Association of Alopecia Areata and the Risk of Dementia: A Nationwide Cohort Study

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ABSTRACT

Background: Alopecia areata (AA) is associated with multiple comorbidities and shares a similar inflammatory signature with dementia. The great negative psychosocial impact of AA may result in poor social engagement, a typical risk factor for dementia. However, little is known about the association between AA and dementia.

Methods: Via the Taiwan National Health Insurance Research Database, 2,534 patients with AA (*International Classification of Diseases, 9th Revision, Clinical Modification* code: 704.01) aged ≥ 45 years and 25,340 controls matched for age, sex, residence, income, dementia-related comorbidities, systemic steroid use, and annual outpatient visit were included between 1998 and 2011 for investigation of subsequent dementia from enrollment to the end of 2013. After controlling for potential confounders, stratified Cox regression analysis on each matched pair was applied to assess the dementia risk between the AA and control groups.

Results: Patients with AA were more likely to develop any dementia (adjusted hazard ratio [aHR] = 3.24; 95% CI, 2.14–4.90), Alzheimer's disease (aHR = 4.34; 95% CI, 1.45–12.97), and unspecified dementia (aHR = 3.36; 95% CI, 2.06–5.48) than the control cohort. Stratification analysis by age and sex revealed increased risks of any dementia and unspecified dementia in both age groups (ie, < 65 and ≥ 65 years) and both sex groups and increased risks of AD in male patients and in those with age at dementia onset ≥ 65 years. Sensitivity analyses after exclusion of the first year or first 3 years of observation showed consistent findings.

Conclusions: Patients with AA had a higher risk of developing dementia. Further studies are needed to elucidate the underlying pathophysiology between AA and dementia risk.

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Alopecia areata (AA) is a common autoimmune disease with an estimated lifetime prevalence of 1.7%.[1–4] It is typically characterized by small patches of baldness on the scalp and/or the body and may progress to alopecia totalis and alopecia universalis.[5,6] Since hair is a vital part of one's outward appearance with very high cosmetic concern, hair loss might have a significant negative emotional and psychosocial impact, leading to personal, social, and work-related problems.[7] Anxiety and depression are common psychological problems in patients with alopecia areata.[8] AA has been associated with other comorbidities such as atopic diseases and autoimmune diseases, including thyroid disease, psoriasis, systemic lupus erythematosus, and vitiligo.[9–12] Although the exact pathogenesis remains unclear, the collapse of immune privilege of the hair follicle is thought to be a key driver of AA.[5]

Dementia is a common disorder characterized by a decline in at least one cognitive function that can impair the performance of daily activities.[13] Alzheimer's disease (AD) is the most frequent subtype and accounts for 60%–80% of all dementia cases, followed by vascular dementia and other neurodegenerative dementias. Epidemiologic studies[14–18] have found an association between dementia and systemic autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and psoriasis. Evidence suggests that autoimmune and inflammatory mechanisms may play a role in the development of AD.[19,20] Dementia, and AD specifically, has been shown to include an inflammatory component that may share some of the same mediators seen in AA, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor–α (TNF-α).[21–23] In addition, the great negative psychosocial impact of AA might further lead to physical inactivity or less social engagement, which are significant risk factors of dementia according to one meta-analysis.[24] Therefore, it is reasonable to hypothesize that AA might be associated with an increased risk of dementia. To evaluate whether or not patients with AA had higher dementia risks than controls, we conducted a nationwide cohort study.

METHODS

Data Source

We analyzed data from the National Health Insurance Research Database (NHIRD) in Taiwan. The National Health Research Institute (NHRI) is in charge of the entire

Clinical Points

- Alopecia areata (AA) shares a similar inflammatory signature with dementia and has great psychological impacts that lead to poor social engagement. However, little is known about the association between AA and dementia.
- Patients with AA had a higher risk of developing any dementia, Alzheimer's disease, and unspecified dementia. Further studies are needed to elucidate the underlying pathophysiology.

insurance claims database and audits and releases the NHIRD for scientific and study purposes. Individual medical records included in the NHIRD are anonymous to protect personal privacy. The NHIRD provides comprehensive information on insured individuals, including demographic data, dates of clinical visits, disease diagnoses, and prescription. Details of the NHIRD have been described in our previous research.[25–30] The accuracy of diagnosis of major diseases in the NHIRD, such as diabetes and ischemic stroke, has been validated.[31–33] The diagnostic codes used were based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*).

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2018-07-016AC).

Study Sample

We included adults aged ≥ 45 years diagnosed with AA (*ICD-9-CM* code 704.01) at least twice by board-certificated dermatologists between January 1, 1998, and December 31, 2011. To identify the incidence of dementia, we excluded patients if they had previous dementia or related diseases, invalid insurance status, unknown sex status, or unknown covariates. For each AA case, we randomly selected 10 controls from the NHIRD Longitudinal Health Insurance Database after eliminating those individuals with prior diagnoses of AA and dementia. The case cohort and control cohort were matched with respect to age, sex, time of enrollment, medical comorbidities, income, and level of urbanization.

The index date for the AA group was the date when AA was diagnosed for the first time, whereas the index date for the control group was the date that AA was diagnosed in the corresponding matched patient with AA. For patients who developed an incident dementia, the length of follow-up was the period from the index date to the date of the first dementia diagnosis. The censored time for patients who did not have an incident dementia was the period from the index date to either December 31, 2013, or death, whichever occurred first.

The primary study outcome was the occurrence of dementia (*ICD-9-CM* codes: 290.0–290.4, 294.1, 294.2, 331.0–331.2, 331.82) ascertained by the board-certified psychiatrist or neurologist at least twice during the follow-up period. The occurrence of specific types of dementia, including AD and vascular dementia, was also identified. AD was defined either by the *ICD-9-CM* code 331.0 without evidence of any cerebrovascular lesions or by the *ICD-9-CM* codes for dementia (290.0–290.3, 294.1, 294.2) with concurrent medications for AD. According to the regulations of National Health Insurance, reimbursable medical therapies for AD are approved only for those without identifiable organic causes, which is a core diagnostic element of AD. Vascular dementia was defined by the specific *ICD-9-CM* code 290.4. Other types of dementia, including *ICD-9-CM* code 331.0 with evidence of any cerebrovascular lesions, were defined as unspecified dementia in our study.

The Charlson Comorbidity Index (CCI)[34] score was used for clinical prognosis and comorbidities adjustments. Other dementia-related comorbidities included cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, diabetes mellitus, major depressive disorder, substance abuse disorder, and alcohol use disorder. Income-related insurance payment amount was classified into 0–500, 501–800, and ≥ 801 US dollars. Residence was classified into 5 levels of urbanization, with level 1 indicating the most urbanized area and level 5 the least urbanized area. Income-related insurance payment amount and urbanization levels were used to represent socioeconomic status. To investigate the effects of systemic AA treatment on subsequent dementia risks, we also adjusted for the use duration of systemic corticosteroids. The use durations of systemic corticosteroids were categorized into < 30, 30 to 364, and ≥ 365 days. The numbers of annual outpatient visit were categorized into < 5, 5 to 9, and ≥ 10.

Statistical Analysis

For between-group comparisons, *t* test or Wilcoxon rank sum test was used for continuous variables and the Pearson test was used for categorical variables. A Cox regression analysis was performed to compare the risk of developing dementia between patients with AA and the control group. As for confounders adjustment, we adjusted for age, sex, monthly premium, residence, comorbidities, Charlson Comorbidity Index score, systemic steroid use, and annual outpatient visit.

To assess the robustness of our results, sensitivity analyses were performed to minimize the influence of potential bias. We assessed the association between AA and dementia after excluding the first year of observation in model 1 and excluding the first 3 years of observation in model 2. A 2-tailed *P* value of < .05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Analysis Software version 9.1 (SAS Institute; Cary, North Carolina).

Data Availability

As participants did not provide consent for their data to be publicly shared, even anonymized, data would be made available only to potential collaborators with ethical approval after they submitted a research proposal to the Bureau of the NHI (https://nhird.nhri.org.tw/).

Table 1. Demographic Data for Subjects With Alopecia Areata and Matched Controls[a]

Variable	AA (n = 2,534)	Controls (n = 25,340)	*P* Value
Age at diagnosis of AA, mean (SD), y	53.9 (7.5)	53.9 (7.5)	.974
Sex			1.000
Male	1,075 (42.4)	10,750 (42.4)	
Female	1,459 (57.6)	14,590 (57.6)	
Monthly premium, USD			1.000
0–500	750 (29.6)	7,500 (29.6)	
501–800	893 (35.2)	8,930 (35.2)	
≥ 801	891 (35.2)	8,910 (35.2)	
Residence			1.000
1 (urbanized)	384 (15.2)	3,840 (15.2)	
2	648 (25.6)	6,480 (25.6)	
3	194 (7.7)	1,940 (7.7)	
4	210 (8.3)	2,100 (8.3)	
5 (rural)	1,098 (43.3)	10,980 (43.3)	
Comorbidities			
Cerebrovascular diseases	199 (7.9)	1,990 (7.9)	1.000
Traumatic head injury	41 (1.6)	410 (1.6)	1.000
Hypertension	818 (32.3)	8,180 (32.3)	1.000
Dyslipidemia	696 (27.5)	6,960 (27.5)	1.000
Diabetes mellitus	389 (15.4)	3,890 (15.4)	1.000
Substance abuse	63 (2.5)	630 (2.5)	1.000
Major depressive disorder	28 (1.1)	280 (1.1)	1.000
Alcohol use disorder	34 (1.3)	340 (1.3)	1.000
Charlson Comorbidity Index score			< .001
0	532 (21.0)	7,095 (28.0)	
1	647 (25.5)	6,527 (25.8)	
2	549 (21.7)	4,805 (19.0)	
3	362 (14.3)	2,965 (11.7)	
≥ 4	444 (17.5)	3,948 (15.6)	
Duration of systemic corticosteroids, d			< .001
< 30	1,445 (57.0)	16,887 (66.6)	
30–364	992 (39.1)	7,700 (30.4)	
≥ 365	97 (3.8)	753 (3.0)	
No. of annual outpatient visits			< .001
< 5	658 (26.0)	8,864 (35.0)	
5–9	554 (21.9)	5,262 (20.8)	
≥ 10	1,322 (52.2)	11,214 (44.3)	

[a]Values are shown as n (%) unless otherwise noted.
Abbreviations: AA = alopecia areata, USD = United States dollars.

Table 2. Incidental Cases and Incidence Rates of Any Dementia and Different Dementia Subtypes

Variable	AA (n = 2,534)	Controls (n = 25,340)	*P* Value
Incidence of any dementia			
Incidental case, n (%)	32 (1.3)	83 (0.3)	< .001
Crude incidence rate/100,000 PY	201.5	52.2	
Age at diagnosis of dementia, mean (SD), y	73.4 (9.3)	78.9 (7.8)	.002
Duration between enrollment and dementia, mean (SD), y	7.2 (3.5)	7.6 (3.9)	.678
Incidence of Alzheimer's dementia			
Incidental case, n (%)	5 (0.2)	10 (0.04)	.001
Crude incidence rate/100,000 PY	31.5	6.3	
Age at diagnosis of dementia, mean (SD), y	76.5 (6.2)	78.0 (9.9)	.771
Duration between enrollment and dementia, mean (SD), y	9.6 (2.1)	7.5 (3.2)	.206
Incidence of vascular dementia			
Incidental case, n (%)	4 (0.2)	14 (0.1)	.053
Crude incidence rate/100,000 PY	25.2	8.8	
Age at diagnosis of dementia, mean (SD), y	74.9 (7.8)	80.3 (4.8)	.103
Duration between enrollment and dementia, mean (SD), y	6.0 (4.4)	8.5 (3.7)	.267
Incidence of other dementia			
Incidental case, n (%)	23 (0.9)	59 (0.2)	< .001
Crude incidence rate/100,000 PY	144.8	37.1	
Age at diagnosis of dementia, mean (SD), y	72.4 (10.2)	78.7 (8.1)	.005
Duration between enrollment and dementia, mean (SD), y	6.9 (3.4)	7.3 (4.1)	.664
Follow-up time, mean (SD), y	6.3 (4.2)	6.3 (4.2)	.909
Summed PY	15,879.4	159,047.6	

Abbreviations: AA = alopecia areata, PY = person-years, USD = United States dollars.

RESULTS

A total of 2,534 patients with AA and 25,340 control subjects were enrolled in our study (Table 1 and Supplementary Figure 1). The mean ± SD age across groups was 53.9 ± 7.5 years, and 56.7% were female. Groups were matched on age, sex, income-related monthly premium, level of urbanization, and comorbidities with no between-group differences. Patients with AA had higher CCI scores ($P < .001$), longer systemic steroid use duration ($P < .001$), and higher numbers of annual outpatient visits ($P < .001$) than the controls.

The crude incidence rates (per 100,000 people per year) in the AA group for any dementia, AD, vascular dementia, and unspecified dementia during the follow-up period were 201.5, 31.5, 25.2, and 144.8, respectively (Table 2). The mean age at diagnosis of any dementia was statistically younger in patients with AA than in controls (73.4 vs 78.9 years, $P = .002$).

After adjusting for potential confounders, patients with AA were more likely to develop dementia (adjusted hazard ratio [aHR] = 3.24; 95% CI, 2.14–4.90), AD (aHR = 4.34; 95% CI, 1.45–12.97), and unspecified dementia (aHR = 3.36; 95% CI, 2.06–5.48) in comparison to the controls (Table 3). Patients with AA had numerically higher risk of vascular dementia without statistical significance than the controls (aHR = 2.05; 95% CI, 0.64–6.63). Age-stratified analysis revealed a significant association between AA and an increased risk of any dementia and unspecified dementia in both age groups and an increased risk of AD in patients with age at dementia onset ≥ 65 years.

Sex-stratified analysis revealed a significant association between AA and an increased risk of any dementia and unspecified dementia in both sexes, and an increased risk of AD in male patients (Table 4). However, we observed no significant association between AA and risk of AD in female patients and vascular dementia in both sexes, potentially due to inadequate sample sizes in these subgroups. Sensitivity analyses after exclusion of the first year or first 3 years of observation yielded consistent findings (Table 5). We checked the proportional hazards assumption using graphical diagnostics of log minus log plots, which showed proportional hazards assumption generally holds. As to the interaction tests, we checked the analytic models incorporating the interaction term of AA × sex and AA × age, which showed nonsignificant results.

Table 3. Cox Proportional Hazards Regression Analyses of Dementia Risk in Patients With Alopecia Areata Compared to Controls, Stratified by Age[a]

	Total					Age at Dementia Onset <65 Years					Age at Dementia Onset ≥65 Years				
Variable	cHR	95% CI	*P*	aHR[b]	95% CI	*P*	cHR	95% CI	*P*	aHR[b]	95% CI	*P*	cHR	95% CI	*P*	aHR[b]	95% CI	*P*
Any dementia	**3.86**	**2.57–5.81**	**<.001**	**3.24**	**2.14–4.90**	**<.001**	**14.98**	**4.23–53.07**	**<.001**	**12.34**	**3.41–44.62**	**<.001**	**3.30**	**2.12–5.14**	**<.001**	**2.92**	**1.87–4.57**	**<.001**
Alzheimer's disease	**5.02**	**1.72–14.68**	**.003**	**4.34**	**1.45–12.97**	**.009**	0.00	…	.9970	0.00	…	1.000	**5.58**	**1.87–16.64**	**.002**	**5.04**	**1.67–15.19**	**.004**
Vascular dementia	2.86	0.94–8.70	.064	2.05	0.64–6.63	.229	…	…	…	…	…	…	2.86	0.94–8.70	.064	2.05	0.64–6.63	.229
Unspecified dementia	**3.91**	**2.41–6.32**	**<.001**	**3.36**	**2.06–5.48**	**<.001**	**19.96**	**4.99–79.81**	**<.001**	**16.68**	**4.06–68.60**	**<.001**	**3.04**	**1.77–5.24**	**<.001**	**2.71**	**1.57–4.68**	**<.001**

[a]Bold type indicates statistical significance.
[b]Adjusted for age, sex, monthly premium, residence, comorbidities, Charlson Comorbidity Index score, systemic steroid use, and annual outpatient visit.
Abbreviations: aHR = adjusted hazard ratio, cHR = crude hazard ratio.

Table 4. Cox Proportional Hazards Regression Analyses of Dementia Risk in Patients With Alopecia Areata Compared to Controls, Stratified by Sex[a]

	Total					Male					Female				
Variable	cHR	95% CI	*P*	aHR[b]	(95% CI)	*P*	cHR	95% CI)	*P*	aHR[b]	95% CI	*P*	cHR	95% CI	*P*	aHR[b]	95% CI	*P*
Any dementia	**3.86**	**2.57–5.81**	**<.001**	**3.24**	**2.14–4.90**	**<.001**	**4.19**	**2.38–7.37**	**<.001**	**3.31**	**1.85–5.90**	**<.001**	**3.55**	**1.97–6.41**	**<.001**	**3.34**	**1.84–6.08**	**<.001**
Alzheimer's disease	**5.02**	**1.72–14.68**	**.003**	**4.34**	**1.45–12.97**	**.009**	**10.12**	**2.04–50.16**	**.005**	**29.47**	**3.02–287.72**	**.004**	2.85	0.59–13.73	.191	2.65	0.53–13.36	.237
Vascular dementia	2.86	0.94–8.70	.064	2.05	0.64–6.63	.229	2.25	0.49–10.43	.298	2.61	0.52–13.09	.245	3.99	0.77–20.56	.098	3.28	0.47–22.76	.230
Unspecified dementia	**3.91**	**2.41–6.32**	**<.001**	**3.36**	**2.06–5.48**	**<.001**	**4.18**	**2.13–8.18**	**<.001**	**3.19**	**1.60–6.38**	**0.001**	**3.65**	**1.83–7.27**	**<.001**	**3.58**	**1.78–7.21**	**<.001**

[a]Bold type indicates statistical significance.
[b]Adjusted for age, sex, monthly premium, residence, comorbidities, Charlson Comorbidity Index score, systemic steroid use, and annual outpatient visit.
Abbreviations: aHR = adjusted hazard ratio, cHR = crude hazard ratio.

The Kaplan-Meier curves of the cumulative incidence rate of dementia indicated that patients with AA had a higher risk of developing dementia ($P < .0001$) than the controls (Figure 1).

To further elucidate the influence of each baseline variable to subsequent dementia risks, we conducted further analysis of the demographic data of subjects with and without dementia (Supplementary Table 1) and the results of dementia risk for alopecia areata and other patient characteristics (Supplementary Table 2).

DISCUSSION

Our study showed a significant association between AA and subsequent risk of developing any dementia, AD, and unspecified dementia after controlling for potential confounding variables. To our knowledge, this study is the first to investigate the association between AA and dementia risk. Sensitivity analyses showed similar results in this association, suggesting the robustness of our results. Our findings alert physicians of the importance of screening for dementia in patients with AA who are ≥45 years of age. In addition, the great negative psychosocial impacts AA brought cannot be overlooked. Poor social engagement and shared inflammatory cytokines might be important links between AA and dementia. Interventions targeting poor social engagement and inflammatory cytokines may be beneficial to AA-associated dementia prevention. Physicians should be more aware of this possible association, help reduce disease discrimination among the public, and encourage more social engagement for AA patients. Further studies are needed to elucidate this association and possible mechanisms underlying AA and dementia.

Because of the important cosmetic and communicational role of human hair, AA can have a significant negative emotional and psychological impacts on individual's life.[8] In addition, AA-related psychological stress may further worsen the AA itself,[35] resulting in a vicious cycle. A recent study[36] has also proved a bidirectional association between AA and depression. Anxiety and depression are common comorbid psychological problems in patients with AA.[8] The great negative psychosocial impact of AA might further lead to physical inactivity or less social engagement, which are significant risk factors of dementia noted in one meta-analysis.[24] In summary, AA

Table 5. Sensitivity Analyses of Dementia Risk in Patients With Alopecia Areata Compared to Controls[a]

Model	cHR	95% CI	*P*	aHR[b]	95% CI	*P*
Primary model	**3.86**	**2.57–5.81**	**<.001**	**3.24**	**2.14–4.90**	**<.001**
Model 1[c]	**4.06**	**2.69–6.13**	**<.001**	**3.41**	**2.24–5.18**	**<.001**
Model 2[d]	**3.90**	**2.52–6.03**	**<.001**	**3.25**	**2.08–5.07**	**<.001**

[a]Bold type indicates statistical significance.
[b]Adjusted for age, sex, monthly premium, residence, comorbidities, Charlson Comorbidity Index score, systemic steroid use, and annual outpatient visit.
[c]Model 1: exclude the first year of follow-up.
[d]Model 2: exclude the first 3 years of follow-up.
Abbreviations: aHR = adjusted hazard ratio, cHR = crude hazard ratio.

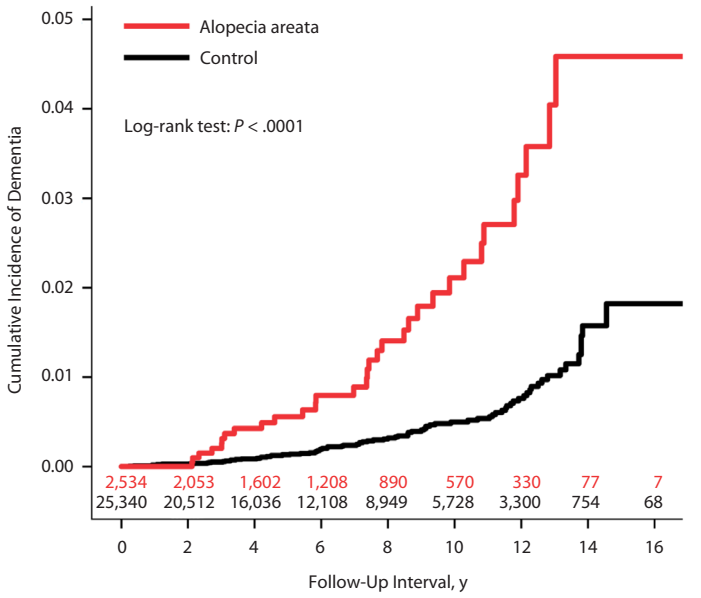
resulted in great negative psychosocial impacts, which may further lead to the poor social engagement and subsequently increase the dementia risk.

Several studies have suggested that patients with AA may be more likely to suffer from neurologic comorbidities.[37,38] One population-based cohort study in Taiwan[39] revealed that patients with AA were at a higher risk for stroke in the 3-year follow-up period, which might explain the increased risk of vascular dementia in AA patients. Growing evidence has suggested a link between dementia and systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and psoriasis.[14–18] For instance, a case-control study using the Clalit Health Care database in Israel[18] showed a significant association between systemic lupus erythematosus and dementia. Another retrospective record-linkage cohort study in the UK[17] disclosed a 1.20 (95% CI, 1.19–1.21) rate ratio for dementia after admission for an autoimmune disease in comparison to a control cohort. Additionally, a cohort study in Taiwan[16] disclosed a significantly higher risk of dementia in middle-aged patients with autoimmune rheumatic diseases. Since AA shares similar genetic and inflammatory signatures with autoimmune diseases, it follows that that AA might be associated with an increased risk of dementia.

Shared underlying inflammatory mechanisms between AA and dementia might explain the association between these 2 distinct diseases. Previous studies[40–42] have found elevated serum levels of IL-1, IL-6, TNF-α, IL-17A, IL-21, IL-22, and IL-23 in AA patients, suggesting a functional role of these cytokines in the pathogenesis of AA. Similarly, emerging evidence suggests that systemic inflammation has a causal role in the development of AD.[43] Previous studies have shown that IL-6 promotes expression of β-amyloid (Aβ) precursor protein[44] and also contributes to neurofibrillary tangle formation by inducing tau phosphorylation.[45] Griffin et al[46,47] found that increased IL-1 and astrocyte-derived neuritogenic cytokine S100B expression was present prior to Aβ plaques or neurofibrillary tangles, indicating that dysregulated inflammation may precede the development of dementia. High levels of α_1-antichymotrypsin, IL-6, and, to a lesser extent, C-reactive protein were associated with an increased risk of dementia.[21] Acute systemic inflammatory events and high baseline levels of TNF-α were also associated with increased rates of cognitive decline. Overall, these findings might partially explain the increased risk of dementia among patients with AA. However, further studies are needed to elucidate the exact mechanisms underlying the association between these two conditions.

The strengths of this study included a large sample size, reliable diagnoses made by dermatologists, and adjustments for potential confounding factors. Nevertheless, this study had several limitations. First, the incidence of dementia and prevalence of AA might be underestimated in the current study because only those seeking medical consultation and treatment were included. Despite the fact that the accuracy of diagnosis of AA and dementia had not been validated before, all diagnoses in our study were given at least twice by board-certificated dermatologists for AA and psychiatrists or neurologists for dementia, creating high diagnostic validity. The diagnosis of AD was defined with concurrent medications for AD. Reimbursable medical therapies for AD are approved only for those without identifiable organic causes, which is a core diagnostic element of AD, further enhancing diagnostic validity. Second, the NHIRD lacks some information on disease severity, the amount of topical or intralesional steroid used, and genetic and environmental factors. These include smoking, alcohol consumption, diet, body mass index, educational status, marital status, lifestyle, and family history, which were potentially unaccounted for as confounding variables. Third, coding errors are possible in any database, including the NHIRD. The accuracy of the identification algorithm in our study, including the AA diagnosis and the dementia diagnosis, has not yet been validated, which could have led to a misclassification bias.

Figure 1. Cumulative Incidence of Dementia for Patients With Alopecia Areata and Controls[a]



[a]Values shown above the x-axis indicate numbers of subjects at risk at each time point.

However, the diagnosis of dementia was confirmed by psychiatrists or neurologists and validated by medications for dementia, suggesting high accuracy within the dementia diagnoses. Fourth, in the current study, we used the longitudinal data to evaluate the temporal relationship between AA and incident dementia, which is important to infer a unidirectional association. Further studies would be required to investigate the prevalence of dementia in patients with AA or the prevalence of AA in patients with dementia. Finally, the small number of events for some outcomes (eg, AD) may reduce the statistical power and caused a wide confidence interval.

In conclusion, patients with AA who were ≥45 years of age had an increased risk of developing any dementia, AD, and unspecified dementia in comparison to the control group. Further studies are required to confirm our findings and clarify the possible pathophysiology between AA and dementia risk.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Association of Alopecia Areata and the Risk of Dementia: A Nationwide Cohort Study

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List of Supplementary Material for the article

1. Table 1 — Demographic data of subjects with and without dementia
2. Table 2 — Cox proportional-hazards regression analyses of dementia risk for alopecia areata and other patient characteristics
3. Figure 1 — Flowchart of the study

Disclaimer

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Supplementary Table 1. Demographic data of subjects with and without dementia

	Dementia cases n = 115		Non-dementia cases n = 27,759		*p* value
AA, n (%)	32	27.8	2502	9.0	<.001
Age at diagnosis of AA (years), mean (SD)	69.9	9.4	53.8	7.4	<.001
Sex, n (%)					0.082
Male	58	50.4	11767	42.4	
Female	57	49.6	15992	57.6	
Monthly premium (USD), n (%)					<.001
0-500	82	71.3	8168	29.4	
501-800	24	20.9	9799	35.3	
≥ 801	9	7.8	9792	35.3	
Residence, n (%)					0.374
1 (urbanized)	15	13.0	4209	15.2	
2	36	31.3	7092	25.6	
3	5	4.4	2129	7.7	
4	7	6.1	2303	8.3	
5 (rural)	52	45.2	12026	43.3	
Comorbidities, n (%)					
Cerebrovascular diseases	60	52.2	2129	7.7	<.001
Traumatic head injury	3	2.6	448	1.6	0.399
Hypertension	88	76.5	8910	32.1	<.001
Dyslipidemia	47	40.9	7609	27.4	0.001
Diabetes mellitus	39	33.9	4240	15.3	<.001
Substance abuse	0	0.0	693	2.5	0.123
Major depressive disorder	1	0.9	307	1.1	0.809
Alcohol use disorder	0	0.0	374	1.4	0.412
Charlson Comorbidity Index					<.001
0	2	1.7	7625	27.5	
1	6	5.2	7168	25.8	
2	11	9.6	5343	19.3	
3	11	9.6	3316	12.0	
≥ 4	85	73.9	4307	15.5	
Duration of systemic corticosteroids (days), n (%)					<.001
< 30	47	40.9	18285	65.9	
30 - 364	57	49.6	8635	31.1	
≥ 365	11	9.6	839	3.0	
Annual outpatient visit, n (%)					<.001

< 5	4	3.5	9518	34.3
6-9	11	9.6	5805	20.9
≥ 10	100	87.0	12436	44.8

Abbreviation: AA, alopecia areata; SD, standard deviation; USD, United States Dollar

Supplementary Table 2. Cox proportional-hazards regression analyses of dementia risk for alopecia areata and other patient characteristics

Patient characteristic	cHR	(95% CI)	*p*	aHR†	(95% CI)	*p*
Alopecia areata	3.86	2.57 - 5.81	<.001	3.24	2.14 - 4.90	<.001
Age at diagnosis of alopecia areata (years)	1.17	1.15 - 1.20	<.001	1.17	1.14 - 1.20	<.001
Sex, male vs. female	1.38	0.96 - 1.99	0.085	1.01	0.68 - 1.51	0.945
Monthly premium (USD)			<.001	0.00		0.769
501-800 vs. 0-500	0.32	0.20 - 0.50	<.001	0.89	0.55 - 1.46	0.653
≥ 801 vs. 0-500	0.12	0.06 - 0.24	<.001	1.20	0.54 - 2.69	0.658
Residence, n (%)			0.565	0.00		0.765
2 vs. 1	1.43	0.78 - 2.60	0.249	0.87	0.46 - 1.65	0.679
3 vs. 1	0.78	0.28 - 2.14	0.628	0.58	0.20 - 1.70	0.321
4 vs. 1	0.96	0.39 - 2.35	0.921	0.69	0.27 - 1.80	0.453
5 vs. 1	1.27	0.71 - 2.25	0.422	0.99	0.54 - 1.81	0.964
Comorbidities						
Cerebrovascular diseases	8.85	6.13 - 12.78	<.001	2.05	1.37 - 3.08	0.001
Traumatic head injury	1.77	0.56 - 5.58	0.328	0.42	0.12 - 1.43	0.164
Hypertension	5.07	3.29 - 7.81	<.001	0.83	0.51 - 1.35	0.455
Dyslipidemia	1.46	1.01 - 2.12	0.047	1.07	0.70 - 1.64	0.757
Diabetes mellitus	2.19	1.48 - 3.22	<.001	0.81	0.53 - 1.22	0.309
Substance abuse	0.00	0.00 - .	0.975	0.00	0.00 - .	0.981
Major depressive disorder	1.18	0.16 - 8.43	0.872	3.09	0.42 - 22.92	0.270
Alcohol use disorder	0.00	0.00 - .	0.975	0.00	0.00 - .	0.988
Charlson Comorbidity Index			<.001	0.00		<.001
1 vs. 0	2.80	0.56 - 13.85	0.208	1.45	0.29 - 7.27	0.648
2 vs. 0	6.40	1.42 - 28.85	0.016	2.15	0.47 - 9.84	0.326
3 vs. 0	9.63	2.13 - 43.46	0.003	2.59	0.56 - 11.98	0.224
≥ 4 vs. 0	49.20	12.10 - 200.05	<.001	6.52	1.52 - 27.95	0.012
Duration of systemic corticosteroids (days)			<.001	0.00		0.909
30 - 364 vs. < 30	2.30	1.56 - 3.38	<.001	1.05	0.70 - 1.56	0.822
≥ 365 vs. < 30	4.13	2.14 - 7.97	<.001	0.91	0.46 - 1.80	0.783
Annual outpatient visit, n (%)			<.001	0.00		0.013
6-9 vs. < 5	3.61	1.15 - 11.33	0.028	3.00	0.94 - 9.58	0.064
≥ 10 vs. < 5	14.76	5.44 - 40.09	<.001	4.55	1.58 - 13.07	0.005

Abbreviation: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; USD, United States Dollar.

[†]Adjusted for age, sex, monthly premium, residence, comorbidities, Charlson Comorbidity Index, systemic steroid use, and annual outpatient visit.

Supplementary Figure 1. Flowchart of the study