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Published in: BMC Neurology

DOI: 10.1186/1471-2377-12-41

2012

Link to publication

Citation for published version (APA):
Zöller, B., Li, X., Sundquist, J., & Sundquist, K. (2012). Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurology, 12. https://doi.org/10.1186/1471-2377-12-41

Total number of authors: 4

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Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden

Bengt Zöller1*, Xinjun Li1, Jan Sundquist1,2 and Kristina Sundquist1

Abstract

Background: Certain immune-mediated diseases (IMDs) have been associated with increased risk for cardiovascular disorders. The aim of the present study was to examine whether there is an association between 32 different IMDs and first hospitalization for ischemic or hemorrhagic stroke.

Methods: All individuals in Sweden hospitalized with a main diagnosis of IMD (without previous or coexisting stroke), between January 1, 1987 and December 31, 2008 (n = 216,291), were followed for first hospitalization for ischemic or hemorrhagic stroke. The reference population was the total population of Sweden. Adjusted standardized incidence ratios (SIRs) for ischemic and hemorrhagic stroke were calculated.

Results: Totally 20 and 15 of the 32 IMDs studied, respectively, were associated with an increased risk of ischemic and hemorrhagic stroke during the follow-up. The overall risks of ischemic and hemorrhagic stroke during the first year after hospitalization for IMD were 2.02 (95 % CI 1.90–2.14) and 2.65 (95 % CI 2.27–3.08), respectively. The overall risk of ischemic or hemorrhagic stroke decreased over time, to 1.50 (95 % CI 1.46–1.55) and 1.83 (95 % CI 1.69–1.98), respectively, after 1–5 years, and 1.29 (95 % CI 1.23–1.35) and 1.47 (95 % CI 1.31–1.65), respectively, after 10+ years. The risk of hemorrhagic stroke was ≥2 during the first year after hospitalization for seven IMDs: ankylosing spondylitis (SIR = 8.11), immune thrombocytopenic purpura (SIR = 8.60), polymyalgia rheumatica (SIR = 2.06), psoriasis (SIR = 2.88), rheumatoid arthritis (SIR = 3.27), systemic lupus erythematosus (SIR = 8.65), and Wegener’s granulomatosis (SIR = 5.83). The risk of ischemic stroke was ≥2 during the first year after hospitalization for twelve IMDs: Addison’s disease (SIR = 2.71), Crohn’s disease (SIR = 2.15), Grave’s disease (SIR = 2.15), Hashimoto’s thyroiditis (SIR = 2.99), immune thrombocytopenic purpura (SIR = 2.35), multiple sclerosis (SIR = 3.05), polymyositis/dermatomyositis (SIR = 3.46), rheumatic fever (SIR = 3.91), rheumatoid arthritis (SIR = 2.08), Sjögren’s syndrome (SIR = 2.57), systemic lupus erythematosus (SIR = 2.21), and ulcerative colitis (SIR = 2.15).

Conclusions: Hospitalization for many IMDs is associated with increased risk of ischemic or hemorrhagic stroke. The findings suggest that several IMDs are linked to cerebrovascular disease.
Background
Ischemic and hemorrhagic stroke are major causes of morbidity and mortality worldwide [1]. During recent years it has become clear that systemic inflammation may enhance atherogenesis [2-4]. Immune-mediated diseases (IMDs) are a heterogenous group of diseases that are characterized by acute or chronic inflammation [2-8]. Some IMDs have been associated with an increased risk for cardiovascular disease [2-8]. IMDs may increase the cardiovascular disease risk through different mechanisms such as autoreactive lymphocytes, autoantibodies, autoantigens, epigenetic mechanisms, and inflammation driving the formation, progression and rupture of atherosclerotic plaques [2-8]. Inflammation may also affect the thrombotic risk by suppressing fibrinolysis, upregulating procoagulants, and downregulating anticoagulants [7]. Thus, certain IMDs such as rheumatoid arthritis (RA) [3,5,6,8-12] and systemic lupus erythematosus (SLE) [3,5,6,8,13-15] have been associated with an increased risk of cardiovascular disease. Enhanced atherogenesis has also been indicated in other IMDs such as Sjögren’s disease [3,5,6,16], systemic vasculitis [3,5], inflammatory bowel disease [3,5,8,17], and psoriasis [8,18]. As a consequence of this, the risk of stroke has been reported to be increased in patients with systemic lupus erythematosus [19] and rheumatoid arthritis [20].

We hypothesized that not only IMDs such as SLE and RA, but also a number of other less well-studied IMDs have an increased risk of cardiovascular disease. More specifically, we aimed at determining whether IMDs increase the risk for hospitalized ischemic or hemorrhagic stroke. In a nationwide follow-up from 1987–2008 we have estimated the rate of hospitalization with stroke in patients hospitalized with 32 different IMDs without previous or coexisting stroke.

Methods
This study was approved by the Ethics Committee of Lund University, Sweden. Data used in this study contained information on all individuals registered as residents of Sweden [21]. It included individual-level information on age, sex, occupation, geographic region of residence, hospital diagnoses, and dates of hospital admissions in Sweden (1964–2008), as well as date of emigration, and date and cause of death [21]. The dataset was constructed using several national Swedish data registers (reviewed by Rosen and Hakulinen) [22], including, but not limited to, the Swedish National Population and Housing Census (1960–1990), the Total Population Register, the Multi-Generation Register, and the Swedish Hospital Discharge Register [23]. The data were released to us from the National Board of Health and Welfare and Statistics Sweden.

Information retrieved from the various registers was linked, at the individual level, via the national 10-digit personal identification number assigned to each resident of Sweden for his or her lifetime. Registration numbers were replaced by serial numbers to preserve anonymity. As well as being used to track all records in the database at the individual level, these serial numbers were used to check that individuals with hospital diagnoses of ischemic or hemorrhagic stroke appeared only once during the follow-up (for the first hospital diagnosis of ischemic or hemorrhagic stroke during the study period).

The follow-up period for analysis of data in the present study started on January 1, 1987 and continued until hospitalization for ischemic or hemorrhagic stroke, death, emigration, or the end of the study period (December 31, 2008). Data for first hospitalization for ischemic or hemorrhagic stroke during the study period were retrieved from the Hospital Discharge Register (1987–2008). This study did not include data for hospital outpatients or patients treated at primary health care centers.

Predictor variable
The predictor variable was hospitalization for an IMD, diagnosed according to ICD-7, ICD-8, ICD-9, and ICD-10 (Additional file 1 Table S1).

Outcome variable
Diagnosis of ischemic stroke was based on the 9th, and 10th revisions of the International Classification of Diseases (ICD-9, and ICD-10). Cases of ischemic stroke were identified using the following ICD codes: 433, 434, 435, 437.0, and 437.1 (ICD-9); and I63 (not I636), I65, I66, I67.2, and I67.8 (ICD-10).

Diagnosis of hemorrhagic stroke was also based on ICD-9, and ICD-10. Cases of hemorrhagic stroke were identified using the following ICD codes: 431 and 432 (ICD-9); and I61 and I62 (ICD-10).

Individual-level variables adjusted for in the model
The individual-level variables were sex, age, time period, geographic region of residence, socioeconomic status (SES), and comorbidity.

Sex: male or female.
Age was divided into 5-year categories. Subjects of all ages were included in the study.
Time period was divided into five time periods in order to allow for adjustment for any change in hospitalization rates over time: 1987–1991, 1992–1996, 1997–2001, 2002–2008.

Geographic region of residence was included as an individual-level variable to adjust for possible differences in hospital admissions for ischemic or hemorrhagic stroke between different geographic regions in Sweden. It was categorized 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).
Occupation was used as a proxy for SES. We classified each individual's occupation into one of six categories: 1) blue-collar worker, 2) white-collar worker, 3) professional, 4) self-employed, 5) farmer, and 6) non-employed (Individuals without paid employment). Homemakers and students without an occupation were categorized on the basis of their husband's, father's or mother's occupation. If that was not possible, they were included in the “non-employed” category. For individuals aged <20 years, parental occupation was used.

Comorbidity was defined as the first hospital diagnosis at follow up (1987–2008) of the following: 1) chronic lower respiratory diseases (490–496 [ICD-9], and J40–J49 [ICD-10]); 2) obesity (278A [ICD-9], and E65–E68 [ICD-10]); 3) alcoholism and alcohol-related liver disease (291 and 303 [ICD-9], and F10 and K70 [ICD-10]); 4) type 2 diabetes mellitus (250 [age >29 years] [ICD-9], and E11-E14 [ICD-10]); 5) hypertension (401–405 [ICD-9], and I10–I15 [ICD-10]); 6) atrial fibrillation (427D [ICD-9], and J48 [ICD-10]); 7) heart failure (428 [ICD-9], and I50 [ICD-10]); 8) renal disease (580–591 and 753B [ICD-9], and N00-N19, Q61 [ICD-10]); 9) sepsis (036,038 [ICD-9], and A39-A41 [ICD-10]); and 10) coronary heart disease (410–414 [ICD-9], and I20-I25 [ICD-10]).

### Statistical analysis
Person-years at risk (i.e., number of persons at risk multiplied by time at risk) were calculated from the time at which subjects were included in the study (in 1987 or later) until first hospitalization for ischemic or hemorrhagic stroke, death, emigration, or the end of the study period. Person years for IMD patients were calculated from discharge of first hospitalization for IMD (IMD patients with previous stroke before the first IMD hospitalization or at the same hospitalization as the first IMD hospitalization, were excluded). The expected number of cases was based on the number of cases in the reference group. SIRs were calculated as the ratio of observed (O) and expected (E) number of ischemic or hemorrhagic stroke cases using the indirect standardization method [24]:

\[
SIR = \frac{\sum_{i=1}^{J} o_{ij}}{\sum_{i=1}^{J} E_{ij}} = \frac{o}{E},
\]

Where \( o = \sum_{i} o_{ij} \) denotes the total observed number of cases in the study group; \( E \) (expected number of cases) is calculated by applying stratum-specific standard incidence rates \( \lambda_{ij} \) obtained from the reference group to the stratum-specific person-years \( n \) of risk for the study group; \( o \) represents the observed number of cases that the cohort subjects contribute to the \( j \)th stratum; and \( J \) represents the strata defined by cross-classification of the following adjustment variables: age, sex, time period, SES, geographic region of residence, and comorbidity[24]. Ninety-five percent confidence intervals (95 % CIs) were calculated assuming a Poisson distribution [24]. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

### Results
Table 1 shows the number of people admitted to hospital with each of the selected IMDs during the study period.

| Immune-mediated disease                          | Men       | Women     | All       |
|--------------------------------------------------|-----------|-----------|-----------|
| Addison disease                                  | 862       | 1190      | 2052      |
| Amyotrophic lateral sclerosis                     | 2376      | 2055      | 4431      |
| Ankylosing spondylitis                           | 2416      | 1061      | 3477      |
| Autoimmune hemolytic anemia                      | 312       | 391       | 703       |
| Behcet disease                                    | 146       | 138       | 284       |
| Celiac disease                                   | 2639      | 4249      | 6888      |
| Chorea minor                                      | 10        | 25        | 35        |
| Crohn disease                                    | 9522      | 10700     | 22022     |
| Diabetes mellitus type I                         | 9068      | 7664      | 16732     |
| Discoid lupus erythematous                       | 54        | 200       | 254       |
| Grave disease                                    | 3764      | 18298     | 22062     |
| Hashimoto thyroiditis                            | 1440      | 5115      | 6555      |
| Immune thrombocytopenic purpura                   | 1905      | 2039      | 3944      |
| Localized scleroderma                             | 90        | 422       | 512       |
| Lupoid hepatitis                                  | 115       | 274       | 389       |
| Multiple sclerosis                                | 3492      | 6892      | 10384     |
| Myasthenia gravis                                 | 935       | 1149      | 2084      |
| Pernicious anemia                                 | 1663      | 1868      | 3531      |
| Polymyositis nodosa                               | 437       | 386       | 823       |
| Polymyalgia rheumatic                             | 5313      | 11183     | 16496     |
| Polymyositis/dermatomyositis                      | 404       | 667       | 1071      |
| Primary biliary cirrhosis                         | 124       | 675       | 799       |
| Psoriasis                                         | 4471      | 4558      | 9029      |
| Reiter disease                                    | 280       | 58        | 338       |
| Rheumatic fever                                   | 236       | 228       | 474       |
| Rheumatoid arthritis                              | 12080     | 32531     | 42461     |
| Sarcoidosis                                       | 2847      | 2518      | 5365      |
| Sjören syndrome                                  | 125       | 1175      | 1300      |
| Systemic lupus erythematosus                      | 742       | 3437      | 4179      |
| Systemic sclerosis                                | 402       | 1356      | 1758      |
| Ulcerative colitis                                | 12963     | 10647     | 23610     |
| Wegener granulomatosis                            | 1025      | 884       | 1909      |
| All                                              | 82258     | 134033    | 216291    |
period. IMD patients with previous stroke before first hospitalization for IMD or stroke at the same time as first IMD hospitalization were excluded from Table 1. Totally 8113 IMD patient with previous or coexisting ischemic stroke and 1416 with hemorrhagic stroke were excluded. A total of 216,291 individuals were hospitalized with an IMD (82,258 males and 134,033 females) (Table 1). The three most common immune-mediated diseases were rheumatoid arthritis (44,611 cases), ulcerative colitis (23,610), and Graves’ disease (22,062). Totally 66,509 patients with ischemic stroke and 428,031 patients with hemorrhagic strokes from 1987–2008 were included (Table 2), of whom 10,905 (9,437 ischemic and 1,468 hemorrhagic strokes) were subsequently admitted to hospital after a first hospitalization for IMD (Table 2). The comorbidities (defined as main or second hospital diagnosis) adjusted for are presented in Table 2.

Hemorrhagic stroke
A total of 66,509 individuals were hospitalized with a main diagnosis of hemorrhagic stroke (Table 2), of whom 1,468 (2.2 % of hemorrhagic strokes) had been admitted to hospital due to an IMD (Table 2). The risk of hemorrhagic stroke was significantly increased during the whole follow-up period for 15 of the 32 IMDs studied (Table 3). The overall risk of hemorrhagic stroke during the first year after hospitalization for an IMD was 2.65 (95 % CI 2.27–3.08). The overall risk of hemorrhagic stroke decreased over time, to 1.83 after 1–5 years (95 % CI 1.69–1.98), 1.63 after 5–10 years (95 % CI 1.47–1.80) and 1.47 after 10+ years (95 % CI 1.31–1.65).

The risk of hemorrhagic stroke was ≥2 during the first year after hospitalization for seven IMD (Table 3): ankylosing spondylitis, immune thrombocytopenic purpura, polymyalgia rheumatica, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and Wegener’s granulomatosis. For seven IMDs, the risk of hemorrhagic stroke was increased 10+ years after hospitalization (Table 3): ankylosing spondylitis, celiac disease, Crohn’s disease, Graves’ disease, localized scleroderma, polymyalgia rheumatica, and rheumatoid arthritis.

Hemorrhagic stroke and age and sex
The overall risk of hemorrhagic stroke was increased for both sexes at all different follow-up periods (Additional file 1 Tables S2 and S3). The overall risk of hemorrhagic stroke was increased in all age groups for both males and females (<50, 50–59, 60–69, 70–79, and 80+ years) (Additional file 1 Tables S4, S5 and S6).

Ischemic stroke
A total of 428,031 individuals were hospitalized with a main diagnosis of ischemic stroke (Table 2), of whom 9,437 (2.2 % of all ischemic stroke cases) had been admitted to hospital due to an IMD (Table 2). The variables for which the SIRs were adjusted are presented in Table 1. The risk of ischemic stroke was increased during the whole follow-up period for 20 of the 32 IMDs studied (Table 4). The overall risk of ischemic stroke during the first year after hospitalization for an IMD was 2.02 (95 % CI 1.90–2.14). The overall risk of ischemic stroke decreased over time, to 1.50 after 1–5 years (95 % CI 1.46–1.55), 1.38 after 5–10 years (95 % CI 1.33–1.43) and 1.29 after 10+ years (95 % CI 1.23–1.35) (Table 4).

The risk of ischemic stroke was ≥2 during the first year after hospitalization for twelve IMDs (Table 4): Addison’s disease, Crohn’s disease, Grave’s disease, Hashimoto’s thyroiditis, immune thrombocytopenic purpura, multiple sclerosis, polymyositis/dermatomyositis, rheumatic fever, rheumatoid arthritis, Sjögren’s syndrome, systemic lupus erythematosus, and ulcerative colitis. For seven IMDs, the risk of ischemic stroke was increased 10+ years after hospitalization: diabetes mellitus type 1, Graves’ disease, Hashimoto’s thyroiditis, pernicious anemia, polymyalgia rheumatica, psoriasis, and rheumatoid arthritis (Table 4).

Ischemic stroke and age and sex
The overall risk of ischemic or hemorrhagic stroke was increased for both sexes at all different follow-up periods (Additional file 1 Tables S7 and S8). The overall risk of ischemic stroke was increased in all age groups for both sexes (<50, 50–59, 60–69, 70–79, and 80+ years) (Additional file 1 Tables S9, S10 and S11).

Time period and hemorrhagic and ischemic stroke
The overall risk for both hemorrhagic and ischemic stroke was slightly higher between 1987 and 1996 (1.98 95 % CI 1.78–2.20 and 1.51 95 % CI 1.45–1.57, respectively) than between 1997 and 2008 (1.58 95 % CI 1.48–1.69 and 1.38 95 % CI 1.34–1.41, respectively) (Additional file 1 Tables S12 and S13).

Discussion
The present study is the first nationwide study of IMDs and ischemic and hemorrhagic stroke. The results indicate that several IMDs increase the risk of hospitalization for both ischemic and/or hemorrhagic stroke. The relative risk of ischemic and hemorrhagic stroke during the first year after hospitalization with certain IMDs was even higher than the risks associated with many traditional risk factors for ischemic and hemorrhagic stroke [1,25]. Although it declined over time, the overall risk of ischemic and hemorrhagic stroke remained elevated for 10 or more years for some IMDs. The results of our study are in line with previous studies linking rheumatoid arthritis [3,5,6,8-12,20], systemic lupus erythematosus [3,5,6,8,13-15,19], Sjögren’s disease [3,5,6,16], systemic vasculitis [3,5], inflammatory bowel disease [3,5,8,17], and psoriasis [8,18] to an increased risk of
cardiovascular disease. However, what distinguishes our study from these other studies is its comparison of large numbers of patients and 32 types of IMDs with the general population in a nationwide setting, as well as a long-term follow-up of patients and the determination of risk for both ischemic and hemorrhagic stroke. Moreover, we also found a number of novel associations between IMDs and ischemic and hemorrhagic stroke. The results of the present study suggest that increased risk of subsequent ischemic and hemorrhagic stroke is a common feature of several IMDs, not just selected conditions such as systemic lupus erythematosus [19] and rheumatoid arthritis [20].

Although the increased risk of ischemic and hemorrhagic stroke may have different underlying causes in different IMDs, a general link between systemic inflammation and atherothrombosis has been indicated [2-8]. In some conditions, such as in immune thrombocytopenic purpura,
Table 3 SIR for subsequent hemorrhagic stroke of patients with IMD

| Follow-up interval (years) | <1 | 1-5 | 5-10 | > = 10 | All |
|---------------------------|----|-----|------|--------|-----|
| Immune-mediated diseases  |    |     |      |        |     |
| Addison’s disease         | 2  | 0.25| 9.94 | 0.04   | 4.21|
| Amyotrophic lateral sclerosis | 1  | 0.47| 2.68 | 1.30   | 1.82|
| Ankylosing spondylitis     | 6  | 8.11| 2.92 | 17.76  | 3.43|
| Autoimmune hemolytic anemia| 1  | 3.13| 1.97 | 0.93   | 1.15|
| Behcet’s disease           | 1  | 1.11| 0.00 | 191.08 | 2.33|
| Celiac disease             | 2  | 3.57| 1.31 | 6.08   | 2.69|
| Chorea minor               | 0  | 0   | 0    | 0      | 0   |
| Crohn disease              | 5  | 1.47| 1.06 | 5.04   | 2.60|
| Diabetes mellitus type 1   | 0  | 0   | 0    | 0      | 0   |
| Discoid lupus erythematosus| 1  | 11.11| 63.69| 2.33   | 1.87|
| Grave’s disease            | 8  | 1.53| 0.65 | 3.02   | 1.77|
| Hashimoto’s thyroiditis    | 4  | 1.47| 0.38 | 0.39   | 2.01|
| Immune thrombocytopenic purpura | 8  | 8.60| 3.67 | 17.03  | 2.81|
| Localized scleroderma      | 0  | 0   | 0    | 0      | 0   |
| Lupoid hepatitis           | 0  | 0   | 0    | 0      | 0   |
| Multiple sclerosis         | 4  | 1.82| 0.47 | 4.70   | 1.36|
| Myasthenia gravis          | 1  | 1.22| 0.00 | 6.99   | 2.09|
| Penicillous anemia         | 4  | 2.15| 0.56 | 3.94   | 2.09|
| Polycartitis nodosa        | 2  | 5.41| 0.51 | 19.88  | 0.00|
| Polymyalgia rheumaticia    | 21 | 206 | 1.28| 3.16   | 1.42|
| Polymyositis/dermatomyositis| 1  | 2.63| 0.00 | 15.08  | 1.95|
| Primary biliary cirrhosis  | 1  | 2.08| 0.00 | 11.94  | 1.76|
| Psoriasis                  | 9  | 2.88| 1.31| 5.50   | 1.83|
| Reiter’s disease           | 0  | 1   | 2.94| 0.00   | 1.25|
| Rheumatic fever            | 1  | 7.69| 0.00| 4.09   | 0   |
| Rheumatoid arthritis       | 65 | 3.27| 1.52| 4.17   | 1.76|
| Sarcoidosis                | 3  | 2.48| 0.74| 12.08  | 1.37|
| Sjögren’s syndrome         | 0  | 3   | 1.35| 0.25   | 1.03|
| Systemic lupus erythematosus| 9  | 8.65| 3.92| 16.50  | 1.89|
| Systemic sclerosis         | 2  | 3.17| 0.30| 11.67  | 2.67|
| Ulcerative colitis         | 7  | 1.45| 0.57| 3.00   | 1.45|
| Wegener’s granulomatosis   | 6  | 5.83| 2.10| 12.76  | 1.92|

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 chronic lower respiratory diseases, obesity, alcoholism, hypertension, diabetes, atrial fibrillation, heart failure, renal disease, sepsis, and coronary heart disease.
Table 4 SIR for subsequent ischemic stroke of patients with IMD

| Follow-up interval (years) | SIR | 95 % CI | SIR | 95 % CI | SIR | 95 % CI | SIR | 95 % CI | SIR | 95 % CI |
|---------------------------|-----|---------|-----|---------|-----|---------|-----|---------|-----|---------|
| Immune-mediated diseases  |     |         |     |         |     |         |     |         |     |         |
| Addison’s disease         | 14  | 2.71    | 1.48 | 4.56    | 28  | 1.17    | 0.78 | 1.69    | 30  | 1.90    |
| Amyotrophic lateral sclerosis | 7   | 0.53    | 0.21 | 1.10    | 16  | 1.52    | 0.87 | 2.47    | 7   | 1.77    |
| Ankylosing spondylitis    | 8   | 1.62    | 0.69 | 3.21    | 44  | 1.55    | 1.13 | 2.08    | 24  | 0.98    |
| Autoimmune hemolytic anemia | 4   | 1.45    | 0.38 | 3.75    | 12  | 1.00    | 0.51 | 1.75    | 19  | 2.51    |
| Behcet’s disease          | 1   | 4.00    | 0.00 | 22.93   | 1   | 0.65    | 0.00 | 3.70    | 0   | 1.43    |
| Celiac disease            | 9   | 2.17    | 0.99 | 4.14    | 29  | 1.28    | 0.86 | 1.84    | 21  | 1.17    |
| Chorea minor              | 0   | 1.27    | 0.00 | 13.03   | 0   | 0.00    | 0   | 1       | 1.11  |
| Crohn disease             | 49  | 2.15    | 1.59 | 2.84    | 160 | 1.33    | 1.13 | 1.55    | 103 | 1.11    |
| Diabetes mellitus type I | 1   | 6.25    | 0.00 | 35.83   | 2   | 0.45    | 0.04 | 1.65    | 5   | 2.75    |
| Discoid lupus erythematous | 3   | 4.23    | 0.80 | 12.51   | 3   | 0.99    | 0.19 | 2.92    | 1   | 0.47    |
| Grave’s disease           | 101 | 2.15    | 1.76 | 2.62    | 402 | 1.39    | 1.26 | 1.53    | 348 | 1.36    |
| Hashimoto’s thyroiditis   | 77  | 2.99    | 2.36 | 3.74    | 211 | 1.73    | 1.50 | 1.98    | 115 | 1.39    |
| Immune thrombocytopenic purpura | 16 | 2.35    | 1.34 | 3.83    | 55  | 1.77    | 1.33 | 2.30    | 19  | 0.94    |
| Localized scleroderma     | 2   | 1.28    | 0.12 | 4.71    | 13  | 1.25    | 0.66 | 2.14    | 18  | 1.72    |
| Lupoid hepatitis          | 3   | 4.48    | 0.84 | 13.25   | 4   | 1.98    | 0.52 | 5.12    | 0   | 7       |
| Multiple sclerosis        | 40  | 3.05    | 2.18 | 4.15    | 73  | 1.09    | 0.85 | 1.37    | 55  | 1.11    |
| Myasthenia gravis         | 6   | 1.01    | 0.36 | 2.21    | 38  | 1.36    | 0.96 | 1.87    | 23  | 1.20    |
| Pernicious anemia         | 25  | 1.56    | 1.01 | 2.31    | 138 | 1.49    | 1.25 | 1.76    | 89  | 1.23    |
| Polymyxositis/dermatomyositis | 10 | 3.46    | 1.65 | 6.39    | 13  | 1.19    | 0.63 | 2.03    | 6   | 1.07    |
| Primary biliary cirrhosis | 4   | 1.54    | 0.40 | 3.98    | 11  | 1.45    | 0.72 | 2.60    | 4   | 0.91    |
| Psoriasis                 | 44  | 1.92    | 1.39 | 2.58    | 217 | 1.65    | 1.44 | 1.89    | 163 | 1.53    |
| Reiter’s disease          | 0   | 1.01    | 0.36 | 2.21    | 38  | 1.36    | 0.96 | 1.87    | 23  | 1.20    |
| Rheumatic fever           | 5   | 3.91    | 1.23 | 9.19    | 10  | 1.66    | 0.79 | 3.06    | 14  | 3.04    |
| Rheumatoid arthritis      | 345 | 2.08    | 1.86 | 2.31    | 1266| 1.66   | 1.57 | 1.75    | 663 | 1.45    |
| Sarcoidosis               | 9   | 0.97    | 0.44 | 1.85    | 70  | 1.43    | 1.12 | 1.81    | 51  | 1.12    |
| Sjögren’s syndrome        | 10  | 2.57    | 1.22 | 4.75    | 28  | 1.38    | 0.92 | 1.99    | 15  | 0.96    |
| Systemic lupus erythematosus | 19 | 2.21    | 1.33 | 3.46    | 88  | 2.33    | 1.87 | 2.87    | 54  | 1.92    |
| Systemic sclerosis        | 11  | 1.90    | 0.94 | 3.41    | 28  | 1.22    | 0.81 | 1.77    | 11  | 1.19    |
| Ulcerative colitis        | 71  | 2.15    | 1.68 | 2.71    | 231 | 1.27    | 1.11 | 1.45    | 162 | 1.09    |
| Wegener’s granulomatosis  | 11  | 1.66    | 0.82 | 2.98    | 12  | 0.47    | 0.24 | 0.83    | 26  | 1.54    |

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 chronic lower respiratory diseases, obesity, alcoholism, hypertension, diabetes, atrial fibrillation, heart failure, renal disease, sepsis, and corona heart disease.

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hemorrhagic stroke may occur as the direct result of thrombocytopenia. The formation of autoantibodies may, in special cases, also contribute to stroke [26]. The increased risk of stroke may be specific for more severe cases of IMDs, since the patients in our study had been admitted to hospital. The effects of treatment—corticosteroids promote hemostasis [27]—and the effect of inflammation on coagulation [7] may also contribute to the identified associations. Hypothetically, the fact that the risk of ischemic and hemorrhagic stroke decreased over time may suggest that it is linked to the inflammatory activity of the IMDs, which is likely to decrease over time due to the treatment. In line with this hypothesis, in several studies disease activity appears to be linked with atherosclerosis progression [2-8,28,29]. However, as we lack treatment data, we cannot prove this hypothesis but in this context it is interesting that the relative risk of both hemorrhagic and ischemic stroke was lower between 1997 and 2008 than between 1987 and 1996 (Additional file 1 Tables S12 and S13).

The present study has certain limitations. For example, we had no data on general cardiovascular disease risk factors such as weight, smoking, and diet. It is unrealistic to gather such data for an entire national population. However, we did adjust for socioeconomic status, which is associated with risk factors such as smoking. Aspirin and non-steroidal anti-inflammatory drugs (NSAID) may affect the risk of ischemic and hemorrhagic stroke [30,31]. However, we had no access to treatment data. Adjustment was, however, made for several comorbidities (chronic lower respiratory diseases, obesity, alcoholism and alcohol-related liver disease, type 2 diabetes mellitus, hypertension, atrial fibrillation, coronary heart diseases, heart failure, renal disease and sepsis). Still, residual bias may remain due to hospitalization of the most severe cases with IMD. However, all cases with previous or coexisting stroke were excluded to avoid selection bias. Totally, 8113 IMD patients with previous or coexisting ischemic stroke and 1416 with hemorrhagic stroke were excluded from the study, which in turn instead may underestimate the stroke risk. In fact, our results are within the limit for published cardiovascular disease risk in IMDs like RA [3,5,6,8-12,20] and SLE [3,5,6,8,13-15,19]. Thus, the estimated risks of stroke in IMD patients appear to be fairly valid. Anyway, the present study reflects the real world risks for stroke among hospitalized IMD (without previous stroke or at the same time as first hospitalization for IMD). All cases of ischemic and hemorrhagic stroke in Sweden should, according to official guidelines, be treated at hospitals [32]. Moreover, hospitalization incidence rates were calculated for the whole follow-up period, divided into five time periods, and adjustments were made for possible changes in hospitalization rates over time.

This study also has a number of strengths. The study reflects the situation in real world medicine during 22 years in a country with a high standard in the medical diagnosis [22,23,33-35]. The study population included all individuals clinically diagnosed with IMD and ischemic and hemorrhagic stroke in hospital during the study period, which eliminated recall bias. Because of the personal identification number assigned to each resident in Sweden, it was possible to trace all subjects for the whole follow-up period. Data on occupation were 99-2 % complete (1980 and 1990 censuses), which enabled us to adjust our models for socioeconomic status. A further strength of the present study was the use of validated hospital discharge data. The Hospital Discharge Register has high validity [22,23,33-35], especially for cardiovascular disorders such as stroke, for which approximately 95 % of diagnoses have been shown to be correct [33-35]. Though, the positive predictive value (PPV) may differ between diagnoses in the Swedish Hospital Discharge Register, the PPV is generally around 85-95 % [35].

Conclusions
In summary, the risk of hospitalization for ischemic and hemorrhagic stroke was, for several immune-mediated diseases studied, found to be significantly associated. The risk of ischemic and hemorrhagic stroke during the first year after hospitalization with an immune-mediated disease was high for certain IMDs. Although it decreased over time, for some IMDs the risk of ischemic and hemorrhagic stroke remained elevated for more than 10 years. The findings of the present study suggest that many IMDs are linked to cerebrovascular disease. Future studies could elucidate the mechanisms behind stroke in specific IMDs.

Additional file

**Table S1:** ICD codes of IMD and related conditions. Table S2. SIR for subsequent hemorrhagic stroke of male patients with IMD. Table S3. SIR for subsequent hemorrhagic stroke of female patients with IMD. Table S4. SIR for subsequent hemorrhagic stroke of patients with IMD after one year of follow-up. Table S5. SIR for subsequent ischemic stroke of male patients with IMD. Table S6. SIR for subsequent ischemic stroke of female patients with IMD after one year of follow-up. Table S7. SIR for subsequent ischemic stroke of male patients with IMD. Table S8. SIR for subsequent ischemic stroke of female patients with IMD. Table S9. SIR for subsequent ischemic stroke of patients with IMD after one year of follow-up. Table S10. SIR for subsequent ischemic stroke of male patients with IMD after one year of follow-up. Table S11. SIR for subsequent ischemic stroke of female patients with IMD after one year of follow-up. Table S12. SIR for subsequent hemorrhagic stroke of patients with IMD after one year of follow-up. Table S13. SIR for subsequent ischemic stroke of patients with IMD after one year of follow-up.

**Abbreviations**
CI: Confidence interval; E: Expected; ICD: international classification of diseases; IMD: immune-mediated disease; O: Observed; RA: rheumatoid arthritis; SES: socioeconomic status; SIR: standardised incidence ratio; SLE: systemic lupus erythematosus.

**Competing interests**
The authors declare that they have no competing interests.
Authors’ contributions
All authors contributed to the conception and design of the study; JS and KS contributed to the acquisition of data; all authors contributed to the analysis and interpretation of data; BZ drafted the manuscript; and all authors revised it critically and approved the final version. All authors had full access to all of the data (including statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of its analysis.

Acknowledgements
The authors wish to thank the CPF’s Science Editor Stephen Gilliver for his useful comments on the text. The registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare. This work was supported by grants to Bengt Zöller from the Swedish Heart and Lung Foundation and Region Skåne (REGSKANE-124611), and to Kristina and Jan Sundquist from the Swedish Research Council (2008–3110 and 2008–2638), the Swedish Council for Working Life and Social Research (2006–0386, 2007–1754 and 2007–1962), and Formas (2006–4255-6596-99 and 2007–3132). No funding bodies played any role in the design, in the collection, analysis, and interpretation of data or in the writing and decision to publish this manuscript.

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Received: 22 November 2011 Accepted: 18 June 2012
Published: 18 June 2012

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