomic status-, geographic region of residence, and comorbidities. Ninety-five percent confidence intervals (95% CI) were calculated assuming a Poisson distribution [13]. Follow-up time was divided in for periods, namely less than 1, 1 to 4, 5 to 9 and more 9 years, allowing the assessment of the effect of follow-up time.

Ethical considerations

The Ethic Committee at the Lund University, Sweden, approved this study.

**RESULTS**

The database covered the years 1964 to 2007 in the Swedish Hospital Discharge Register and included 310 522 cases of 33 types of autoimmune and related disorders (supplementary table 1). The largest diagnostic groups were rheumatoid arthritis 52 994 patients, Graves/hyperthyroidism 34 735 patients, and ulcerative colitis 27 881 patients.

During the study period, totally 26 791 individuals were admitted with a main diagnosis of PD (Table 1). Of these, 932 represented cases of PD who also had been admitted to hospital due to an autoimmune disorder. Age-specific incidence rates of PD are shown in Figure 1, for people who were hospitalized for first primary PD and the corresponding rates of subsequent PD in people who were hospitalized for autoimmune and related disorders. For all ages, the rate of PD was significantly higher among patients with autoimmune and related disorders than patients without a history of autoimmune and related disorders.

A total of 6 autoimmune disorders had increased risks for PD (Table 2); the largest increases were found for amyotrophic lateral sclerosis (3.77) and hashimoto/hypothyroidism (2.40). Many common autoimmune disorders, such as rheumatoid arthritis, Crohn disease, and ulcerative colitis were not at increased risk for PD. The overall risk of PD was 1.33. The overall risk was 1.19 and 1.06, respectively, when the follow-up was one ('All 1+') or five years ('All 5+') after hospitalization for autoimmune disorders. For some patients hospitalized for an autoimmune and related disorder and PD in the same year the risk was very high; data for 1+ for the whole period was calculated separately (data not shown). The high risks may be because of a concomitant diagnosis of PD and an autoimmune and related disorder. However, significant increases in SIRs were correlated for the whole period and the 1+ period for PD. The overall risks of PD decreased with follow-up time and significant risks were found during the initial 10 years period (data not shown). The highest SIR of 20.00 was noted for Reiter's disease for follow-up intervals of 1-4 years (data not shown). The overall increases of SIRs after 1+ were noted for amyotrophic lateral sclerosis (3.95), Graves/hyperthyroidism (1.42), hashimoto/hypothyroidism (1.93), and pernicious anemia (1.40). Multiple sclerosis and polymyalgia rheumatica showed increased risks when the follow-up time was 1-4 years (data not shown). The SIR for PD decreased when patients were diagnosed with Crohn's disease after 'All 1+' and 'All 5+'.

Table 3 shows the effect of age at hospitalization for PD. We only show follow-up data after one year after hospitalization for an autoimmune and related disorder. For all types, higher risks were observed for those hospitalized at a younger age. There were large differences in the trends for age at hospitalization of PD for amyotrophic lateral sclerosis, chronic rheumatic heart disease, Graves/hyperthyroidism, hashimoto/hypothyroidism, multiple sclerosis, and Wegener's granulomatosis. For these conditions, there was an increased risk of PD before the age of 65 years. For ankylosing spondylitis, there was an increased risk of PD between the ages of 75 to 79 years. Pernicious anemia had a significantly increased risk for PD in those hospitalized over 80 years of age. Rheumatoid arthritis showed a decreased risk of PD for hospitalization over 80 years.

## DISCUSSION

The main finding of this follow-up study is the strong association between PD and some types of autoimmune and related disorders after accounting for gender, age, period, socioeconomic status, geographic region of residence, and comorbidities. Overall, a 33% excess incidence of PD was noted, and the risk was still significantly increased comparing to the reference group (1.19) when excluding cases diagnosed during the first year of follow-up. The risk of PD was influenced according to age at hospitalization but whether the age effect implied and increased or decreased risk depended on the type of autoimmune and related disorder. After 'All 5+' periods, there was no overall association between a diagnosis of autoimmune disease and risk for subsequent PD (SIR=1.06, 95% CI 0.97-1.16). Our results are consistent with the previous population-based case-control study from Denmark (odds ratio 0.96, 95% CI 0.85-1.08) [10].

The highest risk for subsequent PD after an autoimmune related disorder was shown during the first year (Table 2). The likely explanation is that these diseases presented synchronously with each other, or, these diseases were diagnosed during the treatment, presenting a lead-time bias in the results. However, these early cases of PD were so few that the SIRs calculated for the whole follow-up period and for the whole period minus the first year (1+) were not essentially different. Moreover, the lead-time bias only shifts the diagnoses earlier and as such, the diagnostic accuracy is not compromised; even the early cases are “true” examples of PD. Complete hospital discharge information has been recorded in the Swedish Hospital Discharge Register, suggesting that diagnostic misclassification could not have been an issue in the current study.

For specific autoimmune and related conditions, some of the observed associations have been reported earlier and our study provided further evidence for these associations. Amyotrophic lateral sclerosis and multiple sclerosis have been associated with a high risk for PD. Previous studies have suggested that these three types of disorders have common pathogenic features, including inflammation, genetic mutation, inappropriate protein aggregates, and biochemical defects leading to apoptosis, such as oxidative stress and mitochondrial dysfunction [6]. The association of PD with hyperthyroidism/hypothyriodism has been suggested to be due to thyroid dysfunction [5, 14].

Polymyalgia rheumatica is a chronic autoimmune inflammatory rheumatic disorder that typically affects elderly people, characterized by inflammatory pain and stiffness of the shoulder and/or pelvic girdles. Polymyalgia rheumatica occurs in an association with temporal arteritis and it is known to also occur in patients with other rheumatologic diseases such as rheumatoid arthritis

and systemic lupus erythematosus. Two cases of patients with polymyalgia rheumatica have been reported presenting a form of akinetic-rigid parkinsonism after corticosteroid therapy [15].

Ankylosing spondylitis is a systemic rheumatic disease. Existing evidence suggests that there is a genetic predisposition to ankylosing spondylitis. Genetic research shows that a specific human leukocyte antigen (HLA) tissue type known as HLA-B27 occurs in approximately 90–95% of individuals with ankylosning spondylitis [16, 17]. Reiter's disease, also called reactive arthritis, is an autoimmune disorder with a most common type of inflammatory polyarthritis in young men. The cause of the disease is unknown. However, as 75% to 85% of patients with Reiter's disease test positive for HLA-B27, genetic susceptibility is likely [18]. In our study, Reiter's disease was associated with the highest risk of PD. There was also an increased risk of PD among patients with ankylosing spondylitis during follow-up time of 1-4 years. To our knowledge this is the first study to report an increased risk of PD among patients with ankylosing spondylitis and Reiter's disease. However, only a few cases were observed.

PD risks depended on the age at last hospitalization but the trends varied somewhat according to autoimmune and related disorder types. The SIRs declined by age at hospitalization. When the hospitalization took place before the age 65 years, the SIR was particularly high, i.e. 9.68 for amyotrophic lateral sclerosis, 4.92 for multiple sclerosis, 3.89 for hashimoto/hypothyroidism, 4.00 for Wegener granulomatosis, and 1.72 for Graves/hyperthyroidism. It should be recommended that patients diagnosed before the age 65 years should undergo medical surveillance for early detection of autoimmune and related disorders.

The present study has some limitations. For example, we had no data on most individual risk factors for hospitalization for PD. In a register that includes an entire population, it is not feasible to include individual data on smoking, drinking and other individual risk factors. However, we did adjust for socioeconomic status and COPD, which are associated with factors such as smoking. Adjustment was also done for comorbidities of alcoholism and alcohol related liver disease.

Moreover, we were unable to test for validity of the PD diagnoses as our data were based on the entire population. However, we only used main diagnoses for PD recorded in the hospital registers, i.e., all patients were hospitalized mainly for PD, which increases the possibility that the diagnoses for PD are valid. In addition, we had no access to pharmacy databases or outpatient records. It is possible that older persons or those with more severe PD were more likely to be admitted to the hospital. For example, PD patients are often hospitalized due to acute events, such as vascular events, falls and infections, or need for treatment adjustment, which tend to occur at a relatively late stage. The use of hospitalizations to calculate the PD incidence in a chronic disorder could therefore have led to an underestimation of the actual incidence of the disease.

Our data gave us the opportunity to perform a large-scale follow-up study of the association between 33 subtypes of autoimmune and related disorders and PD. In addition, the availability of hospital data in the entire population eliminated potential recall bias. The unique Swedish Population Registers are highly complete; very little data is missing. For example, information regarding occupational status was almost 100% complete (99.2%). Furthermore, use of the national civic registration number in the database (removed and replaced with a serial number for the purpose of anonymity) made it possible to track each individual in different registers, e.g. the

migrant register, which allowed calculation of exact risk time. Furthermore, we were able to account for the influence of geographical region, so that differing regional practice in hospitalization for PD and autoimmune and related disorders was taken into consideration.

Hospitalizations for PD and other nervous system disorders normally require a doctor's referral from the primary care service. Thus each hospitalized patient is seen by at least two medical doctors. The one in the hospital is likely to be a neurologist. Thus, diagnostic accuracy is probably high for hospitalized PD patients. With respect to autoimmune and related disorders, the overall diagnostic validity of the Swedish Inpatient Register is around 90% [19], and validations of the discharge diagnosis of, for example, Crohn's disease and ulcerative colitis indicate an overall validity close to 96% for these diagnoses [20].

In summary, the follow-up of patients with autoimmune and related disorders showed an increased risk of subsequent PD, which calls for continuous follow-up of autoimmune and related disorder patients with individual information on the treatment.

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**DECLARATION OF INTEREST**

There are no conflicts of interest.

**Figure legends**

Figure 1. Age-specific hospitalizations of first primary Parkinson disease and of subsequent Parkinson disease after autoimmune disorders

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**Table 1. Number of cases of Parkinson diseases and subsequent Parkinson disease of autoimmune disease patients**

| | All Parkinson disease | | Subsequent Parkinson disease of autoimmune disease patients | | Parkinson disease patients without autoimmune disease | |
|---|---|---|---|---|---|---|
| Characteristics | No. | % | No. | % | No. | % |
| **Gender** | | | | | | |
| Males | 14986 | 55.9 | 421 | 45.2 | 14565 | 56.3 |
| Females | 11805 | 44.1 | 511 | 54.8 | 11294 | 43.7 |
| **Age at diagnosis (yrs)** | | | | | | |
| <50 | 727 | 2.7 | 12 | 1.3 | 715 | 2.8 |
| 50-59 | 1756 | 6.6 | 45 | 4.8 | 1711 | 6.6 |
| 60-69 | 5390 | 20.1 | 152 | 16.3 | 5238 | 20.3 |
| 70-79 | 12088 | 45.1 | 453 | 48.6 | 11635 | 45.0 |
| >=80 | 6830 | 25.5 | 270 | 29.0 | 6560 | 25.4 |
| **Period (yrs)** | | | | | | |
| 1964-73 | 1271 | 4.7 | 17 | 1.8 | 1254 | 4.8 |
| 1974-83 | 5187 | 19.4 | 121 | 13.0 | 5066 | 19.6 |
| 1984-93 | 9636 | 36.0 | 364 | 39.1 | 9272 | 35.9 |
| 1994-03 | 7688 | 28.7 | 323 | 34.7 | 7365 | 28.5 |
| 2004-07 | 3009 | 11.2 | 107 | 11.5 | 2902 | 11.2 |
| **Socioeconomic status** | | | | | | |
| Farmers | 2841 | 10.6 | 106 | 11.4 | 2735 | 10.6 |
| Self-employed | 2070 | 7.7 | 68 | 7.3 | 2002 | 7.7 |
| Professionals | 1888 | 7.0 | 58 | 6.2 | 1830 | 7.1 |
| White collar workers | 7582 | 28.3 | 263 | 28.2 | 7319 | 28.3 |
| Manual workers | 11458 | 42.8 | 404 | 43.3 | 11054 | 42.7 |
| Others | 952 | 3.6 | 33 | 3.5 | 919 | 3.6 |
| **Region of residence** | | | | | | |
| Big cities | 9116 | 34.0 | 315 | 33.8 | 8801 | 34.0 |
| Northern Sweden | 5120 | 19.1 | 177 | 19.0 | 4943 | 19.1 |
| Southern Sweden | 12555 | 46.9 | 440 | 47.2 | 12115 | 46.9 |
| **Hospitalization for obstructive pulmonary disease** | | | | | | |
| Yes | 921 | 3.4 | 58 | 6.2 | 863 | 3.3 |
| No | 25870 | 96.6 | 874 | 93.8 | 24996 | 96.7 |
| **Hospitalization for alcoholism and alcohol related liver disease** | | | | | | |
| Yes | 410 | 1.5 | 21 | 2.3 | 389 | 1.5 |
| No | 26381 | 98.5 | 911 | 97.7 | 25470 | 98.5 |
| All | 26791 | 100.0 | 932 | 100.0 | 25859 | 100.0 |

**Table 2. Standardized incidence ratio for subsequent Parkinson disease of patients with autoimmune disorders.**

| | Follow-up interval (yrs) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | | | | All 1+ | | | | All 5+ | | | |
| Autoimmune condition | O | SIR | 95% CI | | O | SIR | 95% CI | | O | SIR | 95% CI | |
| Addison disease | 1 | 0.45 | 0.00 | 2.59 | 0 | | | | 0 | | | |
| Amyotrophic lateral sclerosis | 19 | **3.77** | **2.27** | **5.90** | 15 | **3.95** | **2.20** | **6.53** | 8 | **3.62** | **1.55** | **7.17** |
| Ankylosing spondylitis | 14 | 1.51 | 0.82 | 2.53 | 12 | 1.33 | 0.69 | 2.34 | 7 | 0.95 | 0.38 | 1.98 |
| Autoimmune hemolytic anemia | 2 | 1.03 | 0.10 | 3.79 | 2 | 1.14 | 0.11 | 4.18 | 1 | 0.99 | 0.00 | 5.68 |
| Behcet disease | 10 | 1.33 | 0.63 | 2.45 | 9 | 1.23 | 0.56 | 2.35 | 8 | 1.38 | 0.59 | 2.74 |
| Celiac disease | 6 | 1.01 | 0.36 | 2.21 | 5 | 0.88 | 0.28 | 2.07 | 3 | 0.71 | 0.13 | 2.09 |
| Chorea minor | 0 | | | | 0 | | | | 0 | | | |
| Chronic rheumatic heart disease | 63 | 1.23 | 0.95 | 1.57 | 55 | 1.14 | 0.86 | 1.48 | 35 | 1.04 | 0.72 | 1.44 |
| Crohn disease | 13 | 0.62 | 0.33 | 1.07 | 9 | **0.46** | **0.21** | **0.87** | 5 | **0.36** | **0.11** | **0.84** |
| Diabetes mellitus type I | 2 | 3.03 | 0.29 | 11.14 | 2 | 3.03 | 0.29 | 11.14 | 2 | 3.17 | 0.30 | 11.67 |
| Discoid lupus erythematosus | 3 | 2.26 | 0.43 | 6.68 | 2 | 1.56 | 0.15 | 5.75 | 2 | 2.02 | 0.19 | 7.43 |
| Graves, hyperthyroidism | 166 | **1.63** | **1.39** | **1.90** | 140 | **1.42** | **1.19** | **1.68** | 91 | 1.17 | 0.94 | 1.44 |
| Hashimoto/hypothroidism | 66 | **2.40** | **1.86** | **3.06** | 50 | **1.93** | **1.43** | **2.54** | 28 | **1.57** | **1.04** | **2.28** |
| Immune thrombocytopenic purpura | 3 | 0.87 | 0.16 | 2.57 | 2 | 0.64 | 0.06 | 2.34 | 2 | 1.12 | 0.11 | 4.13 |
| Localized scleroderma | 2 | 0.65 | 0.06 | 2.38 | 2 | 0.68 | 0.06 | 2.48 | 2 | 0.96 | 0.09 | 3.52 |
| Lupoid hepatitis | 1 | 2.56 | 0.00 | 14.70 | 1 | 2.70 | 0.00 | 15.49 | 1 | 3.33 | 0.00 | 19.11 |
| Multiple sclerosis | 23 | **1.66** | **1.05** | **2.50** | 20 | 1.53 | 0.94 | 2.37 | 6 | 0.66 | 0.24 | 1.44 |
| Myasthenia gravis | 7 | 1.38 | 0.55 | 2.86 | 5 | 1.07 | 0.34 | 2.51 | 1 | 0.34 | 0.00 | 1.95 |
| Pernicious anemia | 56 | **1.49** | **1.13** | **1.94** | 50 | **1.40** | **1.04** | **1.84** | 32 | 1.34 | 0.92 | 1.89 |
| Polyarteritis nodosa | 5 | 2.04 | 0.64 | 4.80 | 5 | 2.21 | 0.70 | 5.20 | 2 | 1.32 | 0.12 | 4.87 |
| Polymyalgia rheumatica | 95 | **1.25** | **1.01** | **1.53** | 83 | 1.17 | 0.93 | 1.45 | 43 | 0.97 | 0.70 | 1.31 |
| Polymyositis/dermatomyositis | 2 | 0.87 | 0.08 | 3.18 | 2 | 0.94 | 0.09 | 3.45 | 2 | 1.43 | 0.13 | 5.25 |
| Primary biliary cirrhosis | 4 | 2.90 | 0.75 | 7.49 | 3 | 2.48 | 0.47 | 7.34 | 1 | 1.39 | 0.00 | 7.96 |
| Psoriasis | 48 | 1.25 | 0.92 | 1.65 | 41 | 1.11 | 0.80 | 1.51 | 28 | 1.03 | 0.68 | 1.49 |
| Reiter disease | 2 | 5.56 | 0.52 | 20.43 | 2 | 5.88 | 0.55 | 21.63 | 0 | | | |
| Rheumatic fever | 12 | 1.15 | 0.59 | 2.02 | 12 | 1.18 | 0.60 | 2.06 | 11 | 1.26 | 0.62 | 2.26 |
| Rheumatoid arthritis | 132 | 1.07 | 0.89 | 1.26 | 103 | 0.90 | 0.74 | 1.10 | 54 | 0.81 | 0.61 | 1.05 |
| Sarcoidosis | 32 | 1.33 | 0.91 | 1.88 | 30 | 1.28 | 0.86 | 1.82 | 26 | 1.31 | 0.86 | 1.92 |
| Sjören syndrome | 5 | 2.01 | 0.63 | 4.72 | 4 | 1.72 | 0.45 | 4.46 | 2 | 1.40 | 0.13 | 5.14 |
| Systemic lupus erythematosus | 8 | 1.00 | 0.43 | 1.97 | 7 | 0.93 | 0.37 | 1.93 | 5 | 0.95 | 0.30 | 2.22 |
| Systemic sclerosis | 12 | 0.91 | 0.47 | 1.60 | 11 | 0.88 | 0.43 | 1.57 | 10 | 1.08 | 0.52 | 2.00 |
| Ulcerative colitis | 46 | 1.23 | 0.90 | 1.64 | 37 | 1.04 | 0.73 | 1.43 | 23 | 0.90 | 0.57 | 1.36 |
| Wegener granulomatosis | 72 | 1.15 | 0.90 | 1.45 | 69 | 1.15 | 0.89 | 1.46 | 47 | 1.12 | 0.82 | 1.49 |
| All | 932 | **1.33** | **1.24** | **1.42** | 790 | **1.19** | **1.11** | **1.28** | 488 | 1.06 | 0.97 | 1.16 |

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval

Bold type: 95% CI does not include 1.00.

Adjusted for age, period, socioeconomic status, region of residence, hospitalization of COPD, and alcoholism and alcohol related liver disease.

**Table 3. Standardized incidence ratio for subsequent Parkinson disease of patients with autoimmune disorders. Follow-up was started one year after autoimmune disorders**

| | Age at diagnosis of Parkinson disease (yrs) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <65 | | | | 65-74 | | | | 75-79 | | | | >=80 | | | |
| Autoimmune condition | O | SIR | 95% CI | | O | SIR | 95% CI | | O | SIR | 95% CI | | O | SIR | 95% CI | |
| Addison disease | 0 | | | | 0 | | | | 0 | | | | 0 | | | |
| Amyotrophic lateral sclerosis | 3 | **9.68** | **1.82** | **28.65** | 8 | **7.21** | **3.08** | **14.27** | 0 | | | | 4 | 3.10 | 0.81 | 8.02 |
| Ankylosing spondylitis | 1 | 0.42 | 0.00 | 2.42 | 4 | 1.19 | 0.31 | 3.09 | 6 | **3.28** | **1.18** | **7.18** | 1 | 0.71 | 0.00 | 4.07 |
| Autoimmune hemolytic anemia | 0 | | | | 1 | | | | 1 | 2.08 | 0.00 | 11.94 | 0 | | | |
| Behcet disease | 0 | | | | 3 | 1.44 | 0.27 | 4.25 | 3 | 1.65 | 0.31 | 4.88 | 3 | 1.31 | 0.25 | 3.88 |
| Celiac disease | 1 | 1.22 | 0.00 | 6.99 | 2 | 1.14 | 0.11 | 4.18 | 1 | 0.68 | 0.00 | 3.93 | 1 | 0.60 | 0.00 | 3.43 |
| Chorea minor | 0 | | | | 0 | | | | 0 | | | | 0 | | | |
| Chronic rheumatic heart disease | 7 | 2.41 | 0.95 | 4.98 | 24 | 1.54 | 0.98 | 2.29 | 15 | 0.97 | 0.54 | 1.61 | 9 | 0.62 | 0.28 | 1.19 |
| Crohn disease | 2 | 0.46 | 0.04 | 1.70 | 2 | 0.33 | 0.03 | 1.20 | 2 | 0.44 | 0.04 | 1.63 | 3 | 0.63 | 0.12 | 1.87 |
| Diabetes mellitus type I | 2 | 3.03 | 0.29 | 11.14 | 0 | | | | 0 | | | | 0 | | | |
| Discoid lupus erythematosus | 0 | | | | 1 | 2.33 | 0.00 | 13.33 | 0 | | | | 1 | 2.94 | 0.00 | 16.86 |
| Graves, hyperthyroidism | 18 | **1.72** | **1.02** | **2.73** | 47 | **1.57** | **1.15** | **2.08** | 37 | 1.40 | 0.98 | 1.93 | 38 | 1.20 | 0.85 | 1.65 |
| Hashimoto/hypothroidism | 7 | **3.89** | **1.54** | **8.06** | 16 | **2.37** | **1.35** | **3.86** | 13 | 1.78 | 0.94 | 3.05 | 14 | 1.39 | 0.76 | 2.33 |
| Immune thrombocytopenic purpura | 0 | | | | 2 | 2.50 | 0.24 | 9.19 | 0 | | | | 0 | | | |
| Localized scleroderma | 1 | 6.67 | 0.00 | 38.22 | 0 | | | | 0 | | | | 1 | 0.79 | 0.00 | 4.55 |
| Lupoid hepatitis | 0 | | | | 0 | | | | 0 | | | | 1 | 9.09 | 0.00 | 52.11 |
| Multiple sclerosis | 13 | **4.92** | **2.61** | **8.44** | 3 | 0.60 | 0.11 | 1.78 | 2 | 0.64 | 0.06 | 2.37 | 2 | 0.87 | 0.08 | 3.21 |
| Myasthenia gravis | 1 | 2.44 | 0.00 | 13.98 | 2 | 1.69 | 0.16 | 6.23 | 0 | | | | 2 | 1.08 | 0.10 | 3.95 |
| Pernicious anemia | 0 | | | | 7 | 1.08 | 0.43 | 2.24 | 13 | 1.35 | 0.72 | 2.32 | 30 | **1.59** | **1.08** | **2.28** |
| Polyarteritis nodosa | 1 | 5.26 | 0.00 | 30.17 | 1 | 1.47 | 0.00 | 8.43 | 1 | 1.56 | 0.00 | 8.96 | 2 | 2.67 | 0.25 | 9.81 |
| Polymyalgia rheumatica | 6 | 1.44 | 0.52 | 3.14 | 24 | 1.54 | 0.98 | 2.29 | 24 | 1.26 | 0.80 | 1.87 | 29 | 0.90 | 0.60 | 1.30 |
| Polymyositis/dermatomyositis | 0 | | | | 1 | 1.41 | 0.00 | 8.07 | 0 | | | | 1 | 1.52 | 0.00 | 8.69 |
| Primary biliary cirrhosis | 1 | 6.67 | 0.00 | 38.22 | 2 | 4.65 | 0.44 | 17.11 | 0 | | | | 0 | | | |
| Psoriasis | 6 | 1.19 | 0.43 | 2.61 | 11 | 0.95 | 0.47 | 1.71 | 14 | 1.45 | 0.79 | 2.44 | 10 | 0.93 | 0.44 | 1.72 |
| Reiter disease | 1 | 14.29 | 0.01 | 81.89 | 0 | | | | 0 | | | | 1 | 16.67 | 0.01 | 95.54 |
| Rheumatic fever | 2 | 1.26 | 0.12 | 4.63 | 3 | 0.87 | 0.16 | 2.58 | 3 | 1.17 | 0.22 | 3.47 | 4 | 1.53 | 0.40 | 3.96 |
| Rheumatoid arthritis | 11 | 1.58 | 0.79 | 2.84 | 33 | 1.07 | 0.73 | 1.50 | 32 | 0.94 | 0.64 | 1.33 | 27 | **0.64** | **0.42** | **0.94** |
| Sarcoidosis | 6 | 1.48 | 0.53 | 3.24 | 13 | 1.55 | 0.82 | 2.65 | 5 | 0.84 | 0.27 | 1.98 | 6 | 1.18 | 0.43 | 2.59 |
| Sjören syndrome | 0 | | | | 3 | 4.17 | 0.79 | 12.33 | 1 | 1.64 | 0.00 | 9.40 | 0 | | | |
| Systemic lupus erythematosus | 1 | 0.98 | 0.00 | 5.62 | 2 | 0.77 | 0.07 | 2.82 | 3 | 1.50 | 0.28 | 4.44 | 1 | 0.53 | 0.00 | 3.02 |
| Systemic sclerosis | 0 | | | | 6 | 1.71 | 0.62 | 3.75 | 2 | 0.56 | 0.05 | 2.06 | 3 | 0.69 | 0.13 | 2.05 |
| Ulcerative colitis | 4 | 0.65 | 0.17 | 1.68 | 13 | 1.21 | 0.64 | 2.08 | 10 | 1.14 | 0.54 | 2.10 | 10 | 1.00 | 0.48 | 1.85 |
| Wegener granulomatosis | 4 | **4.00** | **1.04** | **10.34** | 14 | 1.21 | 0.66 | 2.03 | 19 | 1.05 | 0.63 | 1.64 | 32 | 1.09 | 0.75 | 1.55 |
| All | 99 | **1.60** | **1.30** | **1.95** | 248 | **1.35** | **1.19** | **1.53** | 207 | 1.13 | 0.98 | 1.30 | 236 | 1.00 | 0.88 | 1.14 |

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval

Bold type: 95% CI does not include 1.00.

Adjusted for age, period, socioeconomic status, region of residence, hospitalization of COPD, and alcoholism and alcohol related liver disease.