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Epidemiology of Allergic Disease

Bidirectional association between alopecia areata and atopic dermatitis: A population-based cohort study in Taiwan

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Abstract**Background:** An association between alopecia areata (AA) and atopic dermatitis (AD) has been reported in previous studies. However, the temporality of this relationship remains unclear based on prior cross-sectional and case-control studies.**Objective:** This study aimed to investigate the bidirectional association between AA and AD.**Methods:** Participants were recruited from the National Health Insurance Research Database of Taiwan. In analysis 1, we included 12 022 AA patients and 48 088 matched controls to assess the association between AA and AD risks. In analysis 2, 40 307 AD patients and 161 228 matched controls were included to assess the association between AD and AA risks. A Cox regression model was used to calculate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs).**Results:** Compared with controls, AA patients had a significantly increased risk of developing AD (aHR: 5.47; 95% CI: 4.76-6.28) after adjustment for potential confounders. Likewise, AD patients had a significantly increased risk of developing AA (aHR: 6.00; 95% CI: 5.04-7.14).**Conclusions:** Our study demonstrated a bidirectional association between AA and AD, suggesting that these two diseases may share common pathogenic mechanisms. This finding has implications for follow-up and screening of AA patients for AD and vice versa.**KEYWORDS**

Alopecia areata, atopic dermatitis, cohort study, epidemiology, Taiwan's National Health Insurance Research Database

1 | INTRODUCTION

Alopecia areata (AA) is a T cell-mediated autoimmune disease characterized by the sudden onset of hair loss without significant inflammation or scarring. The prevalence of AA ranges from 0.1% to 0.2%, while the lifetime risk of developing AA is approximately 2%.^{1,2} As a disease causing significant disfigurement, AA, characterized by oval or patchy area of hair loss mainly on the scalp, imposes a significant psychosocial burden on affected individuals.³⁻⁵ Although several

therapies are available, the treatment for extensive AA remains challenging.⁶⁻⁸ The exact cause of AA remains elusive, but it is believed that AA results from collapse of the immune privilege of the hair follicle, autoimmune-mediated hair follicle destruction and the up-regulation of inflammatory pathways.⁹

Atopic dermatitis (AD) is a chronic inflammatory disease featured by recurrent pruritus, xerosis and dermatitis in typical anatomic sites. Although there is no cure for AD, many treatment modalities are effective in controlling the associated symptoms.¹⁰⁻¹² The pathogenesis of AD is multifactorial, including barrier dysfunction, alterations in

cell-mediated immune responses, immunoglobulin E (IgE)-mediated hypersensitivity and environmental factors.¹³ Epidemiologic studies have shown that AD is associated with multiple autoimmune diseases.¹⁴⁻¹⁶

Many previous studies have demonstrated an association between AA and AD. A meta-analysis of 17 studies concluded that AA patients have an increased risk of AD.¹⁷ Furthermore, Anderson et al reported that AD was significantly associated with AA (odds ratio [OR]: 26.31).¹⁴ However, the interpretation of these findings is hampered by the cross-sectional or case-control nature of the studies, which is prone to bias. Therefore, the direction and magnitude of the association between AA and AD remain unclear. In this population-based cohort study, we used a nationwide database to assess the bidirectional association between AA and AD.

2 | METHODS

2.1 | Data source

Taiwan initiated a single-payer National Health Insurance (NHI) programme since 1995. More than 23 million residents are enrolled in the programme, representing approximately 99.6% of Taiwan's entire population. The NHI Research Database (NHIRD) provides comprehensive information about the insured individuals, including demographic information and claims data. Before the data were released to the researchers, the identification numbers of the participants were encrypted to protect individual privacy. The NHIRD data have been used widely for research.¹⁸⁻²⁶ The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

2.2 | Study population, exposure and outcome

2.2.1 | Analysis 1: AA as a risk factor for AD

A bidirectional cohort study was performed to investigate the longitudinal association between AA and AD. In analysis 1, we included

patients with age at AA onset ≥ 3 years during 1998 and 2008 (Figure 1). The primary outcome evaluated was the incident AD. AA was identified by ICD-9-CM code 704.01, and AD was identified by ICD-9-CM code 691. Diagnoses of AA and AD were made at least three times by board-certified dermatologists or rheumatologists during the observation period. To identify incident AD in the AA cohort, participants with a previous AD diagnosis, invalid insurance status, unknown sex status or unknown covariates were excluded.

Since age, sex, socio-economic status and some comorbidities were associated with the occurrence of both AA and AD,²⁷⁻³⁰ we selected 1:4 age-, sex-, monthly premium-, residence- and comorbidity-matched controls from the Longitudinal Health Insurance Database (LHID). Residence was classified into five levels of urbanization, with level 1 indicating the most urbanized area and level 5 the least urbanized area. Monthly premium was classified into 0-500, 501-800 and ≥ 801 US Dollars. Monthly premium and residence were used to represent socio-economic status. Prior use of systemic treatment, including systemic corticosteroids and cyclosporine, was also assessed. 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 of AA diagnosis of the matched AA patient. The AA patients and controls were followed up until AD diagnosis, death or 31 December 2011.

2.2.2 | Analysis 2: AD as a risk factor for AA

In analysis 2, patients with age at AD onset ≥ 3 years during 1998 and 2008 were included in the study cohort. The primary outcome assessed was the incident AA. Likewise, to identify incident AA, we excluded participants with a previous hair-related diagnoses (ICD-9-CM code 704), invalid insurance status, unknown sex status or unknown covariates. For each AD patient, 4 matched controls were selected from the LHID after matching for age, sex, monthly premium, residence and comorbidities. We also investigated prior phototherapy and use of systemic treatment, including systemic corticosteroids, cyclosporine, azathioprine, methotrexate and mycophenolate mofetil. The index date for the AD group was the date when AD was diagnosed for the first time,

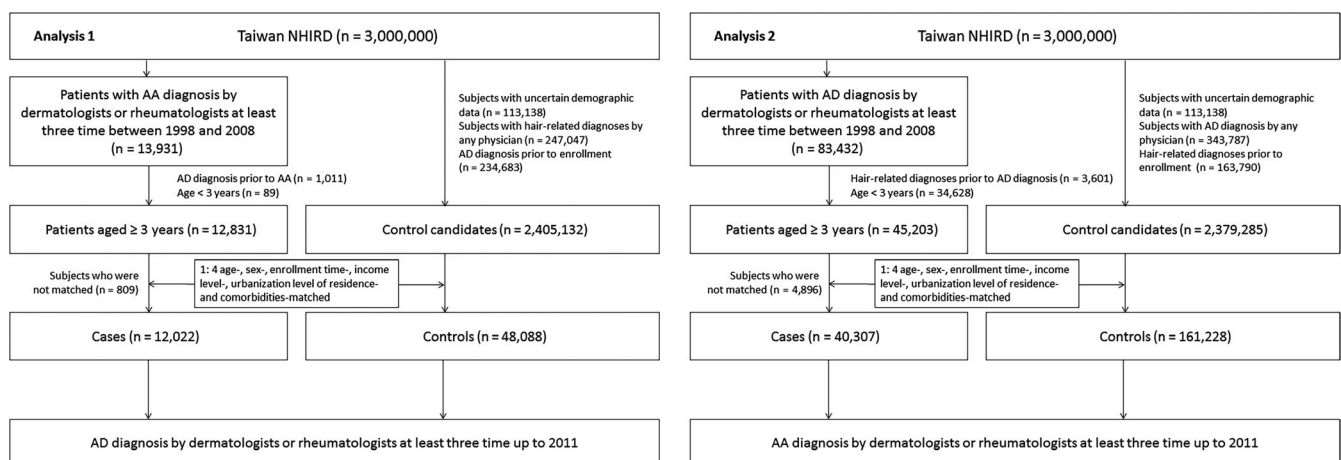


FIGURE 1 Flow chart of study cohort selection

whereas the index date for the control group was the date of AD diagnosis of the matched AD patient. The AD patients and controls were followed up until AA diagnosis, death or 31 December 2011.

2.3 | Comorbidities

The comorbidities considered in this study included allergic conjunctivitis (ICD-9-CM codes 372.05, 372.10 and 372.14), allergic rhinitis (ICD-9-CM code 477), asthma (ICD-9-CM code 493), cancer (ICD-9-CM codes 140-208), hypertension (ICD-9-CM codes 401-405), diabetes mellitus (ICD-9-CM code 250), autoimmune disease (ICD-9-CM codes 340, 358, 443.1, 446.0, 446.1, 446.2, 446.4, 446.5, 446.7, 555, 556.0-556.6, 556.8, 556.9, 710.0, 710.1, 710.2, 710.3, 710.4 and

714), hyperlipidaemia (ICD-9-CM code 272), obesity (ICD-9-CM codes 278.0, 649.1, 649.2, V45.86, V85.2, V85.3 and V85.4), psoriasis (ICD-9-CM codes 696.0 and 696.1) and thyroid disease (ICD-9-CM codes 240-246). An individual was considered to have comorbidity only if the condition was recorded at ≥ 3 outpatient visits.

2.4 | Statistical analysis

The t test or Wilcoxon rank-sum test was used to compare continuous variables, including age, between groups. Pearson's chi-squared test was used to compare categorical variables, including age group, sex, monthly premium, residence and comorbidities. The Cox regression model was used to assess the association between AA and AD by computing the

TABLE 1 Demographic data of patients with alopecia areata and controls

	AA n = 12 022		Controls n = 48 088		P value
Age (years), median (IQR)	30.8	(22.5-41.2)	30.8	(22.5-41.3)	.9933
Age group (years), n (%)					.9983
<20	2227	(18.5)	8906	(18.5)	
20-39	6465	(53.8)	25 890	(53.8)	
40-59	2933	(24.4)	11 697	(24.3)	
≥ 60	397	(3.3)	1595	(3.3)	
Sex, n (%)					1.0000
Male	5880	(48.9)	23 520	(48.9)	
Female	6,142	(51.1)	24 568	(51.1)	
Monthly premium (USD), n (%)					1.0000
0-500	3941	(32.8)	15 764	(32.8)	
501-800	3596	(29.9)	14 384	(29.9)	
≥ 801	4485	(37.3)	17 940	(37.3)	
Residence, n (%)					1.0000
1 (urbanized)	3342	(27.8)	13 368	(27.8)	
2	4167	(34.7)	16 668	(34.7)	
3	1432	(11.9)	5728	(11.9)	
4	1105	(9.2)	4420	(9.2)	
5 (rural)	1976	(16.4)	7904	(16.4)	
Comorbidity, n (%)					
Allergic conjunctivitis	1568	(13.0)	6272	(13.0)	1.0000
Allergic rhinitis	2535	(21.1)	10 140	(21.1)	1.0000
Asthma	1101	(9.2)	4404	(9.2)	1.0000
Cancer	136	(1.1)	544	(1.1)	1.0000
Hypertension	994	(8.3)	3976	(8.3)	1.0000
Diabetes mellitus	390	(3.2)	1560	(3.2)	1.0000
Autoimmune disease	22	(0.2)	88	(0.2)	1.0000
Hyperlipidaemia	850	(7.1)	3400	(7.1)	1.0000
Obesity	137	(1.1)	548	(1.1)	1.0000
Psoriasis	111	(0.9)	444	(0.9)	1.0000
Thyroid disease	386	(3.2)	1544	(3.2)	1.0000
Systemic treatment, n (%)	151	(1.3)	0	(0.0)	<.0001

Abbreviations: AA, alopecia areata; IQR, interquartile range; USD, US Dollar.

adjusted hazard ratios (aHRs) and their corresponding 95% confidence intervals (CIs). Two-sided *P* values <.05 were considered statistically significant. Survival curves for time-to-event variables were estimated using the Kaplan-Meier method. Survival curves were compared using the log-rank test. Data management and analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Analysis 1: AA as a risk factor for AD

A total of 12 022 patients with AA and 48 088 controls were included in the analysis 1 (Table 1). Age, sex, monthly premium, residential status and comorbidities were well-matched between the groups.

During the follow-up period, 487 AA patients and 355 non-AA individuals developed AD. The incidence rate of AD in the AA and control groups was 541.4 and 96.1 cases per 100 000 person-years, respectively. The median (interquartile range [IQR]) age at diagnosis of AD in the AA and control groups was 29.8 (22.3-39.9) and 30.7 (25.0-39.7), respectively (*P* = .1533). As shown in Table 2, after adjustment for potential confounders, AA patients had a 5.47-fold higher risk of AD than controls. Sex-stratified analysis showed a significant association between AA and AD risks in both sexes. Men had a lower risk of developing AD (aHR: 0.58; 95% CI: 0.50-0.67) compared with women. Other independent risk factors for incident AD were allergic conjunctivitis, allergic rhinitis, asthma and systemic treatment. The Kaplan-Meier survival curves for the time to AD occurrence for AA patients were lower compared with those for the controls (Figure 2).

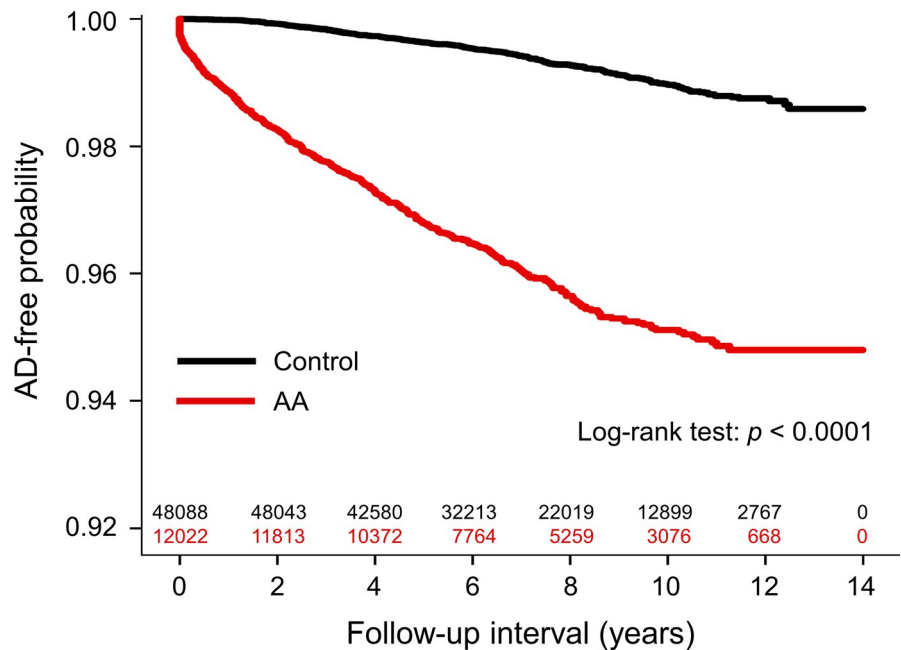
	cHR	(95% CI)	<i>P</i> value	aHR ^a	(95% CI)	<i>P</i> value
AA vs. control	5.63	(4.91-6.45)	<.0001	5.47	(4.76-6.28)	<.0001
Age, year	0.98	(0.97-0.98)	<.0001	0.98	(0.98-0.98)	<.0001
Sex, male vs. female	0.55	(0.48-0.63)	<.0001	0.58	(0.50-0.67)	<.0001
Monthly premium (USD)			.0198			.9443
501-800 vs. 0-500	0.89	(0.75-1.05)	.1657	1.02	(0.86-1.21)	.8394
≥801 vs. 0-500	0.79	(0.68-0.93)	.0051	1.03	(0.87-1.23)	.7363
Residence, n (%)			.8590			.6206
2 vs. 1	1.07	(0.90-1.27)	.4287	1.06	(0.89-1.26)	.5264
3 vs. 1	1.03	(0.81-1.30)	.8124	1.02	(0.81-1.30)	.8438
4 vs. 1	0.97	(0.75-1.26)	.8311	0.96	(0.74-1.25)	.7746
5 vs. 1	0.97	(0.78-1.21)	.7958	0.90	(0.72-1.12)	.3228
Comorbidity						
Allergic conjunctivitis	2.01	(1.71-2.36)	<.0001	1.53	(1.29-1.81)	<.0001
Allergic rhinitis	1.89	(1.64-2.18)	<.0001	1.58	(1.35-1.84)	<.0001
Asthma	1.70	(1.41-2.06)	<.0001	1.31	(1.07-1.60)	.0091
Cancer	0.29	(0.09-0.90)	.0317	0.44	(0.14-1.36)	.1528
Hypertension	0.63	(0.47-0.84)	.0020	1.02	(0.73-1.44)	.8938
Diabetes mellitus	0.48	(0.28-0.81)	.0060	0.73	(0.41-1.29)	.2796
Autoimmune disease	2.46	(0.92-6.57)	.0724	1.19	(0.42-3.35)	.7380
Hyperlipidaemia	0.67	(0.49-0.91)	.0100	1.01	(0.71-1.44)	.9630
Obesity	0.82	(0.41-1.64)	.5703	0.84	(0.42-1.69)	.6216
Psoriasis	0.83	(0.39-1.74)	.6148	1.01	(0.48-2.12)	.9881
Thyroid disease	1.09	(0.76-1.57)	.6489	0.99	(0.68-1.43)	.9488
Systemic treatment	10.79	(7.13-16.33)	<.0001	4.08	(2.63-6.33)	<.0001

TABLE 2 Cox regression analyses of factors associated with the risk of atopic dermatitis

Abbreviations: AA, alopecia areata; aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; USD, US Dollar.

^aAdjusted for age, sex, monthly premium, residence, comorbidities and systemic treatment.

FIGURE 2 Kaplan-Meier curves of atopic dermatitis (AD)-free survival for patients with alopecia areata (AA) and controls with number of participants at risk



3.2 | Analysis 2: AD as a risk factor for AA

In analysis 2, we included 40 307 patients with AD and 161 228 individuals as controls (Table 3). Individuals with and without AD were well-matched for age, sex, monthly premium, residential status and comorbidities.

Overall, 327 patients with AD and 214 non-AD individuals developed AA. The incidence rate of AA in the AD and control groups was 101.4 and 16.5 cases per 100 000 person-years, respectively. The median (IQR) age at diagnosis of AA in the AD and control groups was 26.1 (14.9-38.6) and 24.4 (18.8-35.2), respectively ($P = .9749$). After adjustment for potential confounders, AD patients had a 6.00-fold higher risk of AA than controls (Table 4). The association between AD and AA risks remained significant when we stratified the participants by sex. Other independent risk factors for incident AA were higher monthly premium, psoriasis and systemic treatment. The Kaplan-Meier survival curves for the time to AA occurrence for AD patients were lower compared with those for the controls (Figure 3).

4 | DISCUSSION

In the current study, we found a bidirectional association between AA and AD. That is, AA increased the risk of AD, and AD increased the risk of AA. To the best of our knowledge, this is the first large population-based cohort study to investigate a bidirectional association between AA and AD. AD patients are known to have an increased risk of AA and other autoimmune comorbidities than controls.^{14,15} Conversely, associations between AA and risk of atopic diseases have been reported in several studies. For examples, Chu *et al* found that patients with AA have an increased risk of atopic diseases and noted that the association between AA and AD is

particularly strong.³¹ Magen *et al* found that the prevalence of allergic rhinitis, asthma and AD was higher in Israeli AA patients.³² In a meta-analysis involving 13,810 AA patients and 784,787 controls, Mohan and Silverberg found that AA patients had a higher risk of AD than control patients without AA (OR: 2.57; 95% CI: 2.25-2.94, $P < .001$).¹⁷ Nevertheless, the cross-sectional nature of previous studies precludes determination of the temporal relationship between AA and AD. Our results added to the existing body of knowledge on the direction and strength of the association between AA and AD. However, the interpretation of a direct cause-effect relationship should not be made based on our study.

The aetiology of AD and AA mainly involves genetic factors, inflammatory cascades and environmental triggers such as psychosocial stress. Some shared pathogenic mechanisms underlying AA and AD may account for this bidirectional association. First, genome-wide research has found several IL-4 promotor polymorphisms in AD patients.^{33,34} IL-4 plays a key role in the Th2 immune responses, and dysregulated IL-4 production is associated with AD susceptibility. Similarly, Kalkan *et al* concluded that the functional IL-4 gene intron 3 variable number of tandem repeat polymorphism may be a risk factor for AA development in Turkish individuals.³⁵ In addition to the IL-4 gene, genetic variants of the IL-13 gene have also been reported to be related to AA and AD susceptibility. Jagielska *et al* identified IL-13 as a susceptibility locus for AA and found that the variant rs20541 was associated with a significantly increased risk of AA.³⁶ Furthermore, Namkung *et al* found that IL-13 gene polymorphisms rs20541 and rs3091307 were associated with the allergic type of AD.³⁴ Genetic polymorphisms in the genes encoding cytokines result in inter-individual variation in autoimmunity and inflammatory responses, which play crucial roles in the pathogenesis of AA and AD. At last, filaggrin mutation, a strong risk factor for AD, was found to be associated with a severe form of AA.³⁷

TABLE 3 Demographic data of patients with atopic dermatitis and controls

	AD n = 40 307		Controls n = 161 228		P value
Age (years), median (IQR)	20.6	(8.8-37.9)	20.6	(8.8-37.9)	.9397
Age group (years), n (%)					.9888
<20	19 752	(49.0)	78 864	(48.9)	
20-39	11 374	(28.2)	45 622	(28.3)	
40-59	6266	(15.6)	25 080	(15.6)	
≥60	2915	(7.2)	11 662	(7.2)	
Sex, n (%)					1.0000
Male	17 761.0	(44.1)	71 044.0	(44.1)	
Female	22 546	(55.9)	90 184	(55.9)	
Monthly premium (USD), n (%)					1.0000
0-500	23 526	(58.4)	94 104	(58.4)	
501-800	8547	(21.2)	34 188	(21.2)	
≥801	8234	(20.4)	32 936	(20.4)	
Residence, n (%)					1.0000
1 (urbanized)	9745	(24.2)	38 980	(24.2)	
2	12 263	(30.4)	49 052	(30.4)	
3	4074	(10.1)	16 296	(10.1)	
4	3840	(9.5)	15 360	(9.5)	
5 (rural)	10 385	(25.8)	41 540	(25.8)	
Comorbidity, n (%)					
Allergic conjunctivitis	10 085	(25.0)	40 340	(25.0)	1.0000
Allergic rhinitis	15 485	(38.4)	61 940	(38.4)	1.0000
Asthma	9599	(23.8)	38 396	(23.8)	1.0000
Cancer	507	(1.3)	2028	(1.3)	1.0000
Hypertension	3743	(9.3)	14 972	(9.3)	1.0000
Diabetes mellitus	1607	(4.0)	6428	(4.0)	1.0000
Autoimmune disease	47	(0.1)	188	(0.1)	1.0000
Hyperlipidaemia	2344	(5.8)	9376	(5.8)	1.0000
Obesity	344	(0.9)	1376	(0.9)	1.0000
Psoriasis	311	(0.8)	1244	(0.8)	1.0000
Thyroid disease	744	(1.9)	2976	(1.9)	1.0000
Phototherapy, n (%)	256	(0.6)	0	(0.0)	<.0001
Systemic treatment, n (%)	1114	(2.8)	0	(0.0)	<.0001

Abbreviation: AD, atopic dermatitis; IQR, interquartile range; USD, US Dollar.

Second, AD has been described as a biphasic T cell-mediated disease. T helper type 2 (Th2) cells dominate in the early-phase, whereas Th1 cells dominate in the late-phase.¹⁶ Th1-derived interferon (IFN)-gamma, Th2-derived IL-4 and Th1-derived IL-13 are the major cytokines involved in the pathogenesis of AD.¹⁶ While AA is traditionally viewed as a Th1/ IFN- γ -mediated condition, emerging evidence suggests that Th2 immune pathways play a role in AA. High levels of Th2-related cytokines (IL-4, IL-5 and IL-10), IgE and eosinophils have been found in AA patients.^{9,38-40} Several reports have shown that dupilumab, a dual IL-4/IL-13 antagonist, promotes significant

hair regrowth in patients with concomitant AA and AD, suggesting an involvement of the Th2 pathway in the pathogenesis of both diseases. Conversely, hair loss has also been reported during dupilumab treatment.^{41,42} Furthermore, autoreactive cytotoxic CD8⁺ T cells and Langerhans cells are both involved in the pathogenesis of AA and AD.^{9,16,39} In AA, a cluster of inflammatory cells comprised primarily of CD8⁺ T cells accumulates around the hair bulb. The density of CD8⁺ T cells correlates with disease severity. Autoreactive CD8⁺ T cells have also been found to promote the production of autoreactive IgE antibodies, which exacerbates and perpetuates AD.¹⁶ A previous study

TABLE 4 Cox regression analyses of factors associated with the risk of alopecia areata

	cHR	(95% CI)	P value	aHR ^a	(95% CI)	P value
AD vs. control	6.15	(5.17-7.30)	<.0001	6.00	(5.04-7.14)	<.0001
Age, year	1.00	(0.99-1.00)	.2652	1.00	(0.99-1.01)	.6464
Sex, male vs. female	1.07	(0.90-1.26)	.4625	1.11	(0.93-1.32)	.2474
Monthly premium (USD)			.0026			.0096
501-800 vs. 0-500	1.35	(1.10-1.66)	.0043	1.39	(1.11-1.76)	.0049
≥801 vs. 0-500	1.34	(1.09-1.65)	.0057	1.33	(1.05-1.69)	.0193
Residence, n (%)			.4189			.8176
2 vs. 1	0.93	(0.75-1.16)	.5121	0.95	(0.76-1.18)	.6439
3 vs. 1	0.86	(0.62-1.18)	.3358	0.86	(0.62-1.18)	.3476
4 vs. 1	0.84	(0.60-1.17)	.2928	0.87	(0.62-1.22)	.4213
5 vs. 1	0.80	(0.63-1.02)	.0671	0.89	(0.69-1.14)	.3567
Comorbidity						
Allergic conjunctivitis	1.08	(0.89-1.30)	.4444	1.10	(0.90-1.34)	.3758
Allergic rhinitis	1.09	(0.92-1.29)	.3288	1.20	(0.98-1.45)	.0721
Asthma	0.83	(0.67-1.02)	.0711	0.80	(0.64-1.01)	.0641
Cancer	0.57	(0.21-1.52)	.2595	0.68	(0.25-1.86)	.4567
Hypertension	0.58	(0.40-0.84)	.0040	0.69	(0.44-1.09)	.1111
Diabetes mellitus	0.69	(0.41-1.15)	.1556	1.12	(0.62-2.03)	.7139
Autoimmune disease	1.62	(0.23-11.52)	.6297	1.02	(0.14-7.53)	.9865
Hyperlipidaemia	0.60	(0.38-0.95)	.0288	0.71	(0.42-1.19)	.1908
Obesity	1.05	(0.44-2.53)	.9120	1.01	(0.42-2.43)	.9883
Psoriasis	2.58	(1.42-4.68)	.0019	2.29	(1.24-4.22)	.0078
Thyroid disease	0.82	(0.41-1.65)	.5766	0.81	(0.40-1.64)	.5614
Phototherapy	2.51	(0.81-7.80)	.1125	0.75	(0.23-2.41)	.6284
Systemic treatment	4.47	(2.89-6.91)	<.0001	2.00	(1.26-3.16)	.0033

Abbreviations: AD, atopic dermatitis; aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; USD, US Dollar.

^aAdjusted for age, sex, monthly premium, residence, comorbidities, phototherapy and systemic treatment.

revealed that autoreactive CD8 + T cells isolated from AD patients produced more IL-17, IL-22 and IFN upon stimulation.⁴³ Autoreactive T cells are therefore thought to be involved in AD pathogenesis.

Third, psychosocial stress may exacerbate both AA and AD. Previous studies have shown that psychosocial stress is a risk factor for AA,^{5,9,44} as increased levels of stress hormones may promote inflammation.³⁹ In AD, glucocorticoid up-regulation may inhibit the synthesis of ceramides, cholesterol and free fatty acids, all of which normally maintain the barrier function of the skin.¹⁶

Our study has several strengths, namely that it involved a large number of participants and that diagnoses were made by appropriate specialists and were thus reliable. Most importantly, the cohort study design allowed the determination of the temporal relationship between AA and AD. However, this study has some limitations. First, the algorithm used to identify AA and AD in our study has not

been validated, which may lead to misclassification bias. In addition, the incidences of AA and AD may have been underestimated since only those who sought consultation and treatment were identified in the study. However, outcome misclassification generally leads to bias towards the null. Second, the NHIRD does not include data on some important confounding factors, including smoking status, alcohol consumption, body mass index, lifestyle factors and stressful life events. Laboratory data such as serum IgE level are also lacking. Third, our database does not contain information regarding disease severity of AA and AD, therefore precluding the evaluation of the association between disease severity and primary outcome. Finally, almost all participating individuals were residents of Taiwan, so the validity of our findings in other populations remains unclear.

In conclusion, patients with AA have a higher risk of developing AD than individuals without AA and vice versa. Our data suggest

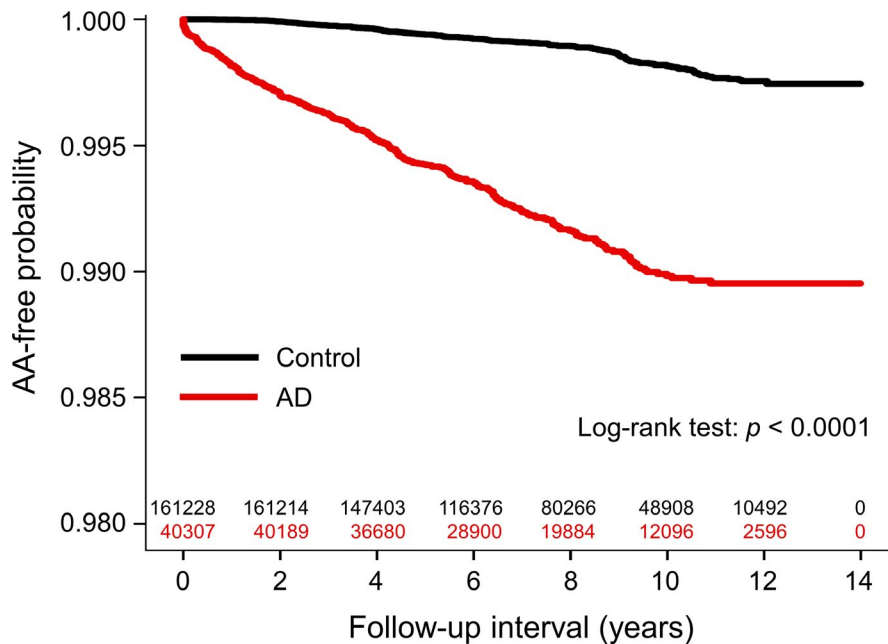


FIGURE 3 Kaplan-Meier curves of atopic dermatitis (AA)-free survival for patients with atopic dermatitis (AD) and controls with number of participants at risk

that there is a need to monitor patients with AA for the potential of AD development and vice versa. Further investigations are required to elucidate the pathogenic mechanisms shared between AA and AD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors conceived and designed the study. Yu-Hsun Wei, Ying-Xiu Dai and Mu-Hing Chen performed the literature search and evaluated the quality of the study. Ying-Hsuan Tai performed the statistical analyses. Yu-Hsun Wei wrote the first draft of the paper with the support of Ying-Xiu Dai, which was critically revised by all other authors. All authors gave final approval of the version to be submitted and agreed to be accountable for the whole paper.

DATA AVAILABILITY STATEMENT

Data are available from the National Health Insurance Research Database (NHIRD) published by Taiwan National Health Insurance (NHI) Bureau. Due to legal restrictions imposed by the government of Taiwan in relation to the "Personal Information Protection Act," data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD (<http://nhird.nhri.org.tw>).

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