Associations between autoimmune diseases and amyotrophic lateral sclerosis: a register-based study

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Abstract
Objective: To assess the associations of 43 autoimmune diseases with the subsequent risk of ALS and further evaluate the contribution of familial confounding to these associations.
Methods: We conducted a nationwide register-based nested case-control study including 3561 ALS patients diagnosed during 1990–2013 in Sweden and 35,610 controls that were randomly selected from the general population and individually matched to the cases on age, sex, and county of birth. To evaluate the contribution of familial factors on the studied association, we additionally studied the first-degree relatives (siblings and children) of ALS patients and their controls.
Results: Patients with ALS had a 47% higher risk of being previously diagnosed with autoimmune disease (OR 1.47, 95% confidence interval [CI] 1.31–1.64), compared with controls. A positive association was noted for several autoimmune diseases, including myasthenia gravis, polymyositis or dermatomyositis, Guillain-Barre syndrome, type 1 diabetes diagnosed younger than 30 years, multiple sclerosis, and hypothyrosis. The increased risk of any autoimmune disease was greatest during the year before ALS diagnosis, likely due to misdiagnosis. A statistically significantly increased risk was also noted during 2–5 years, but not earlier, before ALS diagnosis. First-degree relatives of ALS patients had however no increased risk of autoimmune diseases compared with first-degree relatives of controls.
Conclusions: Although it is difficult to completely remove the potential effects of misdiagnosis, there is likely a positive association between autoimmune disease (such as type 1 diabetes and multiple sclerosis) and ALS, which is not fully explained by shared familial confounding factors.
Keywords: Amyotrophic lateral sclerosis, autoimmune diseases, inflammation, nested case-control study, association

Introduction
Chronic inflammation has been proposed to promote the development of amyotrophic lateral sclerosis (ALS) (1,2). Typical pathological signs of neuroinflammation, such as astrogliosis and microgliosis, can be observed in the postmortem human samples and rodent models of ALS (3). Peripheral immune infiltration has also been detected in the central nervous system, along with significant changes in the peripheral immune system, of ALS patients (4). Previous studies have examined the association between ALS and autoimmune diseases, suggesting a higher-than-expected overlap between ALS and several classical autoimmune diseases, including type 1 diabetes, celiac disease, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, polymyositis, ulcerative colitis, and Sjögren syndrome (5–7). In our earlier studies, we found a positive association between ALS and type 1 diabetes (8) but not celiac disease (9).

The noted associations raise the possibility of shared risk factors or disease mechanisms between ALS and autoimmune diseases. Shared genetic risk factors might contribute, as one study showed...
a higher-than-expected risk of Behcet’s disease, multiple sclerosis, ulcerative colitis, and Wegener granulomatosis among the offspring of ALS patients (6). Further, C9orf72, a prevalent genetic cause of ALS, has also been related to the development of autoimmune diseases (10,11). Based on such previous knowledge, we performed a nationwide register-based nested case-control study to comprehensively assess the associations of 43 autoimmune diseases with the subsequent risk of ALS in Sweden. To evaluate the contribution of familial confounding to these associations, we also performed a follow-up study among the first-degree relatives of the cases and controls.

Materials and methods

Study base

Our study population included all individuals that were born between 1932 and 2013 in Sweden, according to the Swedish Total Population Register (12) \(N = 8,575,515\). We followed this population from 1 January 1990 or date of birth, whichever came later, until date of ALS diagnosis, death, emigration out of Sweden, or 31 December 2013, whichever came first, through cross-linkages to the Swedish Patient Register (13), Causes of Death Register (14), and Migration Register (a part of the Total Population Register) using the unique personal identification numbers (15). All individuals that died, migrated out of Sweden, or were diagnosed with ALS before start of follow-up were excluded, leaving 8,269,319 persons (96%) in the final cohort.

Ascertainment of ALS

The Swedish Patient Register began to collect information on hospital discharge records in 1964 and reached national coverage in 1987 (13). From 2001 it also collected data on hospital-based outpatient specialist care. Diagnoses are classified according to the Swedish revisions of the International Classification of Disease (ICD) codes (ICD-7 before 1969, ICD-8 during 1969–1986, ICD-9 during 1987–1996, and ICD-10 from 1997 onward). Through this register, we identified all individuals of the above cohort that had a newly diagnosed ALS (ICD-9 335.2 or ICD-10 G12.2) during follow-up \(N = 3561\) and used date of the first hospital visit concerning ALS as the date of ALS diagnosis. In a validation study in Stockholm during 2013–2014, an ALS diagnosis based on the Swedish Patient Register was shown to have a positive predictive value of 91% (16).

Nested case-control study

We conducted a nested case-control study within the above study base to evaluate the associations of different autoimmune diseases with the risk of ALS. We defined cases as individuals that were diagnosed with ALS during follow-up. Using the method of incidence density sampling (17), we randomly selected 10 controls per case that were individually matched to the case by age, sex, and county of birth. Controls had to be alive and free of ALS before and on the diagnosis date of the case. The date of diagnosis for the cases and the date of selection for the controls were used as the index date.

Ascertainment of autoimmune diseases

We then linked the cases and controls to the Patient Register again to ascertain history of autoimmune diseases from 1 January 1964 until index date. We studied 43 major autoimmune diseases including diseases of nervous system, gastrointestinal system, skin and subcutaneous tissue, musculoskeletal system, circulatory system, and endocrine system. The corresponding ICD codes for the autoimmune diseases are listed in Supplementary Table e-1. We identified diagnoses of autoimmune diseases through a hospital visit concerning a specific autoimmune disease and defined the date of first hospital visit as the diagnosis date of the respective disease, according to the Patient Register. In the main analysis, we used at least one hospital visit with an autoimmune disease as either the primary diagnosis or a secondary diagnosis as the definition of autoimmune diseases. In a sensitivity analysis however, we restricted the definition to either at least one hospital visit with an autoimmune disease listed as the primary diagnosis or at least two hospital visits concerning the same autoimmune disease. To allay concern about misdiagnosis, in another sensitivity analysis, we excluded multiple sclerosis, polymyositis/dermatomyositis, myasthenia gravis and Guillain-Barré syndrome–conditions with greater similarity in symptomology as ALS–from the definition of autoimmune diseases.

Follow-up studies of first-degree relatives of ALS patients and controls

To assess if familial factors, genetic and non-genetic, could contribute to the association between autoimmune diseases and ALS, we also studied if first-degree relatives of ALS patients were at a higher risk of autoimmune diseases than first-degree relatives of the controls. We identified full siblings and children of ALS patients \(N = 5375\) full siblings, \(N = 6805\) children) and their controls \(N = 53,365\) full siblings, \(N = 68,184\) children) from the Swedish Multi-Generation Register, which includes familial links for vast majority of the Swedish residents born since 1932 (18). We then followed these first-degree relatives from 1
Table 1. Characteristics of patients with amyotrophic lateral sclerosis (ALS), their matched controls, and the respective relatives of both groups, a nested case-control study in Sweden, 1990–2013.

| Characteristics                        | Patients with ALS | Controls | Siblings of ALS patients | Siblings of controls | Children of ALS patients | Children of controls |
|----------------------------------------|-------------------|----------|--------------------------|----------------------|--------------------------|----------------------|
| Total                                   | 3561              | 35,610   | 5013                     | 48,751               | 6589                     | 65,980               |
| Sex, n (%)                              |                   |          |                          |                      |                          |                      |
| Male                                    |                   |          |                          |                      |                          |                      |
|                                        | 2136 (59.98)      | 21,360   | 2625 (52.36)             | 24,954 (51.19)       | 3378 (51.27)             | 33,755 (51.16)       |
| Female                                  | 1425 (40.02)      | 14,250   | 2388 (47.64)             | 23,797 (48.81)       | 3211 (48.73)             | 32,225 (48.84)       |
| Mean age at index date or cohort entry (SD)* | 60.58 (11.22)    | 60.58 (11.21) | 41.40 (10.17) | 41.41 (10.20) | 17.17 (9.74) | 16.98 (9.95) |
| Education, n (%)                        |                   |          |                          |                      |                          |                      |
| ≤9 years                                | 1164 (32.69)      | 11,683   | 1566 (31.24)             | 15,450 (31.69)       | 529 (8.03)               | 5069 (7.68)          |
| 10–12 years                             | 1514 (42.52)      | 14,762   | 2232 (44.52)             | 21,255 (43.60)       | 3069 (46.58)             | 30,181 (45.74)       |
| University+                             | 839 (23.81)       | 8911     | 1181 (23.56)             | 11,682 (23.96)       | 2583 (39.20)             | 26,178 (39.68)       |
| Missing                                 | 44 (1.24)         | 254      | 34 (0.68)                | 364 (0.75)           | 408 (6.19)               | 4552 (6.90)          |
| Socioeconomic status, n (%)             |                   |          |                          |                      |                          |                      |
| Blue-collar                             | 1253 (35.19)      | 12,770   | 2063 (41.15)             | 19,704 (40.42)       | 1772 (26.89)             | 17,305 (26.23)       |
| White-collar                            | 1508 (42.35)      | 15,084   | 1784 (35.59)             | 18,390 (37.72)       | 1006 (15.27)             | 10,277 (15.58)       |
| Farmers/ self-employed                  | 240 (6.74)        | 2418     | 340 (6.78)               | 3122 (6.40)          | 62 (0.94)                | 761 (1.15)           |
| Others                                  | 110 (3.09)        | 1185     | 204 (4.07)               | 1819 (3.73)          | 404 (6.13)               | 3931 (5.96)          |
| Missing                                 | 450 (12.64)       | 4153     | 622 (12.41)              | 5716 (11.72)         | 3345 (50.77)             | 33,706 (51.09)       |

*Mean age at index date or cohort entry (SD): mean age at index date for patients with ALS and controls, and mean age at cohort entry for siblings and children of ALS patients and siblings and children of controls.

January 1990 or date of birth, whichever came later, until date of diagnosis of any autoimmune disease, death, emigration out of Sweden, or 31 December 2013, whichever came first. Because we aimed to study incident autoimmune diseases in this analysis, we defined the study period as 1990 onward because the Swedish Patient Register was nationwide complete for inpatient care records since 1987. In this analysis, first-degree relatives that had been diagnosed with any autoimmune disease (191 full siblings and 90 children of ALS patients, and 1862 full siblings and 957 children of controls), emigrated out of Sweden (115 full siblings and 38 children of ALS patients, and 1239 full siblings and 385 children of controls) or died (56 full siblings and 88 children of ALS patients, and 513 full siblings and 862 children of controls) before cohort entry were excluded, leaving 5013 full siblings and 6589 children of ALS patients and 48,751 full siblings and 65,980 children of controls in the analysis.

Covariables

For the cases and controls as well as their first-degree relatives, we identified years of education from the Swedish Education Register which was established in 1985 by Statistics Sweden. Education was then categorized as “≤9 years”, “10–12 years”, “university or doctoral studies”, or “unknown”. The information of socioeconomic status was extracted from the Swedish Population and Housing Census in 1990 and categorized as “blue collar”, “white collar”, “self-employed/farmers”, or “other”.

Statistical analysis

All the analyses were performed using Stata ver.16 (StataCorp, College Station, TX, RRID: SCR_012763). In the nested case-control study we used conditional logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of autoimmune diseases with ALS, after adjusting for the matching variables (age, sex, county of birth), education, and socioeconomic status. We also assessed the association in different time windows, namely ≥6 years, 2–5 years, or 0–1 year before the index date. We separated 0–1 year before index date from the other time windows because the diagnostic delay is approximatively one year in Sweden (19). We then divided the remaining time to four time windows with approximately similar numbers of exposed cases, as 0–1 year before the index date, namely 2–5, 6–15, and ≥16 years before the index date. Because the association was not statistically significant for 6–15 and ≥16 years before the index date, we combined these two groups as ≥6 years before the index date. In the follow-up study of the relatives, we used Cox proportional hazard regression model to evaluate the HRs with 95% CIs of autoimmune diseases among relatives of ALS patients, compared with the relatives of controls. The underlying time scale used was attained age, and models were further adjusted for age at cohort entry, sex, county of birth, education, and socioeconomic status of the relatives of patients and matched controls. In addition to any autoimmune disease, we also examined the associations for individual autoimmune diseases that affected at least
Table 2. Association of autoimmune diseases with the risk of amyotrophic lateral sclerosis (ALS), adjusted for age, sex, county of birth, education, and socioeconomic status, a nested case-control study in Sweden, 1990–2013.

| Autoimmune diseases          | Patients with ALS, n (%) | Controls, n (%) | OR (95% CI)a | FDRb |
|------------------------------|--------------------------|-----------------|--------------|------|
| Any autoimmune disease       | 500 (14.04)              | 3743 (10.51)    | 1.47 (1.31–1.64) | 5.04E-11 |
| Myasthenia gravis            | 17 (0.48)                | 11 (0.03)       | 17.2 (7.66–38.6) | 5.04E-11 |
| Polymyositis/dermatomyositis | 17 (0.48)                | 15 (0.04)       | 10.2 (4.82–21.4) | 4.83E-09 |
| Guillain-Barre syndrome      | 46 (1.29)                | 74 (0.21)       | 8.09 (5.24–12.5) | 7.38E-20 |
| Type 1 diabetes, any         | 87 (2.44)                | 844 (2.37)      | 1.01 (0.79–1.29) | 0.944 |
| Type 1 diabetes, <30y        | 14 (0.39)                | 56 (0.16)       | 2.44 (1.26–4.74) | 0.024 |
| Multiple sclerosis           | 25 (0.70)                | 107 (0.30)      | 2.28 (1.37–3.77) | 0.004 |
| Hypothyreosis                | 64 (1.80)                | 419 (1.18)      | 1.49 (1.11–2.01) | 0.024 |
| Ankylosing spondylitis       | 30 (0.84)                | 213 (0.60)      | 1.59 (1.04–2.44) | 0.074 |
| Polymyalgia rheumatica       | 19 (0.53)                | 143 (0.40)      | 1.59 (0.97–2.60) | 0.124 |
| Temporal arteritis           | 12 (0.34)                | 79 (0.22)       | 1.61 (0.85–3.07) | 0.237 |
| Adult rheumatoid arthritis   | 79 (1.96)                | 689 (1.93)      | 1.27 (0.99–1.64) | 0.124 |
| Crohn’s disease              | 19 (0.53)                | 171 (0.48)      | 1.25 (0.76–2.06) | 0.512 |
| Sarcoidosis                  | 13 (0.37)                | 107 (0.30)      | 1.34 (0.75–2.41) | 0.486 |
| Sjögren’s syndrome           | 11 (0.31)                | 92 (0.26)       | 1.18 (0.59–2.36) | 0.775 |
| Ulcerative colitis           | 31 (0.87)                | 293 (0.82)      | 1.12 (0.75–1.66) | 0.737 |
| Hypothyroidism               | 26 (0.73)                | 270 (0.76)      | 1.06 (0.69–1.63) | 0.887 |
| Psoriasis                    | 54 (1.52)                | 546 (1.53)      | 1.03 (0.76–1.39) | 0.899 |

aOR: Odds ratio; CI: confidence interval. Bold numbers indicate significant differences at p < 0.05.
bFDR: false discovery rate. Bold numbers indicate significant differences at FDR < 0.05.

10 ALS cases. To rule out confounding due to increased surveillance, we used appendicitis as a negative control, assuming a null association between appendicitis and ALS. We considered a 2-sided p value ≤0.05 as statistically significant. To account for multiple testing in the main results, we computed the false discovery rates (FDRs) (20). FDR <0.05 was considered statistically significant. This threshold means that less than 5% of the declared significant results are expected to be false positives. We did not apply the multiplicity adjustment to the sensitivity analyses because of low statistical power. The results of the analyses for siblings and children were nearly all statistically insignificant using the standard p values, a multiple-testing adjustment was therefore not applied.

The study was approved by the Regional Ethical Review Board in Stockholm.

Results

Table 1 shows the distributions by sex, age, education and socioeconomic status between ALS patients and their matched controls, as well as among siblings and children of both groups. The mean age at ALS diagnosis was 60.58 years (standard deviation [SD] = 11.22).

Individuals with a previous history of any of the 43 autoimmune diseases had a 47% higher risk of developing ALS than others (OR 1.47, 95% CI 1.31–1.64) (Table 2). Statistically significant associations were noted for myasthenia gravis, polymyositis/dermatomyositis, Guillain-Barré syndrome, type 1 diabetes diagnosed before age 30, multiple sclerosis and hypothyreosis. The results did not change greatly when we restricted the definition of autoimmune diseases by including only primary diagnosis (OR 1.40, 95% CI 1.24–1.59) (Supplementary Table e-2) or including at least two hospital visits concerning the same disease (OR 1.37, 95% CI 1.19–1.57) (Supplementary Table e-3). Excluding multiple sclerosis, polymyositis/dermatomyositis, myasthenia gravis and Guillain-Barré syndrome from the definition of autoimmune diseases led to a diminished but still positive association between any autoimmune disease and ALS (OR 1.25, 95% CI 1.11–1.40).

The association of any autoimmune disease with ALS was strongest during the year before index date (OR 5.11, 95% CI 4.05–6.46), but a statistically significant positive association was also noted during 2–5 years before index date (Table 3). Among individual autoimmune diseases, a positive association was noted for Guillain-Barré syndrome and type 1 diabetes diagnosed before 30 years of age not only during the five years but also more than five years before index date. Among the patients with ALS, 115 had appendicitis whereas among the controls 1206 had appendicitis before index date, leading to a null association between appendicitis and ALS (OR 0.96, 95% CI 0.78–1.18).

There was no increased risk of autoimmune diseases among siblings (HR 0.91, 95% CI 0.91–1.08) or children (HR 1.03, 95% CI 0.91–1.17) of ALS patients, compared with the siblings and children of ALS-free controls (Tables 4, 5). Siblings (HR 0.99, 95% CI 0.78–1.24) and children (HR 0.98, 95% CI 0.79–1.21) of ALS patients did not have increased risk of appendicitis, compared with the siblings and children of the controls.
Discussion

Using a national register-based study sample, we found that previous autoimmune disease was associated with a higher subsequent risk of ALS. In contrast, we found no higher risk of autoimmune diseases among first-degree relatives of ALS patients, namely full siblings and children, when compared with first-degree relatives of ALS-free controls.

Our findings are consistent with previous studies that demonstrated associations of ALS with myasthenia gravis (5,21), polymyositis/dermatomyositis, Guillain-Barre syndrome (23), type 1 diabetes (5,8), multiple sclerosis (5,24) and hypothyreosis (5). Our study is the first to include 43 autoimmune diseases and comprehensively examine their relationships with ALS. The positive association noted between any autoimmune disease and ALS risk might be attributable to different reasons. The finding that the strongest association was noted during the year before ALS diagnosis might support diagnosis uncertainty as a potential explanation. A diagnostic delay of 12 months has been shown in ALS patients in Sweden (19), thus it is possible that some patients with ALS might be misdiagnosed with autoimmune disease first. In the sensitivity analyses, we therefore restricted the definition of autoimmune diseases to hospital visits where autoimmune diseases were noted as the primary diagnosis or at least two hospital visits concerning the same autoimmune disease. The similar results obtained from these analyses alleviated this concern to some extent. To further allay concern about misdiagnosis, we excluded multiple sclerosis, polymyositis/dermatomyositis, myasthenia gravis and Guillain-Barré syndrome—conditions with greater similarity in symptomology as ALS—from the definition of autoimmune diseases, and found a diminished but still positive association between autoimmune diseases and ALS. The positive association noted during the 2–5 years before diagnosis also argues against misdiagnosis as the only explanation for this association. Surveillance bias might be another explanation. Patients with autoimmune diseases might have a greater chance of being diagnosed with another condition, including ALS, due to their closer access to health care. We used appendicitis as a negative control and found indeed no association between appendicitis and ALS, arguing against surveillance bias as the sole explanation for the association noted between autoimmune disease and ALS.

Apart from methodological concerns, a positive association between autoimmune disease and ALS, as noted in the present study and previous research (5,6), is also biologically plausible. Common disease mechanisms might for example include dysfunctional regulatory T cells (25,26) and greater prevalence of C9orf72 intermediate expansions in relation to systemic autoimmune diseases (11). The newly recognized mutation in ALS, TBK1, as
a master regulator of innate immune system signaling, has prominent roles in autophagy and inflammation (27). The IgG purified from a group of sporadic ALS patients was demonstrated to interact with the presynaptic membrane of motor neurons and modulate synaptic transmission, which also suggests an autoimmune mechanism (28). The markedly activated MHC-I and immunoproteasome in motor neurons may also activate a cytotoxic autoimmune response (29).

We found no higher risk of autoimmune diseases among siblings and children of patients with ALS, compared with siblings and children of ALS-free controls. This suggests that the association of autoimmune diseases with ALS is not likely due to genetic or non-genetic confounding factors that are shared between siblings or between parents and children, and may instead indicate a continuum of disease process, namely that autoimmune disease might lead to a chronic inflammation which subsequently contributes to ALS development. The idea that systemic inflammation can initiate or perpetuate neurodegeneration has been supported by previous studies (30–32). A higher risk of hypothyreosis was noted among ALS patients and their siblings, compared with the corresponding controls. Although chance finding cannot be ruled out completely, two large retrospective studies also reported that 20% of ALS patients had a personal or family history of thyroid disease (33,34). A case-control study suggested an increased incidence of hereditary thyroid disease among the

### Table 4. Risk of autoimmune diseases among siblings of patients with amyotrophic lateral sclerosis (ALS), as compared to siblings of ALS-free controls, adjusted for age, sex, county of birth, education, and socioeconomic status.

| Autoimmune diseases                  | Siblings of patients with ALS, n (%) | Siblings of controls, n (%) | HR (95% CI)a |
|--------------------------------------|-------------------------------------|----------------------------|--------------|
| Any autoimmune disease               | 642 (12.81)                         | 4634 (13.2)                | 0.91 (0.91–1.08) |
| Myasthenia gravis                    | 2 (0.04)                            | 18 (0.04)                  | 1.29 (0.29–5.64) |
| Polymyositis/dermatomyositis         | 6 (0.12)                            | 25 (0.05)                  | 2.17 (0.83–5.72) |
| Guillain-Barre syndrome              | 3 (0.06)                            | 57 (0.12)                  | 0.60 (0.19–1.94) |
| Type 1 diabetes, any                 | 119 (2.37)                          | 1232 (2.53)                | 0.96 (0.78–1.17) |
| Type 1 diabetes, <30y                | 1 (0.02)                            | 8 (0.02)                   | 9.46 (0.59–152) |
| Multiple sclerosis                   | 12 (0.24)                           | 137 (0.28)                 | 0.85 (0.44–1.61) |
| Hypothyreosis                        | 147 (2.93)                          | 1200 (2.46)                | 1.30 (1.09–1.56) |
| Ankylosing spondylitis               | 16 (0.32)                           | 143 (0.29)                 | 1.00 (0.57–1.78) |
| Polymyalgia rheumatica               | 48 (0.96)                           | 353 (0.72)                 | 1.46 (1.06–2.00) |
| Temporal arteritis                   | 17 (0.34)                           | 150 (0.31)                 | 1.21 (0.72–2.03) |
| Adult rheumatoid arthritis           | 71 (1.42)                           | 819 (1.68)                 | 0.86 (0.66–1.11) |
| Crohn’s disease                      | 16 (0.32)                           | 187 (0.38)                 | 0.85 (0.49–1.46) |
| Sarcoidosis                          | 14 (0.28)                           | 140 (0.29)                 | 0.97 (0.53–1.73) |
| Sjögren’s syndrome                   | 26 (0.52)                           | 204 (0.42)                 | 1.17 (0.75–1.83) |
| Ulcerative colitis                   | 26 (0.52)                           | 387 (0.79)                 | 0.70 (0.46–1.06) |
| Hyperthyroidism                      | 51 (1.02)                           | 498 (1.02)                 | 0.92 (0.67–1.28) |
| Psoriasis                            | 111 (2.21)                          | 1244 (2.55)                | 0.92 (0.76–1.13) |

### Table 5. Risk of autoimmune diseases among children of patients with amyotrophic lateral sclerosis (ALS), as compared to siblings of ALS-free controls, adjusted for age, sex, county of birth, education, and socioeconomic status.

| Autoimmune diseases                  | Children of patients with ALS, n (%) | Children of Controls, n (%) | HR (95% CI)a |
|--------------------------------------|-------------------------------------|----------------------------|--------------|
| Any autoimmune disease               | 491 (7.45)                          | 4670 (7.08)                | 1.03 (0.91–1.17) |
| Myasthenia gravis                    | 1 (0.02)                            | 9 (0.01)                   | 5.02 (0.45–55.4) |
| Polymyositis/dermatomyositis         | 2 (0.03)                            | 9 (0.01)                   | –            |
| Guillain-Barre syndrome              | 0 (0.00)                            | 26 (0.04)                  | –            |
| Type 1 diabetes, any                 | 47 (0.71)                           | 466 (0.71)                 | 1.06 (0.69–1.63) |
| Type 1 diabetes, <30y                | 23 (0.35)                           | 220 (0.33)                 | 0.24 (0.03–1.72) |
| Multiple sclerosis                   | 14 (0.21)                           | 174 (0.26)                 | 0.67 (0.33–1.37) |
| Hypothyreosis                        | 72 (1.09)                           | 707 (1.07)                 | 0.97 (0.68–1.38) |
| Ankylosing spondylitis               | 14 (0.21)                           | 144 (0.22)                 | 1.00 (0.51–1.99) |
| Polymyalgia rheumatica               | 4 (0.06)                            | 20 (0.03)                  | 2.47 (0.83–7.36) |
| Temporal arteritis                   | 1 (0.02)                            | 14 (0.02)                  | –            |
| Adult rheumatoid arthritis           | 40 (0.61)                           | 341 (0.52)                 | 1.21 (0.81–1.80) |
| Crohn’s disease                      | 32 (0.49)                           | 286 (0.43)                 | 1.08 (0.63–1.84) |
| Sarcoidosis                          | 17 (0.26)                           | 157 (0.24)                 | 0.71 (0.34–1.45) |
| Sjögren’s syndrome                   | 8 (0.12)                            | 56 (0.08)                  | 1.19 (0.47–3.00) |
| Ulcerative colitis                   | 48 (0.73)                           | 509 (0.77)                 | 1.11 (0.76–1.62) |
| Hyperthyroidism                      | 53 (0.80)                           | 377 (0.57)                 | 1.45 (1.02–2.06) |
| Psoriasis                            | 117 (1.78)                          | 1024 (1.55)                | 1.10 (0.85–1.42) |

*HR: Hazard ratio; CI: confidence interval. Bold numbers indicate significant differences at p < 0.05.*
relatives of ALS patients (35) and a cohort study found a higher-than-expected risk of ALS among individuals with a prior diagnosis of severe hypothyroidism, myxedema (5). We focused on incident cases of autoimmune diseases diagnosed after 1990 among the siblings and children, whereas all autoimmune diseases anytime between 1964 and the index date for the proband individuals. The fact that we excluded similar proportions of siblings (3.55% for siblings of ALS patients and 3.49% for siblings of controls) and children (1.32% for children of ALS patients and 1.40% for children of controls) due to prevalent autoimmune diseases before start of follow-up suggested indeed that siblings and children of ALS patients had similar risk of autoimmune diseases even before 1990.

The main strengths of our study are the nationwide study design, the large sample size, the complete follow-up, and the objectively and prospectively collected data. A limitation of the study is the lack of validation for patients with concurrent ALS and autoimmune disease, because of the historical and nationwide nature of data. However, the validity of ALS diagnosis (16) and many autoimmune diseases, including multiple sclerosis (36), rheumatoid arthritis (37), Guillain–Barré syndrome (38), diabetes (39), psoriasis (40), ulcerative colitis and Crohn’s disease (41), polymyalgia rheumatica (42), ankylosing spondylitis (43), celiac disease (44), Wegener’s granulomatosis (45), Sarcoidosis (46), Addison’s disease (47), pemphigoid (48), is known to be satisfactory in the Swedish Patient Register. The similar results noted in the sensitivity analyses where we used more strict definitions of autoimmune diseases also alleviated the concern to some extent. Another limitation of our study is that we lacked genetic and clinical information for patients with ALS and were therefore unable to assess if the association would differ by disease characteristics. Similarly, whether the clinical characteristics of ALS differ by preexisting autoimmune disease remains to be studied. Additionally, number of cases with autoimmune diseases was low among children of patients with ALS and their controls, so the analysis among children suffered from low statistical power. Finally, generalizability of our findings to other countries needs to be further tested.

In summary, we found a positive association between autoimmune diseases and subsequent risk of ALS. Although it is difficult to rule out the possibility of misdiagnosis and surveillance bias, there is likely still a positive association between autoimmune disease (such as type 1 diabetes and multiple sclerosis) and ALS. The lack of increased risk of autoimmune diseases among siblings and children of ALS patients indicates little contribution of genetic and non-genetic familial confounding factors in the association.

Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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