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ORIGINAL PAPER

Bidirectional association between alopecia areata and thyroid diseases: a nationwide population-based cohort study

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Abstract

Alopecia areata (AA) has long been associated with thyroid diseases; however, the temporality of their association remains unclear. This study aimed to investigate the bidirectional association between AA and thyroid diseases. In analysis 1, we included 5929 AA patients and 59,290 matched controls to assess the risk of thyroid diseases. In analysis 2, we included 35,071 patients with thyrotoxicosis, 19,227 patients with Graves' disease, 5460 patients with thyroiditis, 3352 patients with Hashimoto's thyroiditis, and their matched controls (1:10) to assess the risk of AA. Incidence of thyroid diseases and AA were the outcomes in analysis 1 and analysis 2, respectively. After adjusting the potential confounders, AA patients had an increased risk of all thyroid diseases, including toxic nodular goiter, (aHR 10.17; 95% confidence interval [CI] 5.32–19.44), nontoxic nodular goiter (aHR 5.23; 95% CI 3.76–7.28), thyrotoxicosis (aHR 7.96; 95% CI 6.01–10.54), Graves' disease (aHR 8.36; 95% CI 5.66–12.35), thyroiditis (aHR 4.04; 95% CI 2.12–7.73), and Hashimoto thyroiditis (aHR 4.35; 95% CI 1.88–10.04). On the contrary, a significantly increased risk of developing AA was observed among patients with thyrotoxicosis (aHR 9.29; 95% CI, 7.11–12.14), Graves' disease (aHR 8.66; 95% CI 6.03–12.42), and thyroiditis (aHR 6.42; 95% CI 3.15–13.11) but not in patients with Hashimoto's thyroiditis. In conclusion, our study found a bidirectional association between AA and thyroid diseases, suggesting shared biological mechanisms underlying these two diseases.

Keywords Alopecia areata · Cohort study · Epidemiology · Taiwan's National Health Insurance Research Database · Thyroid disease

Introduction

Alopecia areata (AA) is a common autoimmune disease characterized by well-circumscribed patches of hair loss, typically affecting the scalp. The estimated lifetime risk of developing AA is 1.7% [1–3]. Although several therapies are available, treatment for extensive AA remains challenging [4–6]. The exact pathogenesis of AA has not been completely established; however, current evidence suggests that it is a T cell-mediated autoimmune condition due to the collapse of immune privilege in the hair follicles [7].

The autoimmune etiology of AA has been also supported by epidemiological studies assessing the association between AA and various autoimmune diseases, including autoimmune thyroid diseases [8]. Several studies have reported that AA is associated with thyroid dysfunction and the presence of antithyroid autoantibodies, and screening tests for thyroid dysfunction are sometimes recommended for AA patients [9–11]. However, the interpretation of these findings is hampered by several limitations, including small sample

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size, heterogeneous methodology, and cross-sectional or case–control design of previous studies [12]. Therefore, the magnitude and direction of the association between AA and autoimmune thyroid diseases remain unclear. In this population-based cohort study, we used a nationwide database to assess the bidirectional association between AA and thyroid diseases.

Methods

Data source

The Taiwan National Health Insurance (NHI) program was established in 1995 and covered approximately 99.6% of all Taiwanese residents at the end of 2010. The NHI Research Database (NHIRD) contains comprehensive information about the insured individuals, including demographic details (date of birth, sex, and residential location) and claims data (outpatient and inpatient care, medical diagnoses, prescriptions, and operations). The NHIRD has been widely used in epidemiological studies in Taiwan [13–21]. 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 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 population, exposure, and outcome

Analysis 1: alopecia areata (AA) as a risk factor for thyroid diseases

A bidirectional cohort study design was used to investigate the longitudinal association between AA and thyroid diseases. In analysis 1, we identified AA patients from the NHIRD from January 1, 1998 to December 31, 2011. The diagnosis of AA was established according to the ICD-9-CM codes 704.01. Patients were considered to have AA only if the diagnosis was established by dermatologists and the condition was observed at ≥ 3 outpatient visits.

The primary outcome assessed was new-onset thyroid diseases, including toxic nodular goiter (ICD-9-CM codes 242.1, 242.2, and 242.3), nontoxic nodular goiter (ICD-9-CM codes 240 and 241), thyrotoxicosis (ICD-9-CM code 242), Graves' disease (ICD-9-CM code 242.0), thyroiditis (ICD-9-CM code 245), and Hashimoto's thyroiditis (ICD-9-CM code 245.2). The diagnosis of thyroid diseases was established at least three times by board-certified family physicians, internal medicine physicians, pediatricians, endocrinologists, or emergency physicians. To identify the incidence of thyroid diseases, we excluded patients with a previous diagnosis of thyroid diseases (ICD-9-CM codes 240-246 and 648.1), invalid insurance status, unknown sex status, or unknown covariates.

For each AA patient, 10 matched controls were selected from the Longitudinal Health Insurance Database (LHID), which provides longitudinally linked anonymized data of enrollees randomly sampled from the registry for beneficiaries of the NHIRD. These participants were matched for age, sex, monthly premium, and residence. Monthly premium was classified into 0–500, 501–800, and ≥ 801 US dollars. 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 and urbanization levels were used to represent socioeconomic status. The Charlson Comorbidity Index (CCI) was used for clinical prognosis and comorbidity adjustment. 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 was the AA-diagnosed date of the matched AA patient. For patients who developed incident thyroid diseases, the length of follow-up was the period from the index date to the date of the first diagnosis of thyroid diseases. The censored time for patients who did not have an incident thyroid disease was the period from the index date to either December 31, 2013 or the date of withdrawal from the NHI.

Analysis 2: thyroid disease as a risk factor for AA

The cohort in analysis 2 included patients with thyrotoxicosis (ICD-9-CM code 242), Graves' disease (ICD-9-CM code 242.0), thyroiditis (ICD-9-CM code 245), and Hashimoto's thyroiditis (ICD-9-CM code 245.2). The primary outcome assessed was new-onset AA. Similarly, to identify incident AA, we excluded patients with a previous diagnosis of AA, invalid insurance status, unknown sex status, or unknown covariates. For each patient with thyroid diseases, 10 matched controls were selected from the LHID after matching for age, sex, monthly premium, and residence. The index date for the thyroid disease group was the date when thyroid disease was diagnosed for the first time, whereas the index date for the control was the thyroid disease-diagnosed date of the matched thyroid disease patient. For patients who developed an incident AA, the length of follow-up was the period from the index date to the date of the first diagnosis of AA. The censored time for patients who did not have an incident AA was the period from the index date to either December 31, 2013 or the date of withdrawal from the NHI.

Statistical analysis

For between-group comparisons, *t* test or Wilcoxon rank-sum test was used for continuous variables, and Pearson's

test was used for categorical variables. Cox proportional hazards regression model with the adjustment for the potential confounders (including age, sex, monthly premium, residence, and CCI score) was used to assess the bidirectional association between AA and thyroid diseases. The adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) indicate the strength and direction of these associations. A two-sided P value < 0.05 was considered as statistically significant. Data analyses were performed using the Statistical Analysis System (SAS) software (version 9.4, SAS Institute, Cary, NC, USA).

Results

Analysis 1: AA as a risk factor for thyroid diseases

Table 1 shows the demographic characteristics for all participants, including 5929 patients with AA and 59,290 individuals as the study control. Age, sex, monthly premium, and residential status were well-matched without significant between-group differences. AA patients had higher CCI scores compared with controls ($P < 0.0001$). As shown in Table 2, after adjusting the potential confounders, AA patients had an increased risk of developing all thyroid diseases, including toxic nodular goiter (aHR 10.17; 95% CI 5.32–19.44), nontoxic nodular goiter (aHR 5.23; 95% CI 3.76–7.28), thyrotoxicosis (aHR 7.96; 95% CI 6.01–10.54), Graves' disease (aHR 8.36; 95% CI 5.66–12.35), thyroiditis (aHR 4.04; 95% CI 2.12–7.73), and Hashimoto's thyroiditis (aHR 4.35; 95% CI 1.88–10.04).

Analysis 2: thyroid disease as a risk factor for AA

In analysis 2, we included 35,071 patients with thyrotoxicosis,19,227 patients with Graves' disease, 5460 patients with thyroiditis, 3352 patients with Hashimoto's thyroiditis, and their 1:10 matched controls (Table 3). Individuals with and without thyroid diseases were well-matched for age, sex, monthly premium, and residential status. Patients with thyroid diseases had higher CCI scores compared with controls ($P < 0.0001$). As shown in Table 4, after adjusting the potential confounders, a significantly increased risk of developing AA was observed among patients with thyrotoxicosis (aHR 9.29; 95% CI 7.11–12.14), Graves' disease (aHR 8.66; 95% CI 6.03–12.42), and thyroiditis (aHR 6.42; 95% CI 3.15–13.11). However, there was no significant association between Hashimoto's thyroiditis and AA risk.

Table 1 Demographic data of patients with alopecia areata and matched controls

	AA $n = 5929$		Controls $n = 59,290$		P
Age (years), median (IQR)	32.6	(24.0–43.4)	32.6	(24.0–43.4)	0.9962
Sex, *n* (%)					1.0000
Male	3074	51.9	30,740	51.9	
Female	2855	48.2	28,550	48.2	
Monthly premium (USD), *n* (%)					1.0000
0–500	2341	39.5	23,410	39.5	
501–800	1826	30.8	18,260	30.8	
⩾801	1762	29.7	17,620	29.7	
Residence, *n* (%)					1.0000
1 (urbanized)	883	14.9	8830	14.9	
2	1510	25.5	15,100	25.5	
3	518	8.7	5180	8.7	
4	505	8.5	5050	8.5	
5 (rural)	2513	42.4	25,130	42.4	
Charlson comorbidity index					< 0.0001
0	2300	38.8	27,897	47.1	
1	1837	31.0	16,845	28.4	
2	954	16.1	7477	12.6	
3	402	6.8	3396	5.7	
⩾4	436	7.4	3675	6.2	

AA alopecia areata, *IQR* interquartile range, *USD* United States Dollar

Table 2 Incident thyroid diseases among patients with alopecia areata and controls

	Events, *n*	Total PY	Median follow-up years (IQR)	Incidence rate/100,000 PY	HR (95% CI)		*P*	aHR† (95% CI)		*P*
Toxic nodular goiter							< 0.0001			< 0.0001
Controls	18	479,338	7.96 (4.75–11.37)	3.76	1.00	Reference		1.00	Reference	
AA	19	47,443	7.84 (4.69–11.27)	40.05	10.67	(5.60–20.33)		10.17	(5.32–19.44)	
Nontoxic nodular goiter							< 0.0001			< 0.0001
Controls	102	479,381	7.96 (4.75–11.37)	21.28	1.00	Reference		1.00	Reference	
AA	54	47,686	7.89 (4.72–11.31)	113.24	5.33	(3.83–7.41)		5.23	(3.76–7.28)	
Hyperthyroidism							< 0.0001			< 0.0001
Controls	112	479,338	7.96 (4.75–11.37)	23.37	1.00	Reference		1.00	Reference	
AA	89	47,443	7.84 (4.69–11.27)	187.59	8.19	(6.19–10.83)		7.96	(6.01–10.54)	
Graves' disease							< 0.0001			< 0.0001
Controls	57	479,338	7.96 (4.75–11.37)	11.89	1.00	Reference		1.00	Reference	
AA	47	47,443	7.84 (4.69–11.27)	99.07	8.49	(5.76–12.52)		8.36	(5.66–12.35)	
Thyroiditis							< 0.0001			< 0.0001
Controls	32	479,491	7.96 (4.75–11.37)	6.67	1.00	Reference		1.00	Reference	
AA	13	47,871	7.94 (4.74–11.35)	27.16	4.08	(2.14–7.76)		4.04	(2.12–7.73)	
Hashimoto thyroiditis							0.0004			0.0006
Controls	18	479,491	7.96 (4.75–11.37)	3.75	1.00	Reference		1.00	Reference	
AA	8	47,871	7.94 (4.74–11.35)	16.71	4.45	(1.94–10.24)		4.35	(1.88–10.04)	

aHR adjusted hazard ratio, *CI* confidence interval, *HR* hazard ratio, *IQR* interquartile range, *PY* person-years

†Adjusted for age, sex, monthly premium, residence, and Charlson Comorbidity Index

Table 3 Demographic data of patients with thyroid diseases and matched controls

	Thyrotoxicosis $n=35,071$		Controls $n=350,710$		P	Graves' disease $n=19,227$		Controls $n=192,270$		P	Thyroiditis $n=5460$		Controls $n=54,600$		P	Hashimoto thyroiditis $n=3352$		Controls $n=33,520$		P
Age (years), median (IQR)	40.1	(30.0–51.5)	40.1	(30.0 51.5)	0.9809	37.8	(28.4–49.0)	37.8	(28.4–49.0)	0.9677	41.6	(31.5–51.4)	41.6	(31.4–51.4)	0.9775	39.1	(29.3–49.9)	39.1	(29.3–49.9)	0.9938
Sex, *n* (%)					1.0000					1.0000					1.0000					1.0000
Male	7462	21.3	74,620	21.3		3917	20.4	39,170	20.4		586	10.7	5860	10.7		321	9.6	3210	9.6	
Female	27,609	78.7	276,090	78.7		15,310	79.6	153,100	79.6		4874	89.3	48,740	89.3		3031	90.4	30,310	90.4	
Monthly premium (USD), n (%)					1.0000					1.0000					1.0000					1.0000
0-500	13,020	37.1	130,200	37.1		7040	36.6	70,400	36.6		1863	34.1	18,630	34.1		1178	35.1	11,780	35.1	
501-800	12,671	36.1	126,710	36.1		7061	36.7	70,610	36.7		1892	34.7	18,920	34.7		1110	33.1	11,100	33.1	
⩾801	9380	26.8	93,800	26.8		5126	26.7	51,260	26.7		1705	31.2	17,050	31.2		1064	31.7	10,640	31.7	
Residence, *n* (%)					1.0000					1.0000					1.0000					1.0000
1 (urbanized)	4975	14.2	49,750	14.2		2602	13.5	26,020	13.5		917	16.8	9170	16.8		585	17.5	5850	17.5	
2	8728	24.9	87,280	24.9		4625	24.1	46,250	24.1		1409	25.8	14,090	25.8		926	27.6	9260	27.6	
3	2819	8.0	28,190	8.0		1603	8.3	16,030	8.3		380	7.0	3800	7.0		230	6.9	2300	6.9	
4	3004	8.6	30,040	8.6		1751	9.1	17,510	9.1		386	7.1	3860	7.1		207	6.2	2070	6.2	
5 (rural)	15,545	44.3	155,450	44.3		8646	45.0	86,460	45.0		2368	43.4	23,680	43.4		1404	41.9	14,040	41.9	
Charlson comorbidity index					<0.0001					<0.0001					<0.0001					<0.0001
0	9379	26.7	138,598	39.5		5478	28.5	79,806	41.5		1387	25.4	21,561	39.5		941	28.1	13,811	41.2	
1	9123	26.0	93,708	26.7		5151	26.8	52,473	27.3		1413	25.9	14,695	26.9		887	26.5	9094	27.13	
2	6341	18.1	51,629	14.7		3473	18.1	27,538	14.3		1032	18.9	8331	15.3		602	18.0	4954	14.78	
3	4040	11.5	27,796	7.9		2121	11.0	14,008	7.3		703	12.9	4353	8.0		408	12.2	2493	7.44	
⩾4	6188	17.6	38,979	11.1		3004	15.6	18,445	9.6		925	16.9	5660	10.4		514	15.3	3168	9.45	

IQR interquartile range, *USD* United States Dollar

Table 4 Incident alopecia areata among patients with thyroid diseases and controls

	Incident AA, *n*	Total PY	Median follow-up years (IQR)	Incidence rate/100,000 PY	HR (95% CI)	*P*	aHR† (95% CI)	*P*
Controls	116	3322,061	9.76 (6.03–13.20)	3.49	1.00	Reference	<0.0001	1.00	Reference	<0.0001
Thyrotoxicosis	107	331,792	9.75 (6.01–13.20)	32.25	9.24	(7.11–12.02)		9.29	(7.11–12.14)	
Controls	66	1859,215	9.98 (6.34–13.34)	3.55	1.00	Reference	<0.0001	1.00	Reference	<0.0001
Graves' disease	57	185,730	9.96 (6.32–13.33)	30.69	8.65	(6.07–12.32)		8.66	(6.03–12.42)	
Controls	20	477,090	8.65 (5.12–12.42)	4.19	1.00	Reference	<0.0001	1.00	Reference	<0.0001
Thyroiditis	13	47,686	8.65 (5.12–12.42)	27.26	6.50	(3.23–13.07)		6.42	(3.15–13.11)	
Controls	12	294,209	8.68 (5.18–12.45)	4.08	1.00	Reference	0.1551	1.00	Reference	0.1278
Hashimoto thyroiditis	3	29,403	8.67 (5.17–12.45)	10.20	2.50	(0.71–8.87)		2.70	(0.75–9.70)	

aHR adjusted hazard ratio, *CI* confidence interval, *HR* hazard ratio, *IQR* interquartile range, *PY* person-years

†Adjusted for age, sex, monthly premium, residence, and Charlson Comorbidity Index

Discussion

In the current study, we found a bidirectional association between AA and thyroid diseases. That is, AA increased the risk of thyroid diseases, and thyroid diseases increased the risk of AA. To the best of our knowledge, this study is the first to investigate the bidirectional association between AA and thyroid diseases in a large population. Previous studies suggested a significant positive association between AA and thyroid diseases [22]. A recent systematic review and meta-analysis reported that AA was significantly associated with various thyroid diseases, including Graves' disease (odds ratio [OR] 2.07; 95% CI 1.80–2.38) and Hashimoto's thyroiditis (OR 2.15; 95% CI 1.71–2.70). However, there was no significant difference in the prevalence of hypothyroidism and hyperthyroidism between AA and controls [8]. In another systematic review and meta-analysis including 17 studies, Kinoshita-Ise et al. found that AA was significantly associated with the presence of thyroid peroxidase antibody and thyroglobulin antibody but not diagnosed hypothyroidism or hyperthyroidism and serological hypothyroidism or hyperthyroidism [12]. In this study, we found that AA patients had a higher risk of developing thyroid diseases, including thyrotoxicosis, Graves' disease, thyroiditis, and Hashimoto's thyroiditis. Nevertheless, these results should be interpreted cautiously given the wide ranges in the 95% CIs, potentially because of the small number of AA patients. In analysis 2, we found that patients with thyrotoxicosis, Graves' disease, or thyroiditis were at higher risk of developing AA. However, no significant association between Hashimoto's thyroiditis and risk of AA was found, potentially because of the small number of patients with Hashimoto's thyroiditis. Further studies with larger sample sizes are required to confirm our findings. Our results confirmed the close association between AA and thyroid diseases. Additionally, the present study has added to the existing body of knowledge on the direction and strength of the association between AA and thyroid diseases.

Although the exact mechanism linking AA and thyroid diseases has not been well elucidated, potential mechanisms, including shared genetic background and mutual inflammatory process, may account for their association. First, a genome-wide association study of AA revealed several risk loci shared with other autoimmune diseases, in particular cytotoxic T-lymphocyte-associated protein 1, interleukin (IL)-2/IL-21, IL-2RA, and genes critical to regulatory T-cell maintenance [23]. Furthermore, prior studies have reported the association between class II human leukocyte antigen (HLA) haplotypes susceptible or resistant to AA and thyroid autoimmunity [24]. HLA-DQB1*03 shows positive associations with both AA and

autoimmune hypothyroidism; HLA-DRB1*03 has been positively associated with Graves' disease and negatively with AA [25–29]. Additionally, a genetic association study of HLA genes revealed that the haplotype frequency of DRB1*15:01-DQB1*06:02 was significantly higher in TSH receptor antibody-positive patients with AA than in control subjects [24]. These studies provided genetic evidence underlying the association between AA and thyroid diseases. Second, AA is a result of immune dysregulation in the hair follicles driven by $CD8^+NKG2D^+$ cytotoxic T lymphocytes [7]. Regulatory T (Treg) cells are the primary cells playing a pivotal role in human immunological homeostasis, and its imbalance leads to autoimmunity [30]. Previous studies have found that Treg cells in patients with autoimmune thyroid diseases are unable to downmodulate the autoimmune response and tissue damage, which might explain their autoimmunity [31]. Recent studies have reported that an imbalance of T-helper 17 cells and Treg cells might be involved in the pathogenesis of AA [32]. Additionally, immunohistochemical staining in the tissue of AA patients showed that Treg cell is significantly lower in AA compared to other cutaneous diseases [33]. These findings suggested the role of Treg in the autoimmunity linking AA and thyroid diseases.

Despite its several strengths, including a cohort study design comprising a large sample population and reliable diagnoses by corresponding specialists, our study has limitations. First, the identification algorithm for AA and thyroid diseases in our study has not been validated, potentially causing misclassification bias. Moreover, the incidence of AA and thyroid diseases might be underestimated since only patients who sought consultation and treatment were included in the study. However, the misclassification of outcome generally leads to a bias toward the null. Second, the lack of laboratory data precludes the investigation of the association between AA and serological hypothyroidism and hyperthyroidism. Third, the NHIRD lacks some important confounding factors, including smoking, alcohol consumption, body mass index, lifestyle, and stressful life events. Finally, almost all participating individuals were residents of Taiwan; therefore, the validity of our findings in other population remains unclear.

In conclusion, patients with AA have a higher risk of developing thyroid diseases compared to individuals without AA, and vice versa. Our study suggests that AA patients who might potentially develop thyroid diseases should be strictly monitored, and vice versa.

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Author contributions M-HC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: all authors. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: Y-XD. critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Y-HT.

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Availability of data and material The data that support the findings of this study are available on request from the corresponding author, but they are not publicly available due to privacy restrictions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

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