Association between alopecia areata and retinal diseases: A nationwide population-based cohort study

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Background: Growing evidence has revealed abnormalities in the retinal structures of patients with alopecia areata (AA). However, the relationship between AA and retinopathy remains unclear.

Objective: To investigate the association between AA and retinal diseases.

Methods: The study participants were recruited from the National Health Insurance Research Database in Taiwan. We included 9909 patients with AA and 99,090 matched controls to assess the risk of retinal diseases. A Cox regression model was used for all analyses.

Results: Compared with the controls, patients with AA had an adjusted hazard ratio (aHR) of 3.10 (95% confidence interval [CI] 2.26-4.26) for retinal diseases. With respect to individual retinal diseases, Patients with AA had significantly higher risks of developing retinal detachment (aHR 3.98; 95% CI 2.00-7.95), retinal vascular occlusion (aHR 2.45; 95% CI 1.22-4.92), and retinopathy (aHR 3.24; 95% CI 2.19-4.81) than controls.

Limitations: This was a retrospective cohort study. Meanwhile, almost all the participating individuals were residents of Taiwan; therefore, the validity of our findings in other demographics remains unclear.

Conclusion: Patients with AA had a significantly higher risk of retinal disease than controls. Further studies are needed to clarify the pathophysiology of AA and retinal diseases. (J Am Acad Dermatol 2022;87:771-8.)

Key words: alopecia areata; retinal detachment; retinopathy; Taiwan's National Health Insurance Research Database.

INTRODUCTION

Alopecia areata (AA) is a common autoimmune disorder of the hair that has an estimated lifetime risk of 1.7%.[1,2] Patients with AA usually present with oval- or round-shaped, well-circumscribed, variable-sized hairless patches over the scalp. In some cases, diffuse alopecia and generalized hair loss involving the eyebrows, eyelashes, armpit hair, and pubic hair may occur.[3] Although it is not a life-threatening disease, the changes in appearance may lower

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patients' self-esteem and quality-of-life, resulting in an increased risk of several psychological diseases.[4-6]

Several studies have described the abnormalities or changes in retinal structure in patients with AA, including retinal alterations in the form of pigmentary clumping, choroidal sclerosis, and macular degeneration.[7] However, most of these studies were case reports and lacked comparison groups. Thus, the relationship between AA and retinal disorders remains unknown. Investigating the retinal complications associated with AA would provide important information for clinical assessment and optimal management. Therefore, we conducted this nationwide, population-based cohort study to elucidate the association between AA and retinal diseases.

CAPSULE SUMMARY

- Alopecia areata is an autoimmune disease that affects not only hair follicles but also the retina, optic lens, and cardiovascular system.
- Patients with alopecia areata are at risk of developing retinal detachment and retinal arterial occlusion compared to controls. Dermatologists should be aware of this possible comorbidity.

METHODS

Data source

Taiwan initiated a single-payer National Health Insurance (NHI) program in 1995. Currently, there are more than 23 million individuals in this program, representing approximately 99.6% of Taiwan's entire population. The NHI Research Database (NHIRD) provides comprehensive information on insured individuals, including demographic details (sex, date of birth, and residential location) and claims data (outpatient and inpatient care, medical diagnoses, prescriptions, and operations). The NHIRD has been widely used in epidemiologic studies in Taiwan.[8-13] To protect individual privacy, a unique identification number is assigned to each beneficiary and enciphered before the data are released for scientific purposes. The diagnostic codes used herein are based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

Study cohorts and controls

Participants aged ≥3 years were selected from the NHIRD between January 1, 1997, and December 31, 2012. To identify patients with AA, we used the ICD-9-CM code 704.01. Participants were considered to have AA only if the diagnosis was established by dermatologists and the condition was examined at ≥3 outpatient visits.

For each patient with AA, 10 matched subjects without AA were selected from the same database. These participants were matched for age, sex, monthly premium, residence, and comorbidities. Monthly premiums were classified into 3 groups: \$0 to \$500, \$501 to \$800, and >\$801 (US dollars). Residence was classified into 5 levels of urbanization, with level 1 indicating the most urbanized area and level 5 indicating the least urbanized area. The above 2 indicators were used to represent socioeconomic status. The comorbidities considered in this study included hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, major depressive disorder, anxiety disorder, alcohol use disorder, tobacco use disorder, obesity, glaucoma, and uveitis. In addition to the selected comorbidities, the Charlson Comorbidity Index was used for clinical prognosis and comorbidity adjustment.[14] An individual was considered as having a comorbidity only if the condition was examined at ≥3 outpatient visits. Prior use of systemic corticosteroids was categorized based on the duration of treatment, as <30, 30 to 179, or ≥180 days. Meanwhile, previous treatment with systemic or intralesional corticosteroids was also analyzed.

Outcome

The primary outcome was new-onset retinal diseases, including retinal detachment (ICD-9-CM codes 361.0, 361.1, 361.2, 361.8, 361.9, 362.40), other retinopathies (ICD-9-CM codes 362.10, 362.12, 362.13, 362.14, 362.15, 362.16, 362.17, 362.41, 362.42, 362.43, 362.82, 362.83, 362.89), and retinal vascular occlusion (ICD-9-CM codes 362.3, 362.81, 362.84). The diagnosis of retinal diseases was established at least 3 times by board-certified ophthalmologists. To identify the incidence of retinal diseases, we excluded those patients with previous diagnoses of any retinal diseases (ICD-9-CM codes 361 and 362), invalid insurance status, unknown sex status, or unknown covariates. To further confirm the independent relationship between AA and retinal diseases, we excluded patients who had any comorbidities and conducted a sensitivity test.

The index date for the AA group was the first date on which AA was diagnosed, while the index date for the control group was the AA diagnosis date of the matched patient with AA. Participants were followed from the index date until the date of first diagnosis of

Abbreviations used:

AA:	alopecia areata
aHR:	adjusted hazard ratio
ICD-9-CM:	International Classification of Diseases, 9th Revision, Clinical Modification
NHI:	National Health Insurance
NHIRD:	NHI Research Database

retinal disease, the date of withdrawal from the NHI, or December 31, 2013.

Statistical analysis

For intergroup comparisons, the *t* test or Wilcoxon rank sum test was used for continuous variables, and the Pearson test was used for categorical variables. A Cox regression model was used to assess the association between AA and retinal disease. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were calculated to determine the strength of the association. The 2-sided *P* values of <.05 were considered statistically significant. Data management and analyses were performed using SAS software (version 9.4; SAS Institute).

RESULTS

In this study, 9909 patients with AA and 99,090 control patients were included. There were no significant differences in age, sex, monthly premium, residence, or selected comorbidities (Table I).

Overall, 61 patients with AA developed retinal diseases, with an overall rate of 81.85 cases per 100,000 person-years. In contrast, 175 patients without AA had retinal diseases, with an overall rate of 23.38 cases per 100,000 person-years. After adjusting for the potential confounders, patients with AA had an aHR (95% CI) of 3.10 (2.26-4.26) for retinal diseases when compared with controls (Table II). The median (interquartile range) age at diagnosis of retinal disease onset was 43.3 (31.8-50.8) years in patients with AA, compared to 53.9 (40.8-65.1) years in controls ($P < .0001$). With respect to individual retinal diseases, patients with AA had significantly higher risks of developing retinal detachment (aHR 3.98; 95% CI 2.00-7.95), retinal vascular occlusion (aHR 2.45; 95% CI 1.22-4.92), and retinopathy (aHR 3.24; 95% CI 2.19-4.81) (Table III). Stratified analyses showed a significant association between AA and the risk of retinal diseases among the age groups of 20 to 39 years and 40 to 59 years, both sexes, groups with systemic corticosteroid use duration of <30 days and 30 to 179 days, groups with and without previous systemic corticosteroids, and the group without previous intralesional corticosteroids (Table IV). The sensitivity test excluding patients with any recorded comorbidities showed that patients with AA still had an increased risk of retinal diseases (aHR 2.55; 95% CI 1.53-4.27) compared to the controls.

DISCUSSION

In this study, we found that patients with AA were at significantly higher risk of developing retinal diseases, including retinal detachment, retinal vascular occlusion, and retinopathy, than controls. In addition, patients with AA had a younger age of onset of retinal diseases than those without AA. Stratified analysis revealed that the risk of retinal diseases was significantly increased among those aged 20 to 39 years and 40 to 59 years, both sexes, those with systemic corticosteroid use for <30 days and 30 to 179 days, those with and without previous systemic corticosteroid treatment, and those without previous intralesional corticosteroid treatment. To our knowledge, this is the first large, population-based study to investigate the association between AA and the risk of retinal diseases.

The ocular findings in patients with AA have seldom been described in the literature. Andrade et al[15] examined 22 patients with AA and found that common ocular findings included madarosis (54.5%), lens changes (18.2%), and cataracts (13.65%). Retinal changes were also evaluated in this study, and peripheral drusen was the most frequently reported finding (38.6%). Esmer et al[7] suggested that patients with AA had an increased risk of lens abnormalities and posterior segment abnormalities compared to control groups, without interfering with visual acuity. Another study by Pandhi et al[16] investigated 80 patients with AA and found a high frequency of asymptomatic punctate lens opacities (24.1%) along with posterior (7.2%) and anterior (9.6%) subcapsular cataracts. Reported retinal changes included macular degeneration, pigmentary clumping, and abnormal vascular changes. Similar lens and retinal findings were also reported by Tosti et al[17] and Recupero et al.[18] Although several retinal abnormalities were described, no retinal detachment or other retinopathies were disclosed in these studies. However, these studies were mostly case-control studies, and adequate follow-up was not available.

The pathogenesis of AA and retinal diseases has been poorly described in the literature. Melanocyte damage and systemic inflammation may play a role. Some studies have suggested that the melanin pigment system inside the hair follicle is the target antigen in AA, and, thus, melanocytes in other systems may also be involved.[19] In the eye,

Table I. Demographic data of patients with alopecia areata and controls

	AA N = 9909		Controls N = 99,090		*P*
Age* (y), median (IQR)	31.6	23.0-42.2	31.7	22.8-42.3	.9866
Age* group (y)					.6686
<20	1742	17.6	17,814	17.980	
20-39	5220	52.7	51,612	52.090	
40-59	2660	26.8	26,740	26.990	
≥60	287	2.9	2924	2.950	
Sex, n (%)					1.0000
Male	4803	48.5	48,030	48.5	
Female	5106	51.5	51,060	51.5	
Monthly premium (USD), n (%)					1.0000
0-500	4200	42.4	42,000	42.4	
501-800	2882	29.1	28,820	29.1	
≥801	2827	28.5	28,270	28.5	
Residence, n (%)					1.0000
1 (urbanized)	1460	14.7	14,600	14.7	
2	2555	25.8	25,550	25.8	
3	839	8.5	8390	8.5	
4	814	8.2	8140	8.2	
5 (rural)	4,241	42.8	42,410	42.8	
Comorbidity, n (%)					
Hypertension	922	9.3	9220	9.3	1.0000
Diabetes mellitus	399	4.0	3990	4.0	1.0000
Hyperlipidemia	885	8.9	8850	8.9	1.0000
Cerebrovascular disease	185	1.9	1850	1.9	1.0000
Chronic kidney disease	66	0.7	660	0.7	1.0000
Chronic obstructive pulmonary disease	138	1.4	1380	1.4	1.0000
Major depressive disorder	523	5.3	5230	5.3	1.0000
Anxiety disorder	1119	11.3	11,190	11.3	1.0000
Alcohol use disorder	199	2.0	1990	2.0	1.0000
Tobacco use disorder	327	3.3	3270	3.3	1.0000
Obesity	154	1.6	1540	1.6	1.0000
Glaucoma	156	1.6	1560	1.6	1.0000
Uveitis	19	0.2	190	0.2	1.0000
Charlson Comorbidity Index, n (%)					<.0001
0	4090	41.3	47,283	47.7	
1	3196	32.3	29,309	29.6	
2	1467	14.8	12,692	12.8	
3	644	6.5	5332	5.4	
≥4	512	5.2	4474	4.5	
Duration of systemic corticosteroids (days), n (%)					<.0001
<30	9199	92.8	96,823	97.7	
30-179	599	6.1	1905	1.9	
≥180	111	1.1	362	0.4	
Use of systemic corticosteroid	4082	41.2	24,726	25.0	<.0001
Use of intralesional corticosteroids	2038	20.6	0	0.0	<.0001
Annual outpatient visit, n (%)					<.0001
<5	2761	27.9	48,394	48.8	
6-9	3039	30.7	25,338	25.6	
≥10	4109	41.5	25,358	25.6	

AA, Alopecia areata; *IQR*, interquartile range; *USD*, United States Dollar.
*Age at diagnosis of alopecia areata.

melanocytes can be found in the choroid and retinal pigment epithelium, which develop from the neural crest and neural ectoderm, respectively. The melanocytes in the choroid contribute to the pigmentation of the eye, which helps reduce damage from ultraviolet light.[20,21] Additionally, these

Table II. Cox regression analyses of factors associated with the risk of retinal diseases

	HR	95% CI	*P*	aHR*	95% CI	*P*
AA vs. control	3.51	2.62-4.69	<.0001	3.10	2.26-4.26	<.0001
Age, year	1.06	1.06-1.07	<.0001	1.05	1.04-1.06	<.0001
Sex, male vs. female	1.37	1.06-1.78	.0157	1.92	1.45-2.53	<.0001
Monthly premium (USD)			.7578			.4208
501-800 vs. 0-500	1.08	0.79-1.48	.6241	0.84	0.61-1.15	.2641
≥801 vs. 0-500	1.12	0.82-1.53	.4686	0.83	0.60-1.14	.2544
Residence, n (%)			.7798			.8256
2 vs. 1	1.24	0.81-1.92	.3283	1.15	0.74-1.78	.5417
3 vs. 1	1.08	0.59-1.95	.8068	1.26	0.69-2.29	.4527
4 vs. 1	1.40	0.81-2.42	.2332	1.38	0.79-2.41	.2519
5 vs. 1	1.17	0.78-1.76	.4396	1.20	0.80-1.81	.3812
Comorbidity						
Hypertension	3.60	2.73-4.76	<.0001	1.00	0.70-1.44	.9902
Diabetes mellitus	2.88	1.96-4.23	<.0001	1.13	0.72-1.76	.6033
Hyperlipidemia	2.35	1.73-3.21	<.0001	0.83	0.57-1.19	.3063
Cerebrovascular disease	3.66	2.29-5.85	<.0001	1.10	0.65-1.87	.7228
Chronic kidney disease	5.46	2.80-10.63	<.0001	2.66	1.30-5.44	.0073
Chronic obstructive pulmonary disease	1.88	0.89-4.00	.0987	0.69	0.32-1.51	.3529
Major depressive disorder	1.19	0.71-2.01	.5077	1.28	0.60-2.75	.5258
Anxiety disorder	0.98	0.66-1.46	.9104	0.86	0.48-1.56	.6246
Alcohol use disorder	0.54	0.17-1.68	.2852	0.48	0.15-1.51	.2074
Tobacco use disorder	1.45	0.79-2.66	.2257	1.34	0.72-2.48	.3592
Obesity	0.60	0.15-2.41	.4688	0.72	0.18-2.90	.6385
Glaucoma	7.14	4.78-10.67	<.0001	4.12	2.70-6.30	<.0001
Uveitis	4.52	1.45-14.13	.0094	4.19	1.31-13.40	.0156
Charlson Comorbidity Index			<.0001			.7267
1 vs. 0	1.41	1.00-1.99	.0508	0.87	0.61-1.25	.4589
2 vs. 0	2.21	1.51-3.22	<.0001	0.88	0.59-1.32	.5385
3 vs. 0	2.49	1.55-4.00	.0002	0.69	0.41-1.15	.1561
≥4 vs. 0	4.80	3.23-7.15	<.0001	0.84	0.51-1.38	.4896
Duration of systemic corticosteroids (days)			.0030			.7448
30-179 vs. <30	2.51	1.46-4.30	.0009	1.09	0.61-1.95	.7773
≥180 vs. <30	1.79	0.44-7.20	.4132	0.61	0.15-2.50	.4900
Use of systemic corticosteroids	1.52	1.16-1.98	.0021	1.20	0.89-1.62	.2292
Use of intralesional corticosteroids	2.65	1.45-4.85	.0016	0.72	0.37-1.42	.3424
Annual outpatient visit, n (%)			<.0001			<.0001
6-9 vs. <5	2.06	1.36-3.12	.0006	1.78	1.16-2.73	.0082
≥10 vs. <5	6.42	4.54-9.08	<.0001	4.02	2.69-6.01	<.0001

AA, Alopecia areata; *aHR*, adjusted hazard ratio; *CI*, confidence intervals; *HR*, hazard ratio; *USD*, United States Dollar.
*Adjusted for age, sex, monthly premium, residence, comorbidities, Charlson Comorbidity Index, steroid use, and annual outpatient visit.

melanocytes may also contribute to the development and maintenance of the choroid vasculature.[22,23] The retinal pigment epithelium is a specialized monolayer composed of hyperpigmented cuboidal cells, which are essential for repairing the rod's outer segment, metabolic support, and photoprotection of the retina.[24] The melanin produced by these cells may scavenge free radicals, thereby reducing oxidative stress.[25,26] There is some histologic and clinical evidence supporting retinal pigmentary system involvement in patients with AA.[17,24,27,28] Previous studies revealed that melanocytes are important for maintaining the structure and function of the retina. Dysfunction of melanocytes should be correlated with retinal detachment in patients with AA. Although a direct link between ocular melanocyte damage and retinal detachment is still lacking, we might find some clues in Vogt-Koyanagi-Harada disease, which is a rare autoimmune disease that targets melanocyte antigens and results in ocular complications.[29] In these patients, acute inflammation of the retina may induce subsequent serous retinal detachment, which may lead to blindness without timely treatment.[29,30] Another possible factor is systemic inflammatory status. Several rheumatologic diseases, such as sarcoidosis, systemic lupus erythematosus, and rheumatic arthritis, have been reported to trigger serous retinal

Table III. Hazard ratios of individual retinal diseases among patients with alopecia areata

	Events, n	Crude incidence rate/100,000 PY	HR	95% CI	*P*	aHR*	95% CI	*P*
Retinal detachment								
Controls	33	4.41	1.00	Reference		1.00	Reference	
AA	13	17.44	3.96	2.09-7.53	<.0001	3.98	2.00-7.95	<.0001
Other retinopathy								
Controls	108	14.43	1.00	Reference		1.00	Reference	
AA	42	56.35	3.91	2.74-5.59	<.0001	3.24	2.19-4.81	<.0001
Retinal vascular occlusion								
Controls	44	5.88	1.00	Reference		1.00	Reference	
AA	11	14.76	2.52	1.30-4.87	.0062	2.45	1.22-4.92	.0272
Total								
Controls	175	23.38	1.00	Reference		1.00	Reference	
AA	61	81.85	3.51	2.62-4.69	<.0001	3.10	2.26-4.26	<.0001

AA, Alopecia areata; *aHR*, adjusted hazard ratio; *HR*, hazard ratio.
*Adjusted for age, sex, monthly premium, residence, comorbidities, Charlson Comorbidity Index, steroid use, and annual outpatient visit.

Table IV. Hazard ratios of retinal diseases among patients with alopecia areata, stratified by age, sex, and duration of systemic corticosteroids, use of systemic corticosteroids, and use of intralesional corticosteroids

	AA			Controls			AA vs Controls					
	Events, n	PY	Crude incidence rate/ 100,000 PY	Events, n	PY	Crude incidence rate/ 100,000 PY	HR	95% CI	*P*	aHR*	95% CI	*P*
Total	61	74530	81.85	175	748473	23.38	3.51	2.62-4.69	<.0001	3.10	2.26-4.26	<.0001
Age group (y)												
<20	5	14008	35.69	12	143269	8.38	4.24	1.49-12.03	.0067	2.76	0.87-8.75	.0848
20-39	30	39803	75.37	50	395193	12.65	5.98	3.80-9.40	<.0001	5.06	3.10-8.24	<.0001
40-59	20	18740	106.72	77	189809	40.57	2.64	1.62-4.32	.0001	2.36	1.37-4.06	.0019
≥60	6	1979	303.25	36	20201	178.21	1.69	0.71-4.01	.2336	1.68	0.64-4.42	.2932
Sex												
Male	40	35983	111.17	92	361835	25.43	4.38	3.02-6.35	<.0001	3.70	2.46-5.57	<.0001
Female	21	38547	54.48	83	386638	21.47	2.54	1.58-4.11	.0001	2.42	1.45-4.05	.0008
Duration of systemic corticosteroids												
<30	53	68618	77.24	167	730706	22.85	3.40	2.50-4.63	<.0001	3.16	2.27-4.39	<.0001
30-179	7	5001	139.97	7	14818	47.24	2.87	1.01-8.20	.0488	5.03	1.32-19.20	.0180
≥180	1	911	109.80	1	2949	33.91	3.54	0.22-56.76	.3716	0.00	0.00-0.00	1.0000
Use of systemic corticosteroids												
Yes	29	31793	91.22	55	186846	29.44	3.05	1.94-4.78	<.0001	3.09	1.80-5.32	<.0001
No	32	42737	74.88	120	561627	21.37	3.56	2.41-5.26	<.0001	3.10	2.09-4.61	<.0001
Use of intralesional corticosteroids												
Yes	11	14959	73.54	0	0	NA	NA	NA	NA	NA	NA	NA
No	50	59571	83.93	175	748473	23.38	3.60	2.63-4.92	<.0001	3.14	2.29-4.31	<.0001

AA, Alopecia areata; *aHR*, adjusted hazard ratio; *CI*, confidence intervals; *HR*, hazard ratio; *PY*, person-years.
*Adjusted for age, sex, monthly premium, residence, comorbidities, Charlson Comorbidity Index, steroid use, and annual outpatient visit.

detachment by causing fibrinoid necrosis of the choriocapillaris and cystoid macular edema.[31] AA is a systemic autoimmune disease, and the disease pathway shares some similarities with other inflammatory diseases, including psoriasis, systemic lupus erythematosus, and rheumatic arthritis, which show elevation of both type 2 and type 17 cytokines.[32-34] Systemic inflammatory status may further modulate choroidal vascular perfusion and permeability, leading to alterations in the composition of choroidal

interstitial fluid and subsequent serous retinal detachment.[31] Furthermore, Dai et al[35] described an association between AA and endometriosis, suggesting that AA is associated with not only traditional rheumatologic diseases but also several systemic inflammatory conditions.

In our study, we also found an increased risk of retinal vascular occlusion in patients with AA. Although this association has rarely been described in the literature, growing evidence has shown that AA may be correlated with cardiovascular diseases.[36-39] One study revealed elevated serum troponin I levels, which are associated with cardiac remodeling and increased risk of cardiac-related complications, in patients with AA.[36] Another large-scale cohort study in Korea demonstrated a significantly increased risk of acute myocardial infarction in patients with AA.[37] Increased inflammatory cytokines and activation of the hypothalamic–pituitary–adrenal axis may contribute to hyperinsulinemia and metabolic syndrome in patients with AA.[38] Moreover, Kang et al[39] reported an increased risk of all stroke types, including ischemic stroke, in patients with AA. Systemic inflammation can also be quantified by levels of ischemia-modified albumin. Incel-Uysal et al[40] found that the mean serum level of ischemia-modified albumin was significantly higher in patients with AA than in the control group and concluded that raised levels of ischemia-modified albumin may be associated with antioxidant/oxidant imbalance and the risk of cardiovascular disease in patients with AA. As a result, the cardiovascular risk of patients with AA might be considered a risk factor for retinal artery occlusion. This finding is consistent with those of previous studies.[41]

Systemic corticosteroids are commonly used in the treatment of AA. Previous studies have shown that systemic and topical corticosteroids may be linked to the development of central serous chorioretinopathy, which is characterized by the accumulation of serous fluid and subsequent detachment of retinal pigment epithelium.[42,43] However, we did not observe a significant association between the risk of retinopathy and systemic and intralesional corticosteroid therapy. Besides, the association between AA and retinopathy remained significant even in those without the use of systemic or intralesional corticosteroid. Thus, the effect of corticosteroids may not fully explain the association between AA and retinopathy.

This study has some limitations. First, the identification algorithm for retinal diseases in our study has not been validated, potentially causing misclassification bias. Moreover, the incidence of retinal diseases might be underestimated, as only those who sought consultation and treatment were included in the study. However, the misclassification of outcomes generally leads to bias toward the null. Second, the NHIRD lacks some potential confounding factors, including body mass index, family history, and lifestyle. Third, the severity and specific type of retinal detachment were not found in the NHIRD record, and, thus, further analysis was not feasible.[44-46] Finally, almost all the participating individuals were residents of Taiwan; therefore, the validity of our findings in other demographics remains unclear.

In conclusion, this large, population-based cohort study found that patients with AA had a significantly higher risk of retinal diseases, including retinal detachment, retinal vascular occlusion, and retinopathy, than controls. Further studies are needed to clarify the mechanism of retinal diseases in patients with AA.

Conflict of interest

None disclosed.

REFERENCES

1. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ 3rd. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. *Mayo Clin Proc*. 1995;70:628-633.
2. Dai YX, Chen TJ, Chang YT. Skin care services and disease prevalence in Taiwan: a nationwide study. *Dermatol Sin*. 2018;36:124-130.
3. Dai YX, Yeh CP, Chen CC. Efficacy and safety of tofacitinib therapy in Asian patients with severe alopecia areata. *Dermatol Sin*. 2020;38:3-8.
4. Dai YX, Tai YH, Chen CC, Chang YT, Chen TJ, Chen MH. Bidirectional association between alopecia areata and sleep disorders: a population-based cohort study in Taiwan. *Sleep Med*. 2020;75:112-116.
5. Dai YX, Tai YH, Chang YT, Chen TJ, Chen MH. Association between major depressive disorder and subsequent autoimmune skin diseases: a nationwide population-based cohort study. *J Affect Disord*. 2020;274:334-338.
6. Dai YX, Tai YH, Chen CC, Chang YT, Chen TJ, Chen MH. Bidirectional association between alopecia areata and major depressive disorder among probands and unaffected siblings: a nationwide population-based study. *J Am Acad Dermatol*. 2020;82:1131-1137.
7. Esmer O, Karadag R, Cakici O, et al. Ocular findings in patients with alopecia areata. *Int J Dermatol*. 2016;55:814-818.
8. Dai YX, Chen CC, Tai YH, Chang YT, Chen TJ, Chen MH. Increased risk of major depressive disorder among probands with psoriasis and unaffected siblings: a nationwide population-based study. *J Eur Acad Dermatol Venereol*. 2020;34:1510-1515.
9. Dai YX, Wang SC, Chou YJ, et al. Smoking, but not alcohol, is associated with risk of psoriasis in a Taiwanese population-based cohort study. *J Am Acad Dermatol*. 2019;80:727-734.
10. Dai YX, Yeh FY, Shen YJ, et al. Cigarette smoking, alcohol consumption, and risk of alopecia areata: a population-based cohort study in Taiwan. *Am J Clin Dermatol*. 2020;21:901-911.

11. Dai YX, Yeh FY, Chou YJ, et al. Cigarette smoking and risk of rosacea: a nationwide population-based cohort study. *J Eur Acad Dermatol Venereol*. 2020;34:2593-2599.
12. Dai YX, Tai YH, Chang YT, Chen TJ, Chen MH. Bidirectional association between psoriasis and atopic dermatitis: a nationwide population-based cohort study. *Dermatology*. 2021;237:521-527.
13. Dai YX, Tai YH, Lee DD, Chang YT, Chen TJ, Chen MH. Risk of retinal diseases in patients with psoriasis: a population-based cohort study in Taiwan. *J Dermatol*. 2021;48:1550-1556.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
15. De Andrade FA, Giavedoni P, Keller J, Sainz-de-la-Maza MT, Ferrando J. Ocular findings in patients with alopecia areata: role of ultra-wide-field retinal imaging. *Immunol Res*. 2014;60:356-360.
16. Pandhi D, Singal A, Gupta R, Das G. Ocular alterations in patients of alopecia areata. *J Dermatol*. 2009;36:262-268.
17. Tosti A, Colombati S, Caponeri GM, et al. Ocular abnormalities occurring with alopecia areata. *Dermatologica*. 1985;170:69-73.
18. Recupero SM, Abdolrahimzadeh S, De Dominicis M, et al. Ocular alterations in alopecia areata. *Eye (Lond)*. 1999;13:643-646.
19. Rajabi F, Drake LA, Senna MM, Rezaei N. Alopecia areata: a review of disease pathogenesis. *Br J Dermatol*. 2018;179:1033-1048.
20. Plonka PM, Passeron T, Brenner M, et al. What are melanocytes really doing all day long…? *Exp Dermatol*. 2009;18:799-819.
21. Ma SH, Tai YH, Dai YX, Chang YT, Chen TJ, Chen MH. Association of sensorineural hearing loss in patients with alopecia areata: a nationwide population-based cohort study. *JAMA Dermatol*. 2020;156:1262-1264.
22. Shibuya H, Watanabe R, Maeno A, et al. Melanocytes contribute to the vasculature of the choroid. *Genes Genet Syst*. 2018;93:51-58.
23. Schatz O, Zalaudek I, Tabrizi-Wizsy NG, et al. Melanocytes, organogenesis, and angiogenesis: evidence for more than a pigment-producing capability of melanocytes. *Cells Tissues Organs*. 2018;206:6-8.
24. Hu D-N, Simon JD, Sarna T. Role of ocular melanin in ophthalmic physiology and pathology. *Photochem Photobiol*. 2008;84:639-644.
25. Istrate M, Vlaicu B, Poenaru M, Hasbei-Popa M, Salavat MC, Iliescu DA. Photoprotection role of melanin in the human retinal pigment epithelium. Imaging techniques for retinal melanin. *Rom J Ophthalmol*. 2020;64:100-104.
26. Ma SH, Ang MD, Chang YT, Dai YX. Association between vitiligo and hearing loss: a systemic review and metaanalysis. *J Am Acad Dermatol*. January 21, 2021. https://doi.org/10.1016/j.jaad.2020.12.029
27. Gilhar A, Paus R, Kalish RS. Lymphocytes, neuropeptides, and genes involved in alopecia areata. *J Clin Invest*. 2007;117:2019-2027.
28. Tosti A, Colombati S, De Padova MP, Guidi SG, Tosti G, Maccolini E. Retinal pigment epithelium function in alopecia areata. *J Invest Dermatol*. 1986;86:553-555.
29. Lavezzo MM, Sakata VM, Morita C, et al. Vogt-Koyanagi-Harada disease: review of a rare autoimmune disease targeting antigens of melanocytes. *Orphanet J Rare Dis*. 2016;11:1-21.
30. Giordano VE, Schlaen A, Guzman-Sanchez MJ, Couto C. Spectrum and visual outcomes of Vogt-Koyanagi-Harada disease in Argentina. *Int J Ophthalmol*. 2017;10:98-102.
31. Wolfensberger TJ, Tufail A. Systemic disorders associated with detachment of the neurosensory retina and retinal pigment epithelium. *Curr Opin Ophthalmol*. 2000;11:455-461.
32. Malik K, Guttman-Yassky E. Cytokine targeted therapeutics for alopecia areata: lessons from atopic dermatitis and other inflammatory skin diseases. *J Investig Dermatol Symp Proc*. 2018;19:S62-S64.
33. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature*. 2010;466:113-117.
34. Bain KA, McDonald E, Moffat F, et al. Alopecia areata is characterized by dysregulation in systemic type 17 and type 2 cytokines, which may contribute to disease-associated psychological morbidity. *Br J Dermatol*. 2020;182:130-137.
35. Dai YX, Tai YH, Chang YT, Chen TJ, Chen MH. Increased risk of alopecia areata among patients with endometriosis: a longitudinal study in Taiwan. *Dermatol Sin*. 2021;39:41-44.
36. Wang EH, Santos L, Li XY, et al. Alopecia areata is associated with increased expression of heart disease biomarker cardiac troponin I. *Acta Derm Venereol*. 2018;98:776-782.
37. Shin JW, Kang T, Lee JS, et al. Time-dependent risk of acute myocardial infarction in patients with alopecia areata in Korea. *JAMA Dermatol*. 2020;156:763-771.
38. Karadag AS, Ertugrul DT, Bilgili SG, Takci Z, Tutal E, Yilmaz H. Insulin resistance is increased in alopecia areata patients. *Cutan Ocul Toxicol*. 2013;32:102-106.
39. Kang JH, Lin HC, Kao S, Tsai MC, Chung SD. Alopecia areata increases the risk of stroke: a 3-year follow-up study. *Sci Rep*. 2015;5:1-6.
40. Incel-Uysal P, Akdogan N, Alli N, et al. Assessment of metabolic profile and ischemia-modified albumin level in patients with alopecia areata: a case-control study. *Indian J Dermatol*. 2019;64:12-18. https://doi.org/10.4103/ijd.IJD_238_18
41. Callizo J, Feltgen N, Pantenburg S, et al. Cardiovascular risk factors in central retinal artery occlusion: results of a prospective and standardized medical examination. *Ophthalmology*. 2015;122:1881-1888.
42. Nicholson BP, Atchison E, Idris AA, Bakri SJ. Central serous chorioretinopathy and glucocorticoids: an update on evidence for association. *Surv Ophthalmol*. 2018;63:1-8.
43. Shah SP, Desai CK, Desai MK, Dikshit RK. Steroid-induced central serous retinopathy. *Indian J Pharmacol*. 2011;43:607-608.
44. Tielsch JM, Legro MW, Cassard SD, et al. Risk factors for retinal detachment after cataract surgery. *Ophthalmology*. 1996;103:1537-1545.
45. Tuft SJ, Minassian D, Sullivan P. Risk factors for retinal detachment after cataract surgery: a case-control study. *Ophthalmology*. 2006;113:650-656.
46. Polkinghorne PJ, Craig JP. Northern New Zealand Rhegmatogenous Retinal Detachment Study: epidemiology and risk factors. *Clin Exp Ophthalmol*. 2004;32:159-163.