Population-Level Evidence for an Autoimmune Etiology of Epilepsy

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Abstract

Importance—Epilepsy is a debilitating condition, often with neither a known etiology nor an effective treatment. Autoimmune mechanisms have been increasingly identified.

Objective—To conduct a population-level study investigating the relationship between epilepsy and several common autoimmune diseases.

Design, Setting, and Participant—A retrospective population-based study using claims from a nation-wide employer-provided health insurance plan in the United States. Subjects were beneficiaries enrolled between 1999 and 2006 (n= 2,518,034).

Main Outcomes and Measures—We examined the relationship between epilepsy and 12 autoimmune diseases: type 1 diabetes, psoriasis, rheumatoid arthritis, Graves' disease, Hashimoto's thyroiditis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, Sjögren's syndrome, myasthenia gravis and celiac disease.

Results—The risk of epilepsy is significantly heightened among patients with autoimmune diseases (OR 3.8, 95% CI 3.6–4.0, P<0.001), and is especially pronounced in children (OR 5.2, 95% CI 4.1–6.5; P<0.001). Elevated risk is consistently observed across all 12 autoimmune diseases.

Conclusions and Relevance—Epilepsy and AD frequently co-occur and patients with either condition should undergo surveillance for the other. The potential role of autoimmunity must be given due consideration in epilepsy, so we are not overlooking a treatable etiology.

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Introduction

Epilepsy is a debilitating condition affecting 0.5% to 1% of the world's population. Therapies address manifestations rather than the underlying etiology, which remains unelucidated in most patients, one third of which are refractory to anticonvulsant therapy.[1] Surgical interventions are ineffective in many epilepsy patients, with seizures recurring in 50% of patients within 5 years of surgery,[2] and the number of patients who remain seizure free decreases further over the years to 38%.[3] A deeper understanding of the underlying etiologies is necessary to develop new therapeutic approaches.

Specific autoimmune causes, typically associated with autoantibodies, have been increasingly identified in a subset of previously idiopathic seizure disorders.[4–5,6–10] In some of these situations, seizures are associated with other neurological manifestations, while in others they are the only sign of neurologic autoimmunity. Small case studies and disease specific investigations also report a high incidence of seizures in AD such as systemic lupus erythematosus (SLE)[11–12] and Hashimoto's thyroiditis.[13–14] Further, published reports document success in treating a substantial proportion of patients with presumed autoimmune mechanisms for their seizures with immunotherapy.[15]

Establishing an autoimmune basis in patients with idiopathic epilepsy is important, as it highlights opportunities for developing new strategies for the treatment of medically refractory epilepsy. To date, evidence on the role of autoimmune process in epileptogenesis is mainly based on animal studies and small sample, disease-specific clinical observations. Here, we conduct the largest population study to investigate the relationship between epilepsy and several common autoimmune diseases. Since clinical presentation of seizures, their etiology, and the presence of comorbidities in the elderly differ considerably from younger patients, our study focuses on epilepsy in children (<18 years of age) and non-elderly adults (<=65 years of age).

Methods

Study population and design

We conducted a population-based retrospective cohort study, using claims from a major, nation-wide employer-provided health insurance plan in the United States. Data included dates of enrollment in the insurance program, outpatient and inpatient visits, and prescription drugs dispensed. Demographic data included gender and age. All encounters were coded with up to four International Classification of Diseases, ninth version (ICD-9) codes. Prescription drugs were reported using the National Drug Code.

Subjects were beneficiaries between January 1, 1999 and December 31, 2006, excluding elderly adults greater than 65 years of age. To ensure adequate follow-up, we included only individuals continuously enrolled for at least four years, and we considered only individuals diagnosed with epilepsy two or more years after entry into our study, and with at least two years follow-up after the first recorded epilepsy diagnosis.

The Boston Children's Hospital IRB approved the study and granted a waiver of consent.

Outcome measures

We assessed the relationship between epilepsy and 12 AD selected a priori: type 1 diabetes, psoriasis, rheumatoid arthritis, Graves' disease, Hashimoto's thyroiditis, Crohn's disease, ulcerative colitis, SLE, antiphospholipid syndrome, Sjögren's syndrome, myasthenia gravis and celiac disease. Outcomes were stratified based on age groups: (1) children (<18 years of age); (2) non-elderly adults (<=65 years of age).

Further, we examined the potential effects of common therapies used for treating AD, including aminosalicylates, disease-modifying antirheumatic drugs (DMARD), systemic glucocorticoids, non-steroidal anti-inflammatory drugs (NSAID), anti-TNF agents, and other biologics (eTable 1). Only exposures that occurred prior to the first epileptic seizure were considered. Gender and age were included as covariates. Exposure to medications was expressed as a dichotomous variable.

Case identification

Epilepsy was defined as two or more seizures occurring at least 24 hours apart within a period of two years. Individuals with diagnoses of epilepsy and AD were identified using ICD-9 diagnostic codes (eTable 2), according to previously validated criteria:[16] (1) at least one acute inpatient encounter with the relevant ICD-9 as the primary diagnosis; or (2) at least two healthcare encounters with the relevant ICD-9 within a period of two years. These criteria have been demonstrated to achieve high accuracy in identifying patients from administrative data (sensitivity=92.9%; specificity=91.2%).[16] To further strengthen the specificity of epilepsy case identification, we considered only individuals prescribed at least one course of an anticonvulsant.

Statistical analysis

The risk of epilepsy in AD patients was compared against the risk of epilepsy in individuals without AD using logistic regression, expressed as odds ratios (OR) with 95% confidence interval (CI). All analyses were performed using SPSS software version 21. All statistical tests were 2-sided.

Results

Prevalence of epilepsy

A total of 2,518,034 subjects were included in our study. 0.4% of the study population developed epilepsy (Table 1). The risk of epilepsy is significantly heightened among patients with AD (OR 3.8, 95% CI 3.6–4.0, P<0.001) (Figure 1). Collectively, individuals with AD account for 17.5% of epilepsy patients in the study population.

Elevated risk is consistent across different AD. Patients with antiphospholipid syndrome and SLE had the highest risk, with an nine-fold and seven-fold increased risk of epilepsy respectively; followed by patients with type 1 diabetes and myasthenia gravis, eliciting a five-fold increased risk of epilepsy. The risk of epilepsy is especially pronounced in children. Overall, children with AD have a five-fold increased risk of epilepsy (Figure 2). In

comparison, non-elderly adults with AD have a four-fold increased risk of epilepsy (Figure 3).

Timing of epilepsy

Patients experienced their first epileptic seizure both before and after the onset of AD. The onset of epilepsy preceded the diagnosis of AD in 30% of cases. And in 30% of cases, the first epileptic seizure occurred within the first year of disease diagnosis.

Effects of medications

More than 70% patients with AD and epilepsy were not exposed to anticonvulsants for at least two years prior to the diagnosis of AD. The risk of epilepsy in AD patients persists after adjusting for medication use, including aminosalicylates, DMARD, systemic glucocorticoids, NSAID, anti-TNF agents and other biologics (OR 4.1, 95 CI% 3.9–4.3, P<0.001)(Table 2). There is no evidence that any of the medications lead to increased risk of epilepsy. Patients exposed to aminosalicylates, NSAID, anti-TNF agents and other biologics appear to have a reduced risk of epilepsy.

Discussion

Clinicians caring for patients with either AD or epilepsy should be aware of the strong association between them. Indeed, nearly one in five epilepsy patients has a coexisting AD. Elevated epilepsy prevalence has been previously reported in AD where pathology directly involves the brain. SLE is associated with a range of inflammatory mechanisms in the brain, and cerebral ischemia is a common manifestation of antiphospholipid syndrome. Rates of epilepsy in SLE vary between 4 and 51%,[11–12,17] and in antiphospholipid syndrome from 3% to 8%.[18–19] Our analysis is consistent with these published data. In addition, we establish the association across a wide range of AD including those where the primary pathology is not known to directly affect the brain. Of note, patients with myasthenia gravis had a 5-fold increased risk of epilepsy. While our data do not elucidate the underlying causes of this relationship, they strongly support further effort to explore the potential role of autoimmunity in epileptogenesis. A focus on autoimmune mechanisms can focus and guide translational approaches to new therapeutic options.

Seizures tend to occur within the first 1 to 2 years after the AD diagnosis. The risk of epilepsy is consistently higher in children with AD, compared with adults with the same AD. Both clinical and biological features of AD may be influenced by the age at disease onset,[20–21] with childhood onset AD often more severe than adult onset AD.[22–23] Consistent with a previous study[11], our data showed that the female gender is associated with a higher risk of epilepsy.

Effects of medications

Prior studies on the effects of anticonvulsants have produced inconsistent results. Anticonvulsants have been reported to exert anti-inflammatory effects,[24] but also, there are reported cases of SLE-like symptoms caused by carbamazepine;[25] however, evidence for causation remains largely anecdotal and inconsistent, with other studies failing to show a

relationship between anticonvulsant use and SLE.[26] Our main findings are clearly not explained purely by immunological side effects of anticonvulsants, as 70% patients with AD and epilepsy were not exposed to anticonvulsants for at least two years prior to the diagnosis of AD.

We also explore whether specific treatments for AD may cause or prevent seizures. In some prior studies, corticosteroids, certain immunologic agents and NSAID have been found to induce seizures,[27–29] and to reduce the risk of seizures in others.[30–32] We find the risk of epilepsy in patients with autoimmune diseases persists, even after adjustment for these medications in regression models. Exposures to aminosalicylates, NSAID and biologics appear to reduce epilepsy risk. However, since we did not study the duration and dose of exposures, whether or not these medications confer a protective effect against developing epilepsy is unknown, and beyond the scope of this study.

What is the nature of the relationship?

Among the growing list of neuronal autoantibodies identified in some patients with epilepsy, some appear to play a pathogenic role while others may merely be markers of disease. For example, compelling clinical and laboratory evidence supports the pathogenicity of antibodies against the NR1 subunit of the N-methyl D-aspartate receptor (NMDAR). Antibodies from patients with anti-NMDAR encephalitis cause a decrease of the density of NMDAR through antibody-mediated cross-linking and internalization, resulting in the impairment of NMDAR-mediated synaptic function.[33–34] Clinical outcome of these patients has been found to correlate with antibody tires in CSF, and in most cases, symptoms are reversible by immunotherapy.[35–36] On the other hand, the pathogenic role of other autoantibodies, particularly those directed against intracellular antigens such as glutamic acid decarboxylase, is less clear.

The immune response in AD involves the adaptive immune system for which the presence of autoimmune antibodies is just one manifestation, as well as the innate arm, as characterized by the increased synthesis and release of pro-inflammatory cytokines and chemokines. Thus, the occurrence of epilepsy in patients with AD might be attributable to the inflammatory component of AD, as evidenced by the expression of sustained inflammatory response in the resected brain tissue from patients undergoing surgery for refractory epilepsy, including activation of microglia and astrocytes and production of pro-inflammatory molecules.[37–39] Additionally, there is evidence of the anticonvulsant effects of selected anti-inflammatory drugs,[40–41] and the anti-inflammatory properties of some anticonvulsant medications, such as valproate[42] and carbamazepine.[43]

While autoimmunity and neuroinflammation are likely to play a role in a subset of epilepsy in autoimmune patients, seizures may also be a result of the cerebrovascular complications that are commonly associated with many autoimmune conditions, including SLE, RA, Sjögren's syndrome, type 1 diabetes and inflammatory bowel disease. Thus the risk of seizures in these patients is heightened independent of immunologic causes. However, given that susceptibility to cerebrovascular conditions correlates strongly with advancing age, our findings showing children with AD at a much higher risk of epilepsy compared with adults with the same autoimmune condition suggest that the relationship cannot be entirely

attributable to the cerebrovascular complications secondary to AD. Further, the association between epilepsy and AD that do not directly affect the brain, including myasthenia gravis and psoriasis, strongly implicates that other mechanisms are at play.

In reality, epilepsy is not a single disease entity, but a variety of disorders reflecting the underlying brain dysfunction that may result from many different causes. Similarly, it is likely that multiple factors contribute to the risk of epilepsy in patients with autoimmune conditions. First, some patients with AD may have coincidental epilepsy that is unrelated to autoimmune mechanisms; we have accounted for this via the comparison to the non-AD population. Second, some patients with AD may have non-inflammatory brain pathology that gives rise to epilepsy; as above, while this is likely to be true, we do not think it fully explains the heightened risk as described above. Third, some patients with AD and epilepsy may have known autoantibodies such as NMDAR antibodies. Lastly, we speculate that the largest subgroup consists of patients where as yet undefined autoimmune and inflammatory mechanisms lead to their epilepsy. Further studies are needed to elucidate the pathogenesis of epilepsy in autoimmune patients, especially in the latter subgroup. Identifying these mechanisms may also yield insights and novel treatment approaches for patients with epilepsy but without AD, particularly those without a known etiology and/or refractory epilepsy.

Study limitations

There are several limitations to our study. First, claims data have limited resolution and do not permit fine-grained classification of epilepsy type. However, the validity of using ICD codes in administrative data for identifying epilepsy cases has been demonstrated in several studies.[16,44–45] To maximize the specificity of our case identification, we have chosen a stringent case definition for diagnosis of epilepsy that has been previously validated.[16] In addition, we selected only epilepsy patients who were prescribed antiepileptic medications, thus minimizing the likelihood of misclassification of non-epileptic seizures, such as those induced by hypoglycemia, alcohol or drugs. The consistency between our results and published data on the relationships between epilepsy and several AD, including SLE and antiphospholipid syndrome, further validates our approach. Second, because our study participants are privately insured individuals, findings from these data may not generalize to other populations. Third, since our data spanned seven years and the set of AD included in our study is non-exhaustive, incidence of epilepsy in AD patients may be underestimated.

While there are limitations to claims data, the availability of large number of patients makes it possible to study the relationships between rare diseases, which may not have been observable in traditional studies involving chart reviews or surveys. Further, claims data are systematically collected, and provide longitudinal information that cross facilities, geographical locations and population demographics, thereby enhancing the generalizability of the research and limiting selection biases. While our study does not prove that epilepsy and AD indeed share a common pathophysiology, which remains to be elucidated, our data provide important epidemiology evidence that lends support to the hypothesis, and highlights the need for in-depth investigation.

Conclusions

Epilepsy and AD frequently co-occur and patients with either condition should undergo surveillance for the other. Because AD affect 8% of the population, and for reasons unknown their prevalence is rising, the link between autoimmunity and epilepsy will underpin a rise in the global burden of neurological disease. The potential role of autoimmunity must be given due consideration in refractory epilepsy, so we are not overlooking a treatable etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Autoimmune Disease (AD)	N	Epilepsy (%)		Odds Ratio [95% CI]
Antiphospholipid syndrome	5423	3.2		9.0 [7.7 , 10.5]
SLE	9696	2.5		7.4 [6.5 , 8.4]
Type 1 diabetes	43704	1.8		5.2 [4.9 , 5.6]
Myasthenia gravis	1070	1.7		4.9 [3.1 , 7.8]
Celiac disease	1885	1.5		4.5 [3.1 , 6.5]
Sjögren's syndrome	3614	1.5		4.3 [3.2 , 5.6]
Rheumatoid arthritis	22890	1.2		3.5 [3.1 , 4.0]
Crohn's disease	8774	1.1		3.1 [2.5 , 3.8]
Ulcerative colitis	10690	0.9		2.5 [2.1 , 3.1]
Hashimoto's thyroiditis	9830	0.8		2.4 [2.0 , 3.0]
Grave's disease	9758	0.8		2.2 [1.8 , 2.8]
Psoriasis	23542	0.7		1.9 [1.6 , 2.3]
Any of the above AD	135394	1.3		3.8 [3.6 , 4.0]

1.0   2.0   4.0   8.0   16.0

Odds ratio (log scale)

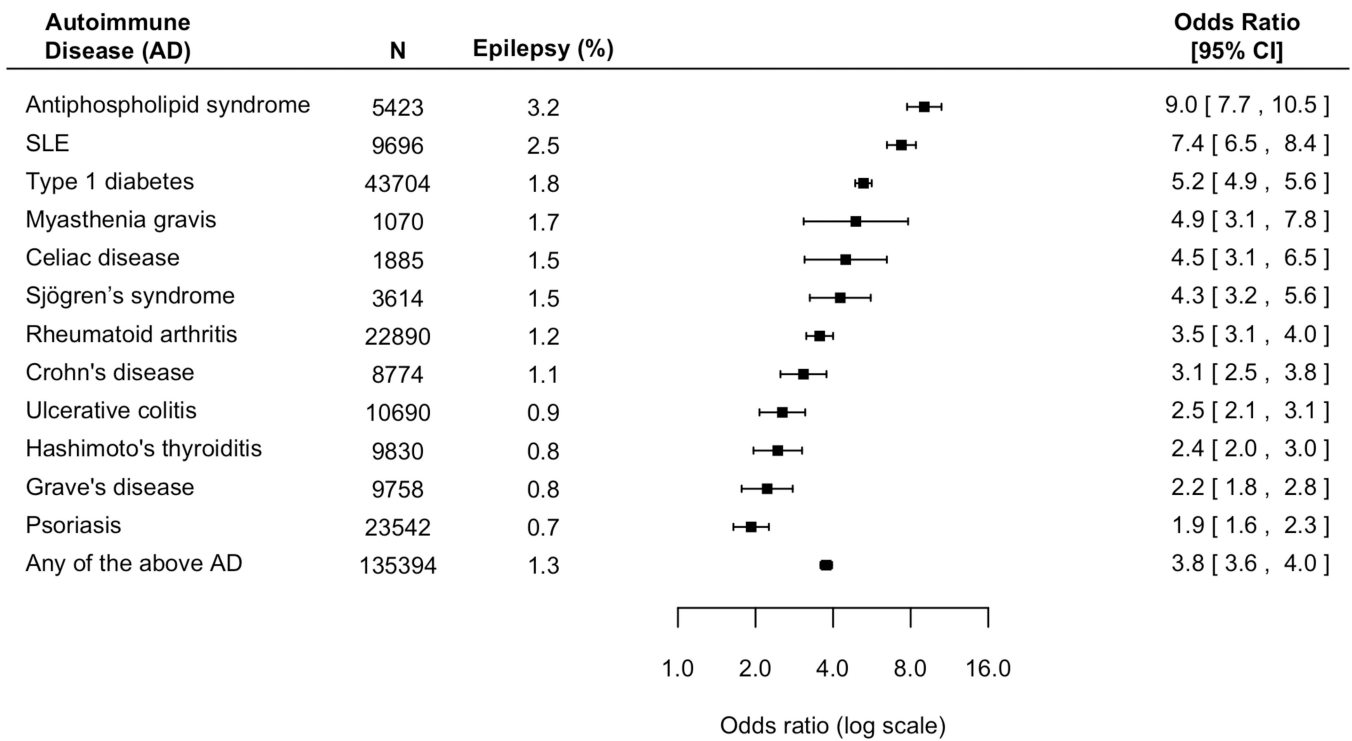**Figure 1. The risk of epilepsy in children (<18 years of age) and non-elderly adults (<=65 years of age) with autoimmune diseases, compared with individuals without autoimmune diseases**
Epilepsy susceptibility is consistently heightened in patients with autoimmune disorders (P<0.001). Collectively, patients with any of the autoimmune diseases under study constituted 17.5% of the total epilepsy population.

Autoimmune Disease (AD)	N	Epilepsy (%)		Odds Ratio [95% CI]
SLE	123	7.3		21.6 [11.0 , 42.7]
Celiac disease	261	5.7		16.7 [9.9 , 28.2]
Ulcerative colitis	201	3		8.4 [3.7 , 19.0]
Hashimoto's thyroiditis	369	2.4		6.8 [3.5 , 13.3]
Crohn's disease	360	2.2		6.2 [3.1 , 12.6]
Grave's disease	118	1.7		4.7 [1.2 , 19.1]
Type 1 diabetes	1354	1.4		3.9 [2.5 , 6.1]
Rheumatoid arthritis*	533	1.1		3.1 [1.4 , 7.0]
Psoriasis**	1017	0.9		2.4 [1.3 , 4.7]
Any of the above AD	4163	1.8		5.2 [4.1 , 6.5]

Odds ratio (log scale)

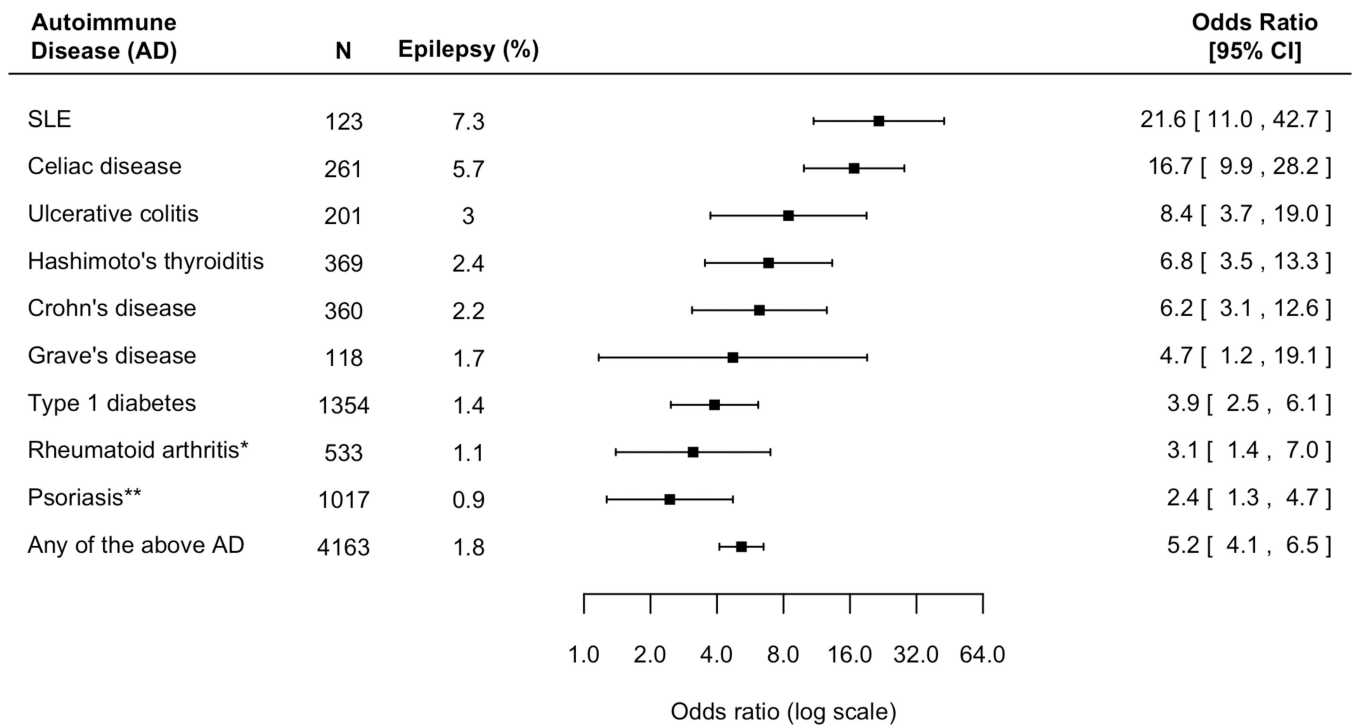1.0   2.0   4.0   8.0   16.0   32.0   64.0

Figure 2. The risk of epilepsy in children (<18 years of age) with autoimmune diseases, compared with children without autoimmune diseases

Overall, children with an autoimmune condition have a five-fold increased risk of epilepsy (P<0.001 in all cases, except otherwise indicated; *P=0.006; **P=0.008).

Autoimmune Disease (AD)	N	Epilepsy (%)		Odds Ratio [95% CI]
Antiphospholipid syndrome	5394	3.2		9.5 [8.1 , 11.1]
SLE	9573	2.4		7.3 [6.4 , 8.3]
Type 1 diabetes	42350	1.8		5.3 [5.0 , 5.8]
Myasthenia gravis	1043	1.7		5.1 [3.2 , 8.1]
Sjögren's syndrome	3603	1.5		4.3 [3.3 , 5.7]
Rheumatoid arthritis	22357	1.2		3.6 [3.2 , 4.1]
Crohn's disease	8414	1		3.0 [2.4 , 3.7]
Celiac disease	1624	0.9		2.5 [1.5 , 4.3]
Ulcerative colitis	10489	0.8		2.5 [2.0 , 3.0]
Hashimoto's thyroiditis	9461	0.8		2.3 [1.8 , 2.9]
Grave's disease	9640	0.8		2.2 [1.8 , 2.8]
Psoriasis	22525	0.7		1.9 [1.6 , 2.3]
Any of the above AD	131231	1.3		3.8 [3.6 , 4.0]

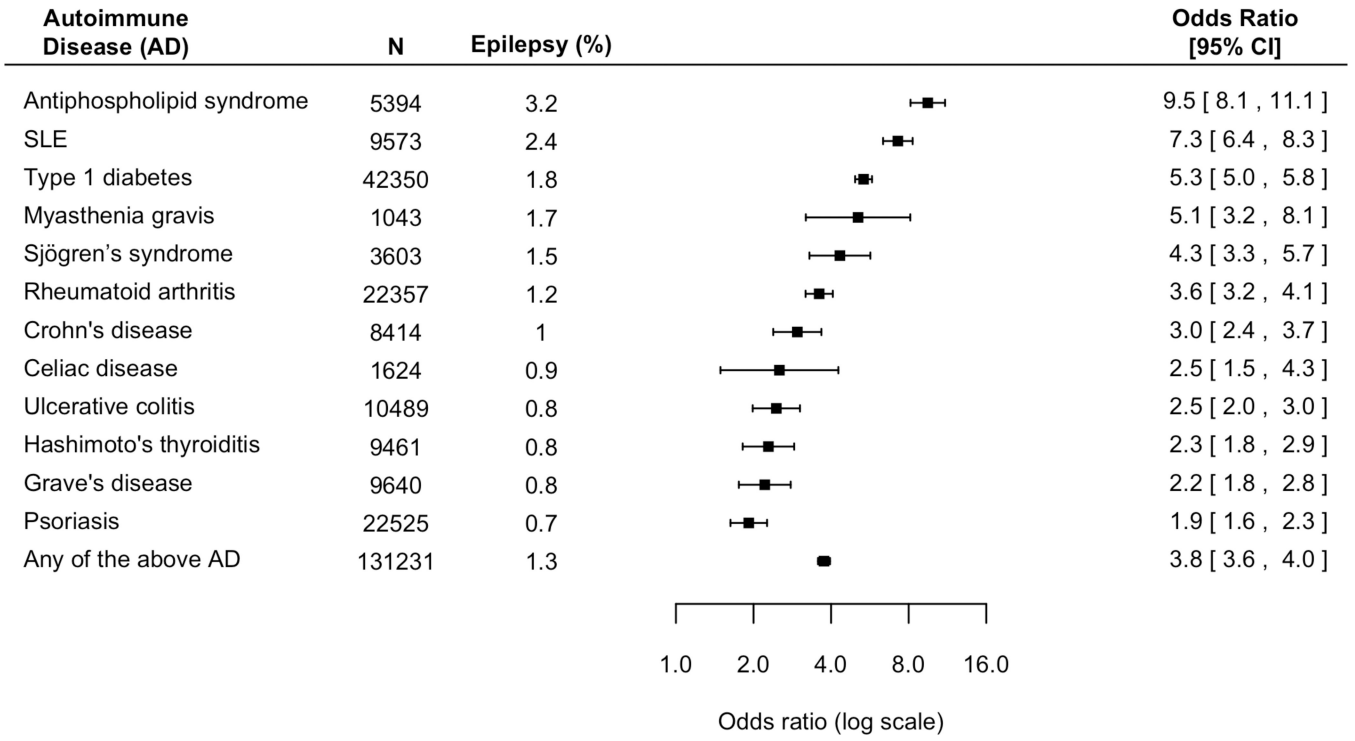1.0   2.0   4.0   8.0   16.0

Odds ratio (log scale)

Figure 3. The risk of epilepsy in non-elderly adults (<=65 years of age) with autoimmune diseases, compared with non-elderly adults without autoimmune diseases

Overall, adults with an autoimmune condition have a four-fold increased risk of epilepsy (P<0.001 in all cases).

Table 1

Demographic characteristics.

Patients, n	2,518,034
Gender, n (%)	
Female	1,302,709 (51.7)
Male	1,215,325 (48.3)
Age, n (%)	
Children (<18 years old)	476,805 (18.9)
Adults (<=65 years old)	2,041,229 (81.1)
Length of follow-up (days)(mean ± SD)	2571 ± 490
Epilepsy prevalence, n (%)	
All ages	10,041 (0.4)
Children (<18 years old)	1,796 (0.4)
Adults (<=65 years old)	8,245 (0.4)
Autoimmune disease prevalence, n (%)	
Type 1 diabetes	43,704 (1.7)
Psoriasis	23,542 (0.9)
Rheumatoid arthritis	22,890 (0.9)
Ulcerative colitis	10,690 (0.4)
Hashimoto's thyroiditis	9,830 (0.4)
Grave's disease	9,758 (0.4)
Systemic lupus erythematosus	9,696 (0.4)
Crohn's disease	8,774 (0.3)
Antiphospholipid syndrome	5,423 (0.2)
Sjögren's Syndrome	3,614 (0.1)
Celiac disorder	1,885 (0.1)
Myasthenia gravis	1,070 (0.04)
Any of the above AD	137,398 (5.5)
Medications[*], n (%)	
Aminosalicylates	24,303 (1.0)
Disease-modifying antirheumatic drugs	33,557 (1.3)
Systemic glucocorticoids	790,045 (31.4)
Anti-TNF agents	7,114 (0.3)
Other biologics	2,915 (0.1)
Non-steroidal anti-inflammatory agents	945,892 (37.6)

(*excluding medications taken after the first epileptic seizure)

Table 2

The effect of autoimmune therapies on epilepsy risk

We performed a multivariate logistic regression analysis to evaluate epilepsy risk in patients with autoimmune disease, accounting for common autoimmune therapies, as well as gender and age. Even after adjustment, the presence of autoimmune disease remained a strong predictor of epilepsy occurrence.

Variable	Epilepsy Risk OR (95% CI)	P-value
Any autoimmune disease	4.1 (3.9 – 4.3)	<0.001
Gender (female)	1.2 (1.1 – 1.2)	<0.001
Children (< 18 years of age)	1.0 (0.97 – 1.1)	0.370
Aminosalicylates	0.6 (0.5 – 0.8)	<0.001
Disease modifying antirheumatic drugs	1.0 (0.9 – 1.1)	0.977
Systemic glucocorticoids	1.1 (1.0 – 1.1)	0.001
Anti-TNF agents	0.4 (0.3 – 0.6)	<0.001
Other biologics	0.3 (0.1 – 0.8)	0.012
Non-steroidal anti-inflammatory drugs	0.9 (0.8 – 0.9)	<0.001