Association Between Autoimmune Diseases, Treatments, and Dementia Risk:

A Population-Based Case-Control Study From Taiwan

Chi-Shin Wu, MD, PhD; Wei-Lieh Huang, MD, PhD; Shi-Heng Wang, PhD; Ming-Shiang Wu, MS; Kuo-Shu Chen, MD; Sheng-Han Cheng, MD; and Ying-Ming Chiu, MD, PhD

Abstract

Objectives: This study aimed to assess the risk of dementia associated with specific autoimmune diseases and the impact of related pharmacologic treatments.

Methods: Patients 55 years or older diagnosed with dementia by neurologists or psychiatrists between 2010 and 2021 were identified using claims data from Taiwan's National Health Insurance program. We examined 22 autoimmune diseases for their associations with dementia, controlling for age, gender, urbanization level, and comorbidities.

Results: Dementia prevalence was higher among individuals with autoimmune diseases (10.5% in cases vs. 8.7% in comparisons). Thirteen autoimmune diseases were linked with an elevated dementia risk, particularly Behçet disease, multiple sclerosis, and systemic lupus erythematosus. Associations with vascular dementia were stronger than with Alzheimer disease. Although overall dementia risk was higher in women, no significant sex differences were observed for specific autoimmune diseases. Nonsteroidal anti-inflammatory drugs and corticosteroids did not significantly alter dementia risk among individuals with autoimmune diseases; however, immunosuppressants were associated with a reduced risk when used for more than 180 days.

Conclusions: Certain autoimmune diseases are significantly associated with an increased risk of dementia, particularly vascular dementia, highlighting the distinct role of inflammation. Effective prevention or treatment of autoimmune diseases may reduce dementia incidence by 0.8%. While immunosuppressants show potential for risk reduction, further prospective studies are needed to confirm this effect.

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Author affiliations are listed at the end of this article.

Given the global trend of population aging, the prevalence of dementia is steadily increasing. In 2019, there were over 57 million cases of dementia worldwide, a figure projected to surge to 150 million by 2050.[1] Autoimmune diseases are a diverse group of disorders[2] affecting approximately 1 in 10 people globally.[3] Evidence suggests that dysregulation and diseases in autoimmunity are becoming increasingly prevalent.[4]

Previous studies have suggested associations between various autoimmune conditions and all-cause dementia, Alzheimer disease, or vascular dementia.[5–20] Notably, such studies are often based on small sample sizes and focus narrowly on specific autoimmune conditions. Since multiple autoimmune diseases frequently co-occur in the same individual,[3] a study investigating all autoimmune diseases can allow for the direct comparison and ranking of the relative dementia risk associated with each condition. In addition, the simultaneous investigation of multiple autoimmune diseases may highlight both specific and shared biological pathways underlying their association with dementia. To date, only a limited number of studies have examined a wide range of autoimmune diseases simultaneously.[16,21–23]

Emerging evidence suggests that the biological pathways linking systemic immune activation to cognitive decline vary by dementia subtype. Chronic inflammation and immune-mediated endothelial dysfunction foster small-vessel disease, cerebral hypoperfusion, and blood-brain-barrier disruption—mechanisms more directly implicated in vascular dementia than in the amyloid-centric cascade characteristic of Alzheimer disease.[24–26] Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs) have been postulated to mitigate amyloid deposition and microglial activation; however, large randomized trials have yielded null or inconclusive

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Clinical Points

- Dementia risk across autoimmune diseases has been understudied; most research focuses on single conditions.
- Certain autoimmune diseases—such as lupus and multiple sclerosis—carry higher dementia risk, especially vascular dementia. Cognitive screening in these patients may be warranted.
- Long-term use of immunosuppressants may help reduce dementia risk by controlling systemic inflammation.

cognitive outcomes.[27,28] In contrast, prolonged systemic exposure to corticosteroids may be associated with memory impairment in observational imaging studies,[29] although most studies on dementia have reported null or inverse associations with glucocorticoid use.[30] More recently, nationwide cohort analyses have shown that biologic or targeted conventional immunosuppressants that inhibit tumor-necrosis factor-α or interleukin-6 pathways are associated with a reduction in incident dementia among patients with rheumatoid arthritis.[31,32] These mixed findings underscore the importance of delineating the independent contributions of NSAIDs, corticosteroids, and immunosuppressants when assessing dementia risk in individuals with autoimmune diseases.

On this basis, the present nationwide case–control study aimed to (1) quantify dementia risk across 22 autoimmune diseases, (2) compare effect sizes between Alzheimer disease and vascular dementia, and (3) evaluate whether prolonged exposure to NSAIDs, corticosteroids, or immunosuppressants modifies these associations.

METHODS

Data Source

This study utilized a claims database derived from Taiwan's National Health Insurance (NHI) program, which enrolled approximately 23.0 million individuals, representing a coverage rate of 99%. The database provides comprehensive data, including demographic variables, prescription records, and clinical diagnoses. Diagnoses were coded according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*), prior to 2016, after which they were updated to the *Tenth Revision* (*ICD-10*). The accuracy of diagnostic codes for major psychiatric disorders, including dementia, has been extensively validated in previous research.[33]

Study Sample

Patients with dementia between 2010 and 2021 were identified from Taiwan's NHI claims database. Eligible patients were required to be aged 55 years or older, with a dementia diagnosis made by neurologists or psychiatrists. The diagnosis of dementia was based on the relevant *ICD* codes (*ICD-9*: 290.0–290.4, 294.1, 331.0–331.2, 331.82; *ICD-10*: F01-F03, G30, F05.1, G31.83) and was confirmed by at least 2 outpatient visits or 1 inpatient claim. A total of 641,686 individuals with dementia were identified. After excluding those with missing data on sex, birth year, or a recorded death date prior to the dementia diagnosis (n = 7,123), 634,563 cases remained for analysis. Additionally, Alzheimer disease and vascular dementia were further classified using specific *ICD* codes (Alzheimer disease: *ICD-9-CM* 331.0, *ICD-10* G30; vascular dementia: *ICD-9-CM* 290.4, *ICD-10* F01). The index date was defined as the date of the initial diagnosis of dementia.

The comparison group was randomly selected from the NHI claims database using incidence density sampling. It included participants with no prior recorded diagnosis of dementia. To ensure comparability, comparison group participants were matched with the dementia group based on birth year and sex (1:4 matching). The index date for each participant in the comparison group corresponded to the diagnosis date of their matched case in the dementia group. Due to matching limitations, 24 dementia cases could not be matched with 4 comparisons. As a result, a total of 3,172,791 individuals were included in the comparison group.

Autoimmune Diseases

This analysis encompassed 22 autoimmune diseases, as identified from the NHI claims database, spanning from January 1, 2010, until the day prior to the index date. These diseases comprised pernicious anemia, autoimmune hemolytic anemia, Graves disease, Hashimoto thyroiditis, type 1 diabetes, multiple sclerosis, Guillain-Barré syndrome, myasthenia gravis, uveitis, inflammatory bowel disease, pemphigus, psoriasis, rheumatoid arthritis, systemic vasculitis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjogren syndrome, Behçet disease, polymyalgia rheumatica, and ankylosing spondylitis, based on their *ICD* codes (see Supplementary Material).

Pharmacologic Treatment of Autoimmune Disease

Pharmacologic treatments for these autoimmune diseases were identified using Anatomical Therapeutic Chemical (ATC) codes, including NSAIDs (ATC code M01A), corticosteroids (ATC code H02), and immunosuppressants (ATC codes L04AA-L04AG, L04AK, L04AX).[34] As the recommended treatment and duration for different autoimmune diseases vary considerably, depending on the specific condition, severity, and patient

response, and because many autoimmune diseases require prolonged treatment to manage symptoms and prevent complications, we defined long-term treatment as a duration of 180 days or more over the study period. This 180-day threshold was chosen to reflect sustained pharmacologic management, in line with clinical practice and prior pharmacoepidemiologic studies,[35–37] where a 6-month duration is commonly used to distinguish long-term use from short-term treatment.

Covariates

Information about several potential confounding factors that could influence the relationship between autoimmune diseases and dementia was covered by the NIH database, including age, gender, and level of urbanization. We included medical comorbidities that could serve as proxies for lifestyle factors such as smoking and obesity, and those that have been shown to be associated with dementia: myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, liver disease, cancer, hypertension, dyslipidemia, and type 2 diabetes. In addition, pneumonia, cellulitis, and urinary tract infections were included as covariates because they may trigger autoimmunity through immune dysregulation and contribute to cognitive decline via systemic and neuroinflammatory pathways.

Statistical Analysis

Descriptive statistics of dementia cases vs controls were presented as counts and corresponding percentages, detailing demographic characteristics and comorbid conditions.

To assess the association between overall and specific autoimmune diseases and the risk of developing dementia, we employed conditional logistic regression. Adjusted odds ratios (aORs) were calculated for the overall study population with controlling for all the above-mentioned covariates. The population attributable fraction (PAF) for autoimmune diseases was estimated using the formula: PAF = Prcase*(aOR − 1)/aOR, where Prcase is the prevalence of dementia cases with autoimmune disease, and aOR refers to the adjusted odds ratios of dementia.

To adjust for multiple comparisons, we used the false discovery rate (FDR) to control type I errors. The FDR represents the expected proportion of false positives among rejected null hypotheses. The *Q* value, an adjusted *P* value, allows researchers to control the FDR. Statistical significance was determined using 95% confidence intervals (CI) or a *Q* value of less than .05. Additional stratified analyses were conducted for Alzheimer disease and vascular dementia to explore potential underlying mechanisms. We also examined whether the association between autoimmune diseases and dementia risk was modified by sex. Interaction terms between autoimmune diseases and sex were included in the models to assess sex differences.

To address potential surveillance bias, where individuals with autoimmune diseases may have more frequent medical contact that increases the likelihood of dementia diagnosis, we conducted a sensitivity analysis adjusting for health care utilization. Specifically, we included the average number of outpatient visits per year during the preindex period as a covariate in the regression models. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

The mean age of the study subjects at the index date was 78.7 years (SD = 8.1). Dementia cases exhibited a higher prevalence of comorbid conditions, including cerebrovascular disease, hypertension, type 2 diabetes, pneumonia, and urinary tract infection (Table 1).

Among individuals with dementia, the prevalence of any autoimmune disease was 10.5%, compared to 8.7% in the control group. Patients with autoimmune diseases exhibited a higher risk of developing dementia, with an aOR of 1.08 (95% CI, 1.07–1.09). The PAF of overall autoimmune diseases for all-cause dementia is approximately 0.8%. In total, 13 autoimmune diseases were found to be associated with an increased risk of dementia. The highest risks were observed in patients with Behçet disease (aOR = 1.53 [1.29–1.82]), multiple sclerosis (aOR = 1.53 [1.19–1.96]), systemic lupus erythematosus (aOR = 1.24 [1.17–1.32]), and pernicious anemia (aOR = 1.24 [1.11–1.38]). Other autoimmune diseases, including ankylosing spondylitis, Crohn disease/ulcerative colitis, dermatomyositis, Graves disease, Hashimoto thyroiditis, polymyositis, psoriasis, rheumatoid arthritis, Sjögren syndrome, and type 1 diabetes, were associated with dementia, though with aORs below 1.20 (Table 2).

Within the study sample, 110,294 cases were identified as Alzheimer disease and 133,149 as vascular dementia. The demographic and clinical characteristics of these cases are presented in Supplementary Table 1. Notably, the association between overall autoimmune disease and vascular dementia was significant (aOR = 1.10 [1.08–1.13]), but that with Alzheimer disease was not (aOR = 0.98 [0.96–1.01]). The results indicated that most autoimmune diseases were not associated with an increased risk of Alzheimer disease. Contrary to our expectations, ankylosing spondylitis appeared to be inversely associated with Alzheimer disease. In contrast, several autoimmune conditions, including ankylosing spondylitis, Behcet disease, Graves disease, inflammatory bowel disease, rheumatoid arthritis, Sjogren syndrome, systemic sclerosis, and type

Table 1.

Baseline Demographics and Clinical Features in Dementia and Comparison Groups

	Dementia (n = 634,563)	Comparisons (n = 2,538,228)	SMD
Age, mean ± SD, y	78.7 ± 8.1	78.7 ± 8.1	0.00
Age group, N (%)			
55–64 y	27,841 (4%)	111,365 (4%)	0.00
65–74 y	165,161 (26%)	660,637 (26%)	0.00
75–84 y	280,144 (44%)	1,120,564 (44%)	0.00
85+ y	161,417 (25%)	645,662 (25%)	0.00
Sex, N (%)			
Male	272,608 (43%)	1,090,423 (43%)	0.00
Female	361,955 (57%)	1,447,805 (57%)	0.00
Residency, N (%)			
Urban	310,682 (49%)	1,239,924 (49%)	0.00
Suburban	217,782 (34%)	884,572 (35%)	−0.01
Rural	106,099 (17%)	413,731 (16%)	0.01
Comorbid conditions, N (%)			
Myocardial infarction	17,133 (3%)	53,810 (2%)	0.03
Congestive heart failure	90,933 (14%)	279,459 (11%)	0.07
Cerebrovascular disease	216,513 (34%)	468,811 (18%)	0.26
Chronic pulmonary disease	182,564 (29%)	617,043 (24%)	0.07
Chronic liver disease	108,954 (17%)	360,606 (14%)	0.07
Chronic liver disease	105,655 (17%)	352,560 (14%)	0.05
Cancer	66,502 (10%)	248,239 (10%)	0.02
Hypertension	432,962 (68%)	1,580,047 (62%)	0.09
Dyslipidemia	252,620 (40%)	926,199 (36%)	0.05
Type 2 diabetes mellitus	222,668 (35%)	722,126 (28%)	0.10
Sepsis	44,610 (7%)	107,875 (4%)	0.09
Pneumonia	132,877 (21%)	401,801 (16%)	0.09
Cellulitis	179,391 (28%)	598,514 (24%)	0.08
Urinary tract infection	142,332 (22%)	418,808 (17%)	0.11

Abbreviation: SMD = standardized mean difference.

I diabetes, were found to be associated with an elevated risk of vascular dementia (see Table 3).

Table 4 shows the sex-stratified subgroup analysis. The association between autoimmune diseases and dementia was more pronounced in women (aOR = 1.10 [1.09–1.11]) compared to that in men (aOR = 1.05 [1.03–1.06], *P* interaction < .001). However, for all individual autoimmune diseases, the aORs for dementia were generally comparable between men and women. Although uveitis was inversely associated with dementia risk in men, the interaction with sex was not statistically significant.

Table 5 presents the analysis of pharmacologic treatments for autoimmune diseases and their association with dementia risk. Specifically, we found that even with long-term treatment using NSAIDs alone or in combination with corticosteroids, autoimmune diseases were still associated with an increased risk of dementia. In contrast, long-term corticosteroid treatment alone was not significantly associated with dementia risk. Furthermore, among individuals receiving long-term immunosuppressant treatment, whether used alone or combined with other medications, dementia risk did not differ significantly from those without autoimmune diseases.

In the sensitivity analysis, individuals with dementia had higher health care utilization compared to those without dementia (Supplementary Table 2). After adjusting for outpatient visit frequency, the results were generally consistent with the primary analysis (Supplementary Table 3). Most associations remained similar, though uveitis became statistically significant and dermatomyositis was no longer significant.

DISCUSSION

The current study identified 13 autoimmune diseases associated with an increased risk of dementia, with the highest risks observed in patients with Behçet disease, multiple sclerosis, systemic lupus erythematosus, and pernicious anemia. Interestingly, the use of NSAIDs and corticosteroids did not significantly alter the dementia risk in patients with autoimmune diseases. However, patients who received long-term immunosuppressant therapy had a dementia risk comparable to those without autoimmune diseases.

Comparison with Previous Studies

The link between autoimmune diseases and dementia has been extensively studied; however, only

Table 2.

Crude and Adjusted Odds Ratios of Autoimmune Disease Associations With Dementia in Older Adults[a]

Autoimmune diseases	Dementia (n = 634,563) N (%)	Comparisons (n = 2,538,228) N (%)	Crude odds ratio OR (95% CI)	*Q* value	Adjusted odds ratio OR (95% CI)	*Q* value
Overall autoimmune disease	66,790 (10.5)	220,760 (8.7)	**1.24 (1.22–1.25)**	**<0.001**	**1.08 (1.07–1.09)**	**<0.001**
Specific autoimmune diseases						
Ankylosing spondylitis	7,555 (1.2)	24,857 (1.0)	**1.22 (1.19–1.25)**	**<0.001**	**1.07 (1.04–1.10)**	**<0.001**
Autoimmune hemolytic anemia	165 (0.0)	490 (0.0)	**1.35 (1.13–1.61)**	**0.001**	1.14 (0.95–1.36)	0.209
Behcet disease	197 (0.0)	444 (0.0)	**1.78 (1.50–2.10)**	**<0.001**	**1.53 (1.29–1.82)**	**<0.001**
Dermatomyositis	356 (0.1)	1,105 (0.0)	**1.29 (1.14–1.45)**	**<0.001**	**1.15 (1.02–1.30)**	**0.044**
Graves disease	9,537 (1.5)	30,549 (1.2)	**1.25 (1.22–1.28)**	**<0.001**	**1.11 (1.09–1.14)**	**<0.001**
Guillain-Barré syndrome	398 (0.1)	1,148 (0.0)	**1.39 (1.24–1.56)**	**<0.001**	1.08 (0.96–1.21)	0.253
Hashimoto thyroiditis	1,446 (0.2)	4,559 (0.2)	**1.27 (1.20–1.35)**	**<0.001**	**1.11 (1.05–1.18)**	**0.002**
Inflammatory bowel diseases	7,283 (1.1)	24,600 (1.0)	**1.19 (1.16–1.22)**	**<0.001**	**1.05 (1.03–1.08)**	**<0.001**
Multiple sclerosis	98 (0.0)	195 (0.0)	**2.02 (1.58–2.57)**	**<0.001**	**1.53 (1.19–1.96)**	**0.002**
Myasthenia gravis	905 (0.1)	2,878 (0.1)	**1.26 (1.17–1.36)**	**<0.001**	1.02 (0.94–1.10)	0.701
Pemphigus	270 (0.0)	767 (0.0)	**1.41 (1.23–1.62)**	**<0.001**	1.03 (0.90–1.19)	0.708
Pernicious anemia	462 (0.1)	1,285 (0.1)	**1.44 (1.29–1.60)**	**<0.001**	**1.24 (1.11–1.38)**	**<0.001**
Polymyalgia rheumatica	623 (0.1)	2,058 (0.1)	**1.21 (1.11–1.33)**	**<0.001**	1.00 (0.91–1.09)	0.953
Polymyositis	164 (0.0)	524 (0.0)	**1.25 (1.05–1.49)**	**0.012**	1.08 (0.90–1.29)	0.502
Psoriasis	5,725 (0.9)	19,012 (0.7)	**1.21 (1.17–1.24)**	**<0.001**	**1.05 (1.02–1.09)**	**0.002**
Rheumatoid arthritis	11,695 (1.8)	39,654 (1.6)	**1.18 (1.16–1.21)**	**<0.001**	**1.05 (1.03–1.07)**	**<0.001**
Sjogren syndrome	17,571 (2.8)	54,458 (2.1)	**1.30 (1.28–1.32)**	**<0.001**	**1.14 (1.12–1.16)**	**<0.001**
Systemic lupus erythematosus	1,492 (0.2)	4,143 (0.2)	**1.44 (1.36–1.53)**	**<0.001**	**1.24 (1.17–1.32)**	**<0.001**
Systemic sclerosis	259 (0.0)	831 (0.0)	**1.25 (1.08–1.43)**	**0.002**	1.14 (0.99–1.31)	0.108
Systemic vasculitis	649 (0.1)	1,961 (0.1)	**1.32 (1.21–1.45)**	**<0.001**	1.09 (1.00–1.20)	0.073
Type 1 diabetes	4,883 (0.8)	14,193 (0.6)	**1.38 (1.34–1.43)**	**<0.001**	**1.07 (1.04–1.11)**	**<0.001**
Uveitis	4,410 (0.7)	16,754 (0.7)	**1.05 (1.02–1.09)**	**0.002**	0.96 (0.93–1.00)	0.054

[a]Bolded odds ratios indicate statistical significance at *Q* value < 0.05.

a few studies have taken a broader approach, examining a wide range of autoimmune diseases simultaneously.[16,21,23] These studies confirmed an elevated risk of dementia in only certain autoimmune diseases. One study, in particular, demonstrated that after adjusting for infections—commonly preceding autoimmune disease diagnoses and potentially confounding the observed association—the relationship between autoimmune diseases and dementia was significantly attenuated.[23] In our study, we also controlled for infectious diseases as potential confounders and found that the association between autoimmune diseases and dementia remained, albeit with a smaller effect size compared to previous studies.[16,21] This suggests that the connection between autoimmune diseases and dementia is robust, even when accounting for confounders such as infections.

Autoimmune Diseases and Risks of Dementia Subtypes

Our findings showed that several autoimmune conditions were associated with an increased risk of vascular dementia, but not Alzheimer disease. This pattern aligns with previous studies.[16,21] Elevated levels of inflammatory biomarkers, such as C-reactive protein and cytokines, have been linked to increased dementia risk.[38] Chronic systemic inflammation may damage the brain by increasing vascular permeability, allowing inflammatory proteins to enter the brain and trigger neuroinflammation, thereby accelerating neurodegeneration.[39] Potential mechanisms include disruption of the blood-brain barrier, cytokine-mediated injury, and interactions between peripheral and central immune systems.[40,41] Systemic inflammation may also reduce cerebral blood flow, contributing to cognitive decline.[42] The observed inverse association between immunosuppressant use and dementia risk further supports inflammation's role in dementia.[43] In Alzheimer disease, inflammation contributes to amyloid accumulation and neural damage,[44,45] although this link appears less pronounced compared to vascular dementia.

Unexpectedly, our findings suggest that ankylosing spondylitis may be associated with a reduced risk of Alzheimer disease, yet it appears to elevate the risk of vascular dementia. This contrasts with prior research that reported a positive association between ankylosing spondylitis and dementia.[12] Although we adjusted for multiple comparisons, random error may still influence the findings, warranting further research to validate these results.

Table 3.

Prevalence and Adjusted Odds Ratios of Autoimmune Disease Associations With Alzheimer Diseases and Vascular Dementia in Older Adults[a]

	Alzheimer disease (n = 110,294) N (%)	Comparisons (n = 441,176) N (%)	Adjusted OR (95% CI)	*Q* value	Vascular dementia (n = 133,459) N (%)	Comparisons (n = 553,836) N (%)	Adjusted OR (95% CI)	*Q* value	*Q* interaction
Overall autoimmune disease	11,806 (10.7)	40,494 (9.2)	0.98 (0.96–1.01)	0.115	11,694 (8.8)	40,024 (7.5)	1.10 (1.08–1.13)	<0.001	<0.001
Specific autoimmune disease									
Ankylosing spondylitis	1,400 (1.3)	4,507 (1.0)	**0.87 (0.82–0.93)**	**0.001**	1,208 (0.9)	4,639 (0.9)	**1.16 (1.10–1.24)**	**0.000**	<0.001
Autoimmune hemolytic anemia	16 (0.0)	90 (0.0)	0.89 (0.56–1.43)	0.995	25 (0.0)	93 (0.0)	0.66 (0.39–1.13)	0.246	0.680
Behcet disease	39 (0.0)	86 (0.0)	0.81 (0.50–1.31)	0.913	24 (0.0)	85 (0.0)	**1.64 (1.12–2.39)**	**0.032**	0.094
Dermatomyositis	67 (0.1)	217 (0.0)	1.03 (0.75–1.41)	1.017	54 (0.0)	182 (0.0)	1.17 (0.89–1.54)	0.416	0.755
Graves disease	1,775 (1.6)	5,856 (1.3)	1.07 (1.01–1.14)	0.169	1,652 (1.2)	5,316 (1.0)	**1.13 (1.07–1.20)**	**<0.001**	0.349
Guillain-Barré syndrome	49 (0.0)	203 (0.0)	1.05 (0.80–1.39)	0.994	77 (0.1)	204 (0.0)	0.88 (0.65–1.21)	0.574	0.610
Hashimoto thyroiditis	268 (0.2)	876 (0.2)	0.89 (0.75–1.05)	0.515	196 (0.1)	716 (0.1)	1.11 (0.96–1.27)	0.270	0.102
Inflammatory bowel diseases	1,285 (1.2)	4,387 (1.0)	0.99 (0.93–1.06)	1.023	1,289 (1.0)	4,510 (0.8)	1.11 (1.04–1.18)	0.008	0.135
Multiple sclerosis	12 (0.0)	46 (0.0)	1.35 (0.75–2.41)	0.924	20 (0.0)	35 (0.0)	0.89 (0.47–1.68)	0.798	0.619
Myasthenia gravis	134 (0.1)	533 (0.1)	0.93 (0.77–1.12)	0.808	168 (0.1)	515 (0.1)	0.91 (0.75–1.10)	0.476	0.952
Pemphigus	36 (0.0)	128 (0.0)	0.87 (0.63–1.21)	0.798	54 (0.0)	149 (0.0)	0.99 (0.68–1.44)	0.962	0.754
Pernicious anemia	62 (0.1)	209 (0.0)	1.13 (0.85–1.50)	0.852	83 (0.1)	250 (0.0)	1.13 (0.85–1.50)	0.551	1.000
Polymyalgia rheumatica	129 (0.1)	384 (0.1)	0.91 (0.73–1.13)	0.994	121 (0.1)	385 (0.1)	1.26 (1.03–1.54)	0.063	0.087
Polymyositis	25 (0.0)	106 (0.0)	1.01 (0.64–1.59)	0.978	27 (0.0)	90 (0.0)	0.85 (0.55–1.32)	0.572	0.778
Psoriasis	936 (0.8)	3,270 (0.7)	1.01 (0.94–1.08)	1.041	1,105 (0.8)	3,630 (0.7)	1.06 (0.99–1.14)	0.238	0.621
Rheumatoid arthritis	2,114 (1.9)	7,395 (1.7)	1.00 (0.95–1.05)	0.959	2,072 (1.6)	7,292 (1.4)	**1.08 (1.03–1.14)**	**0.007**	0.083
Sjogren syndrome	3,122 (2.8)	10,315 (2.3)	0.99 (0.94–1.03)	1.012	2,752 (2.1)	9,399 (1.8)	**1.13 (1.08–1.18)**	**<0.001**	<0.001
Systemic lupus erythematosus	235 (0.2)	787 (0.2)	1.16 (1.00–1.35)	0.331	254 (0.2)	753 (0.1)	1.11 (0.96–1.29)	0.263	0.826
Systemic sclerosis	58 (0.1)	140 (0.0)	0.93 (0.64–1.36)	1.037	37 (0.0)	144 (0.0)	1.55 (1.14–2.10)	0.018	0.106
Systemic vasculitis	133 (0.1)	332 (0.1)	1.02 (0.81–1.27)	0.983	115 (0.1)	346 (0.1)	**1.45 (1.18–1.77)**	**0.002**	0.101
Type 1 diabetes	1,935 (0.7)	5,615 (0.5)	1.06 (1.00–1.12)	0.114	2,948 (0.8)	8,578 (0.6)	**1.08 (1.03–1.13)**	**0.002**	0.919
Uveitis	1,878 (0.7)	7,330 (0.7)	**0.94 (0.89–0.99)**	**0.047**	2,532 (0.7)	9,424 (0.7)	0.99 (0.94–1.03)	0.663	0.644

[a]Bolded odds ratios indicate statistical significance at *Q* value < 0.05.

Sex Differences in the Association Between Autoimmune Diseases and Dementia Risk

The association between overall autoimmune diseases and dementia risk was slightly stronger in women—a finding consistent with previous research.[21,23] Several factors may underlie this disparity. First, menopausal estrogen loss amplifies peripheral cytokine release and microglial activation, thereby accelerating neuroinflammation and small-vessel pathology.[46,47] Second, females mount stronger adaptive immune responses than males, which can intensify chronic systemic inflammation and blood-brain barrier permeability in late life.[48] Third, X-chromosome–linked immune-regulatory genes and the higher prevalence of the APOE ε4 allele among women with autoimmune disease may further heighten susceptibility to neurodegeneration.[49,50] Together with women's longer life expectancy, these factors plausibly account for the sex difference we observed.

Clinical Implications

Although the associations between autoimmune diseases were generally modest, they remain clinically relevant when considering the high prevalence and chronic nature of both autoimmune diseases and dementia in aging populations. Even modest increases in dementia risk can translate into substantial public health burdens when scaled to the population level.

From a clinical perspective, these findings underscore the importance of enhanced cognitive surveillance and early intervention strategies for older adults with autoimmune conditions. These results suggest that clinicians should maintain a lower threshold for cognitive assessment in patients with autoimmune diseases, particularly in those conditions that show the largest excess risk (eg, Behçet disease, multiple sclerosis, systemic lupus erythematosus, and pernicious anemia). Additionally, strict control of systemic inflammation may help reduce long-term dementia risk. Our findings suggest that prolonged immunosuppressant use, particularly biologic disease-modifying antirheumatic drugs, may offer protective effects against dementia in individuals with autoimmune diseases, consistent with recent reviews.[43] Furthermore, because vascular dementia accounted for a significant portion of the excess risk, optimizing vascular health (through blood pressure, lipid profile, glycemic control, smoking cessation, and physical activity) should be prioritized during autoimmune disease management.

Table 4.

Prevalence and Adjusted Odds Ratios of Autoimmune Disease Associations With Dementia in Older Adults, by Sexes[a]

	Men				Women				
Autoimmune diseases	Dementia (n = 272,608) N (%)	Comparison (n = 1,090,423) N (%)	Adjusted OR (95% CI)	*Q* value	Dementia (n = 361,955) N (%)	Comparison (n = 1,447,805) N (%)	Adjusted OR (95% CI)	*Q* value	*Q* interaction
Overall autoimmune disease	22,436 (8.2)	74,795 (6.9)	**1.05 (1.03–1.06)**	**<0.001**	**44,354 (12.3)**	**145,965 (10.1)**	**1.10 (1.09–1.11)**	**<0.001**	**<0.001**
Specific autoimmune disease									
Ankylosing spondylitis	2,889 (1.1)	9,782 (0.9)	1.03 (0.98–1.07)	0.431	4,666 (1.3)	15,075 (1.0)	**1.10 (1.06–1.13)**	**0.000**	0.430
Autoimmune hemolytic anemia	53 (0.0)	179 (0.0)	0.97 (0.71–1.32)	0.873	112 (0.0)	311 (0.0)	**1.24 (1.00–1.54)**	**0.090**	0.514
Behcet disease	68 (0.0)	146 (0.0)	**1.62 (1.21–2.18)**	**0.008**	129 (0.0)	298 (0.0)	**1.50 (1.21–1.84)**	**0.001**	0.853
Dermatomyositis	129 (0.0)	401 (0.0)	1.13 (0.92–1.39)	0.418	227 (0.1)	704 (0.0)	1.16 (1.00–1.35)	0.086	0.989
Graves disease	2,079 (0.8)	6,554 (0.6)	**1.12 (1.06–1.18)**	**<0.001**	7,458 (2.1)	23,995 (1.7)	**1.12 (1.09–1.15)**	**<0.001**	0.997
Guillain-Barré syndrome	206 (0.1)	563 (0.1)	1.05 (0.90–1.24)	0.690	192 (0.1)	585 (0.0)	1.09 (0.92–1.28)	0.405	0.985
Hashimoto thyroiditis	254 (0.1)	763 (0.1)	1.13 (0.97–1.30)	0.234	1,192 (0.3)	3,796 (0.3)	**1.11 (1.04–1.19)**	**0.005**	0.971
Inflammatory bowel diseases	2,905 (1.1)	10,079 (0.9)	1.03 (0.98–1.07)	0.422	4,378 (1.2)	14,521 (1.0)	**1.07 (1.04–1.11)**	**<0.001**	0.463
Multiple sclerosis	32 (0.0)	57 (0.0)	1.53 (0.98–2.38)	0.141	66 (0.0)	138 (0.0)	**1.53 (1.14–2.06)**	**0.012**	0.993
Myasthenia gravis	379 (0.1)	1,259 (0.1)	0.97 (0.86–1.09)	0.682	526 (0.1)	1,619 (0.1)	1.07 (0.96–1.18)	0.288	0.478
Pemphigus	143 (0.1)	365 (0.0)	1.12 (0.92–1.36)	0.435	127 (0.0)	402 (0.0)	0.95 (0.78–1.17)	0.702	0.573
Pernicious anemia	250 (0.1)	651 (0.1)	**1.28 (1.10–1.49)**	**0.010**	212 (0.1)	634 (0.0)	1.18 (1.01–1.39)	0.066	0.944
Polymyalgia rheumatica	208 (0.1)	648 (0.1)	1.05 (0.89–1.23)	0.692	415 (0.1)	1,410 (0.1)	0.98 (0.88–1.10)	0.762	0.892
Polymyositis	51 (0.0)	190 (0.0)	1.00 (0.73–1.37)	0.987	113 (0.0)	334 (0.0)	1.13 (0.91–1.41)	0.341	0.930
Psoriasis	3,292 (1.2)	11,012 (1.0)	1.04 (1.00–1.09)	0.115	2,433 (0.7)	8,000 (0.6)	**1.06 (1.02–1.11)**	**0.020**	0.850
Rheumatoid arthritis	2,961 (1.1)	10,095 (0.9)	1.02 (0.98–1.06)	0.599	8,734 (2.4)	29,559 (2.0)	**1.07 (1.04–1.09)**	**<0.001**	0.307
Sjogren syndrome	4,283 (1.6)	13,416 (1.2)	**1.11 (1.07–1.15)**	**<0.001**	13,288 (3.7)	41,042 (2.8)	**1.16 (1.14–1.19)**	**<0.001**	0.283
Systemic lupus erythematosus	309 (0.1)	868 (0.1)	1.15 (1.00–1.31)	0.111	1,183 (0.3)	3,275 (0.2)	**1.27 (1.19–1.36)**	**<0.001**	0.508
Systemic sclerosis	44 (0.0)	173 (0.0)	0.92 (0.66–1.28)	0.686	215 (0.1)	658 (0.0)	1.20 (1.03–1.40)	0.043	0.513
Systemic vasculitis	274 (0.1)	821 (0.1)	1.06 (0.92–1.22)	0.575	375 (0.1)	1,140 (0.1)	1.11 (0.99–1.25)	0.107	0.852
Type 1 diabetes	1,935 (0.7)	5,615 (0.5)	1.06 (1.00–1.12)	0.114	2,948 (0.8)	8,578 (0.6)	**1.08 (1.03–1.13)**	**0.002**	0.895
Uveitis	1,878 (0.7)	7,330 (0.7)	**0.94 (0.89–0.99)**	**0.047**	2,532 (0.7)	9,424 (0.7)	0.99 (0.94–1.03)	0.663	0.491

[a]Bolded odds ratios indicate statistical significance at *Q* value < 0.05.

Table 5.

Adjusted Odds Ratios for Dementia Risk in Older Adults With Autoimmune Diseases by Type of Pharmacological Treatment[a]

	Dementia (n = 634,563) N (%)	Comparisons (n = 2,538,228) N (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
No autoimmune disease	567,773 (89.5)	2,317,468 (91.3)	reference		reference	
Autoimmune diseases classified by long-term treatment (>180 days) combinations						
No long-term treatment	37,300 (5.9)	130,498 (5.1)	**1.17 (1.15–1.18)**	**<.001**	**1.06 (1.05–1.08)**	**<.001**
Long-term NSAID	21,158 (3.3)	64,778 (2.6)	**1.33 (1.31–1.36)**	**<.001**	**1.10 (1.09–1.12)**	**<.001**
Long-term corticosteroid	1,757 (0.3)	5,570 (0.2)	**1.29 (1.22–1.36)**	**<.001**	1.04 (0.99–1.10)	.128
Long-term immunosuppressant	117 (0.0)	441 (0.0)	1.08 (0.88–1.33)	.444	0.96 (0.78–1.18)	.719
Long-term NSAID + corticosteroid	4,948 (0.8)	14,332 (0.6)	**1.41 (1.36–1.46)**	**<.001**	**1.13 (1.09–1.16)**	**<.001**
Long-term NSAID + immunosuppressant	223 (0.0)	840 (0.0)	1.08 (0.94–1.26)	.287	0.96 (0.83–1.12)	.616
Long-term corticosteroid + immunosuppressant	282 (0.0)	854 (0.0)	**1.35 (1.18–1.54)**	**<.001**	**1.12 (0.98–1.29)**	**.101**
Long-term all treatments	1,005 (0.2)	3,447 (0.1)	1.19 (1.11–1.28)	<.001	1.02 (0.95–1.10)	.576

[a]Bolded odds ratios indicate statistical significance at *P* < .05.
Abbreviation: NSAID = nonsteroidal anti-inflammatory drug.

Limitations

Limitations of this study include the following: first, although the accuracy of dementia diagnoses in Taiwan's claims records has been documented, the validation of dementia subtypes based on *ICD* codes remains limited. Many cases were classified as unspecified due to diagnostic uncertainties, and a significant number of Alzheimer disease cases were not accurately classified. Additionally, the accuracy of autoimmune disease diagnoses was not fully validated, although we believe it is generally acceptable given the use of stringent criteria. This misclassification is likely nondifferential, potentially leading to underestimation. However, if certain autoimmune conditions are unevenly linked to nonspecific subtypes, bias in either direction may occur. Second, we lacked data on the severity of autoimmune diseases and inflammation status, both of which could influence treatment outcomes and confound our findings. In addition, direct inflammatory biomarkers were not available in the claims database, which precluded examination of the role of systemic inflammation. Future studies should include these inflammatory markers. Third, long-term treatment was defined by prescriptions, but actual adherence was not assessed. Misclassification due to nonadherence could bias the results toward the null. Fourth, as with many observational and registry-based studies, numerous unmeasured confounders exist, such as lifestyle factors, socioeconomic status, and education. While we used chronic conditions as proxy measures for sedentary lifestyles, smoking, and alcohol use, these proxies may not fully account for these confounders. Lastly, the study employed a case-control design, with all exposures and covariates measured before the onset of dementia. However, the temporal relationship between exposures and covariates was unclear, meaning some covariates could be mediators rather than confounders. Additionally, the study design may be susceptible to surveillance bias due to the higher frequency of assessments in the exposed population compared to the nonexposed group. Future studies should use a prospective design to clarify the timing of exposures and covariates and ensure equal assessment frequencies across all groups to reduce surveillance bias.

CONCLUSIONS

This study identifies a significant association between specific autoimmune diseases and an increased risk of dementia, particularly in cases of Behçet disease, multiple sclerosis, systemic lupus erythematosus, and pernicious anemia. These conditions may represent modifiable risk factors, with the potential to lower dementia incidence by 0.8% if effectively prevented or managed. Although NSAIDs and corticosteroids showed no meaningful impact on dementia risk, extended use of immunosuppressant therapy was associated with a reduced risk, comparable to that of individuals without autoimmune diseases. These findings highlight the potential value of addressing selected autoimmune conditions in strategies aimed at preventing dementia, though further confirmation from prospective studies is warranted.

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Author Affiliations: National Center for Geriatrics and Welfare Research, National Health Research Institutes, Zhunan City, Taiwan (C. S. Wu, Wang, M. S. Wu); Department of Psychiatry, National Taiwan University Hospital, Yunlin Branch, Yunlin, Taiwan (C. S. Wu, Huang); Department of Psychiatry, College of Medicine, National Taiwan University, Taipei, Taiwan (C. S. Wu, Huang); Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan (Wang); Department of Allergy, Immunology, and Rheumatology, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan (Chen, Cheng, Chiu); Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan (Chiu); Department of Nursing, Jen Teh Junior College of Medicine, Nursing and Management, Miaoli, Taiwan (Chiu).

Corresponding Author: Ying-Ming Chiu, MD, PhD, Tungs' Taichung MetroHarbor Hospital, Department of Allergy, Immunology, and Rheumatology, No. 699, Section 8, Taiwan Avenue, Wuqi District, Taichung, 435403 Taiwan (ymcgreen@gmail.com).

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Supplementary Material

Article Title: Association Between Autoimmune Diseases, Treatments, and Dementia Risk: A Population-Based Case-Control Study from Taiwan

Authors: Chi-Shin Wu, MD, PhD; Wei-Lieh Huang, MD, PhD; Shi-Heng Wang, PhD; Ming-Shiang Wu, MS; Kuo-Shu Chen, MD; Sheng-Han Cheng, MD; Ying-Ming Chiu, MD, PhD

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1. Baseline Demographics and Clinical Features in Dementia and Comparison Groups by Dementia Subtypes

	Alzheimer's diseases (n=110,294)	**Comparisons (n=441,176)**	**SMD**	**Dementia (n=133,459)**	**Comparisons (n=553,836)**	**SMD**
	N (%)	N (%)		N (%)	N (%)	
Age, year	78.5 ± 8.0	78.5 ± 8.0	0.00	78.5 ± 8.1	78.5 ± 8.1	0.00
55-64	3,232 (3%)	12,926 (3%)	0.00	6,366 (5%)	25,464 (5%)	0.00
65-74	29,934 (27%)	119,735 (27%)	0.00	33,698 (25%)	134,794 (25%)	0.00
75-84	53,206 (48%)	212,823 (48%)	0.00	61,324 (46%)	245,298 (46%)	0.00
85+	23,923 (22%)	95,691 (22%)	0.00	32,070 (24%)	128,281 (24%)	
Sex						0.00
Male	41,647 (38%)	166,588 (38%)	0.00	64,060 (48%)	256,241 (48%)	0.00
Female	68,647 (62%)	274,588 (62%)	0.00	69,399 (52%)	277,595 (52%)	
Residency						0.00
Urban	57,011 (52%)	214,456 (49%)	0.04	64,394 (48%)	259,177 (49%)	0.00
Suburban	35,978 (33%)	154,323 (35%)	-0.04	46,991 (35%)	186,202 (35%)	0.00
Rural	17,305 (16%)	72,397 (16%)	-0.01	22,074 (17%)	88,457 (17%)	
Comorbid conditions						0.05
Myocardial infarction	2,338 (2%)	9,088 (2%)	0.00	4,017 (3%)	10,730 (2%)	0.10
Congestive heart failure	12,364 (11%)	48,485 (11%)	0.00	19,912 (15%)	54,078 (10%)	0.52
Cerebrovascular disease	27,066 (25%)	81,706 (19%)	0.10	66,543 (50%)	93,368 (17%)	0.06

Chronic pulmonary disease	28,809 (26%)	106,853 (24%)	0.03	35,140 (26%)	119,846 (22%)	0.02
Chronic liver disease	18,540 (17%)	63,397 (14%)	0.05	18,150 (14%)	66,302 (12%)	0.02
Chronic liver disease	412 (0%)	1,399 (0%)	0.01	561 (0%)	1,495 (0%)	-0.01
Cancer	11,040 (10%)	43,191 (10%)	0.01	11,664 (9%)	48,793 (9%)	0.18
Hypertension	71,437 (65%)	278,206 (63%)	0.03	95,717 (72%)	318,487 (60%)	0.08
Dyslipidemia	45,982 (42%)	168,309 (38%)	0.05	51,075 (38%)	175,205 (33%)	0.16
Type 2 diabetes mellitus	36,198 (33%)	129,485 (29%)	0.05	49,713 (37%)	143,388 (27%)	0.11
Sepsis	5,426 (5%)	18,662 (4%)	0.02	9,996 (7%)	20,339 (4%)	0.12
Pneumonia	19,026 (17%)	70,235 (16%)	0.03	27,132 (20%)	75,538 (14%)	0.08
Cellulitis	29,823 (27%)	106,103 (24%)	0.05	33,485 (25%)	109,116 (20%)	0.14
Urinary tract infection	21,353 (19%)	75,618 (17%)	0.04	29,975 (22%)	78,901 (15%)	0.00

Supplementary Table 2. Healthcare Utilizations in Dementia and Comparison Groups

	Dementia (n=634,563)	Comparisons (n=2,538,228)	SMD
	N (%)	N (%)	
Health care utilization, per year			
<10	73,419 (12%)	519,068 (20%)	-0.17
10-19	133,639 (21%)	650,040 (26%)	-0.08
20 or more	427,505 (67%)	1,369,120 (54%)	0.20

Supplementary Table 3. Sensitivity Analysis for Crude and Adjusted Odds Ratios of Autoimmune Disease Associations with Dementia in Older Adults

Autoimmune diseases	Dementia (n=634,563)	Comparisons (n=2,538,228)	Crude odds ratios		Adjusted odds ratio	
	N (%)	N (%)	OR 95%CI	Q-value	OR 95%CI	Q-value
Overall autoimmune disease	66,790 (10.5)	220,760 (8.7)	**1.24 (1.22, 1.25)**	**<.001**	**1.07 (1.06, 1.08)**	**<.001**
Specific autoimmune diseases						
Ankylosing Spondylitis	7,555 (1.2)	24,857 (1.0)	**1.22 (1.19, 1.25)**	**<.001**	**1.06 (1.03, 1.06)**	**<.001**
Autoimmune Hemolytic Anemia	165 (0.0)	490 (0.0)	**1.35 (1.13, 1.61)**	**0.001**	1.15 (0.96, 1.15)	0.179
Behcet'S Disease	197 (0.0)	444 (0.0)	**1.78 (1.50, 2.10)**	**<.001**	**1.49 (1.25, 1.49)**	**<.001**
Dermatomyositis	356 (0.1)	1,105 (0.0)	**1.29 (1.14, 1.45)**	**<.001**	**1.05 (1.02, 1.05)**	**0.001**
Graves' Disease	9,537 (1.5)	30,549 (1.2)	**1.25 (1.22, 1.28)**	**<.001**	1.14 (1.01, 1.14)	0.054
Guillain–Barre´ Syndrome	398 (0.1)	1,148 (0.0)	**1.39 (1.24, 1.56)**	**<.001**	**1.27 (1.14, 1.27)**	**<.001**
Hashimoto's Thyroiditis	1,446 (0.2)	4,559 (0.2)	**1.27 (1.20, 1.35)**	**<.001**	1.09 (0.97, 1.09)	0.212
Inflammatory bowel diseases	7,283 (1.1)	24,600 (1.0)	**1.19 (1.16, 1.22)**	**<.001**	**1.09 (1.03, 1.09)**	**0.007**
Multiple Sclerosis	98 (0.0)	195 (0.0)	**2.02 (1.58, 2.57)**	**<.001**	**1.44 (1.12, 1.44)**	**0.009**
Myasthenia Gravis	905 (0.1)	2,878 (0.1)	**1.26 (1.17, 1.36)**	**<.001**	1.02 (0.94, 1.02)	0.823
Pemphigus	270 (0.0)	767 (0.0)	**1.41 (1.23, 1.62)**	**<.001**	1.08 (0.94, 1.08)	0.353
Pernicious Anemia	462 (0.1)	1,285 (0.1)	**1.44 (1.29, 1.60)**	**<.001**	**1.27 (1.14, 1.27)**	**<.001**
Polymyalgia Rheumatica	623 (0.1)	2,058 (0.1)	**1.21 (1.11, 1.33)**	**<.001**	1.01 (0.92, 1.01)	0.905
Polymyositis	164 (0.0)	524 (0.0)	**1.25 (1.05, 1.49)**	**0.012**	1.06 (0.89, 1.06)	0.646
Psoriasis	5,725 (0.9)	19,012 (0.7)	**1.21 (1.17, 1.24)**	**<.001**	**1.05 (1.02, 1.05)**	**0.004**
Rheumatoid Arthritis	11,695 (1.8)	39,654 (1.6)	**1.18 (1.16, 1.21)**	**<.001**	**1.05 (1.02, 1.05)**	**<.001**
SjoGren Syndrome	17,571 (2.8)	54,458 (2.1)	**1.30 (1.28, 1.32)**	**<.001**	**1.14 (1.12, 1.14)**	**<.001**
Systemic Lupus Erythematosus	1,492 (0.2)	4,143 (0.2)	**1.44 (1.36, 1.53)**	**<.001**	**1.23 (1.16, 1.23)**	**<.001**
Systemic Sclerosis	259 (0.0)	831 (0.0)	**1.25 (1.08, 1.43)**	**0.002**	1.13 (0.98, 1.13)	0.160
Systemic vasculitis	649 (0.1)	1,961 (0.1)	**1.32 (1.21, 1.45)**	**<.001**	1.10 (1.00, 1.10)	0.072
Type 1 Diabetes	4,883 (0.8)	14,193 (0.6)	**1.38 (1.34, 1.43)**	**<.001**	**1.07 (1.04, 1.07)**	**<.001**
Uveitis	4,410 (0.7)	16,754 (0.7)	**1.05 (1.02, 1.09)**	**0.002**	**0.96 (0.93, 0.96)**	**0.030**

Adjustment for age, sex, residency, healthcare utilization, and comorbid conditions.

Bolded odds ratios indicate statistical significance at Q-value < 0.05.