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ORIGINAL ARTICLE

The risk of alopecia areata and other related autoimmune diseases in patients with sleep disorders: a Korean population–based retrospective cohort study

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Abstract

Study Objectives: The aim of our study was to investigate the risk of alopecia areata occurrence in patients with sleep disorders.

Methods: This study was a retrospective cohort study based on the National Health Insurance Service-National Sample Cohort database of patients with a sleep disorder, along with age- and sex-matched control subjects from 2003 to 2013. The hazard ratio (HR) of alopecia areata was compared between the patients with sleep disorders and control subjects adjusting comorbid diseases which could affect the incidence of alopecia areata. We also compared the prevalence of comorbid diseases in the patients with sleep disorders and control subjects.

Results: Among the 25,800 patients with sleep disorders and the 129,000 control subjects, patients with sleep disorders were at a significantly increased risk for alopecia areata when compared with control subjects (adjusted HR 1.651 [95% CI 1.382–1.974]), especially in younger age groups (0–24 and 25–44 years). In a multivariate logistic analysis, sleep disorders were not only associated with alopecia areata (OR 1.913 [95% CI 1.717–2.171]), but also with other comorbid diseases, including solid-organ cancers (OR 1.099 [95% CI 1.049–1.151]), Graves' disease (OR 1.717 [95% CI 1.562–1.886]), Hashimoto thyroiditis (OR 1.641 [95% CI 1.413–1.905]), vitiligo (OR 1.539 [95% CI 1.236–1.917]), and rheumatoid arthritis (OR 1.886 [95% CI 1.780–1.998]).

Conclusions: This study demonstrated that sleep disorder is an independent risk factor for alopecia areata, especially in individuals under the age of 45 years old.

Statement of Significance

Sleep exerts a strong regulatory influence on immune functions. To date, the association between sleep and alopecia areata has rarely been reported. Here, we demonstrated that sleep disorders are independent risk factors for alopecia areata, especially in individuals under the age of 45 years old. Sleep disorders were also associated with comorbid diseases, including solid-organ cancers, autoimmune thyroiditis, vitiligo, and rheumatoid arthritis.

Key words: alopecia areata; autoimmune diseases; immunity; sleep and immunity

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Introduction

Sleep exerts a strong regulatory influence on immune functions and the prevalence of sleep disturbance worldwide ranges from 4% to 40% [1, 2]. Autoimmunity is the underlying cause of a broad spectrum of diseases and may arise from defects in immune tolerance, which results in the generation of autoreactive T-cells and autoantibodies [3]. There have been reports on the association of various autoimmune diseases with sleep disturbance, including rheumatoid arthritis, ankylosing spondylitis, fibromyalgia, Sjögren's syndrome, and systemic lupus erythematosus [4]. Another study has also shown that chronic insomnia requiring sleep-inducing pills may be associated with an increased risk for autoimmune diseases, particularly Sjögren's syndrome [5]. The perturbed immunity caused by sleep disturbances may involve a breakdown of immunologic self-tolerance, thereby driving development of autoimmune diseases [6].

Alopecia areata is a common, organ-specific autoimmune disease that affects all ages and has an estimated lifetime risk of 1.7%–2.1% [7, 8]. Severe forms of alopecia areata include alopecia totalis (loss of hair on the entire scalp) and alopecia universalis (total loss of body hair) [9, 10]. The disease course of alopecia areata is variable and characterized by an irregular relapsing course. Although alopecia areata is a nonscarring hair disorder and considered to be medically benign, the health-related quality of life for patients can be detrimentally affected [11].

Studies have reported that the diseases associated with alopecia areata include autoimmune thyroiditis, various types of cancer, atopic dermatitis, lupus erythematosus, psoriasis, and vitiligo [3, 12–17]. However, to date, the association between sleep and alopecia areata has rarely been reported. Therefore, we conducted a Korean population–based cohort study using the National Health Insurance Service–National Sample Cohort (NHIS-NSC) database to investigate the risk of alopecia areata in patients with sleep disorders.

Methods

Study design and database

This study was a retrospective cohort study examining 1,017,468 representative samples from the NHIS-NSC. The NHIS-NSC is a population-based cohort based on the National Health Insurance Service (NHIS) in South Korea [18]. One hundred per cent of the Korean population is covered by the NHIS. These people are divided into three categories: National Health Insurance (NHI) program for employee and self-employed groups and medical aid system. In 2013, 97.2 per cent (n = 49,989,620) of the population was covered by the NHI and the remaining 2.8 per cent (n = 1,458,871) of the population was covered by the medical aid system [19]. Due to the large volume and lack of confidentiality in regard to personal information of the NHID, the NHIS-NSC was constructed as a representative sample database, which has a substantial volume of representative information that does not require privacy regulation. For this study, information from January 2002 until December 2013 in the NHIS-NSC database was utilized. Participants who had been treated for any type of alopecia areata or sleep disorder during the screening period (2002) were excluded. Age, sex, location, income, and diagnostic codes based on the International Classification of Diseases, Tenth Revision (ICD-10) were retrieved. This study was approved by the Ethics Committee of Hanyang University Guri Hospital (GURI 2017-04-002) and was conducted according to the principles of the Declaration of Helsinki. The flowchart of the study is summarized in Figure 1.

Study participants and definition of clinical outcomes

Patients who had ICD-10 codes of F51 (sleep disorders not due to a substance or known physiological condition) or G47 (sleep disorders) were identified from the NHIS-NSC. The outcomes of interest were alopecia areata; therefore, we identified patients who had ICD-10 codes of L63 (alopecia areata), L63.0 (alopecia totalis), L63.1 (alopecia universalis), L63.2 (ophiasis), L63.8 (other alopecia areata), or L63.9 (alopecia areata, unspecified). Patients with comorbidities were defined as those with solid-organ cancers (ICD-10 codes C00-C80), hematologic malignancies (ICD-10 codes C81-C96), Graves' disease (ICD-10 codes E05, E05.0 E05.8, or E05.9), Hashimoto thyroiditis (ICD-10 codes E06.3 or E06.9), vitiligo (ICD-10 codes L80), lupus erythematosus (ICD-10 codes M32, L93.0, L93.1, or L93.2), or rheumatoid arthritis (ICD-10 codes M05 or M06). To improve the accuracy of the analysis, only the participants who had at least two principal diagnostic codes for each disease were included. The date of diseases diagnosis was used as the entry date for the patients with diseases. Control subjects matched for age and sex were selected randomly from the NHIS-NSC database at a frequency of 1:5.

Statistical analyses

To examine the unadjusted comparisons, Pearson's chi-squared test or Fisher's exact test was used to determine whether there was a significant difference between nominal variables. Incidence rates were calculated by dividing the number of events by person-years at risk. Both univariate and multivariate Cox proportional hazards regression models were conducted at $\alpha = 0.05$ significance level to calculate the crude hazard ratio (HR) and mutually adjusted HR with their 95% confidence interval (CI) adjusting location, income, and comorbidities including solid-organ cancers, hematologic malignancies, Graves' disease, Hashimoto thyroiditis, vitiligo, lupus erythematosus, and rheumatoid arthritis which could affect the incidence of alopecia areata. Sensitivity analyses with different definitions of the main outcome (alopecia areata) were performed to ensure the robustness of the results. We performed subgroup analyses with age group and sex. We tested the model fit statistics for Cox regression with −2 log likelihood, Akaike's information criterion, and Schwarz (Bayesian information) criterion ($p < 0.001$, respectively). The probability level of <0.05 suggests that the given model worked well and was better than the null model. The goodness of fit test for logistic regression was tested with Hosmer and Lemeshow test ($p = 0.232$). The test depends mainly on the same principle of chi-square test of testing the differences between observed and predicted frequencies. The survival curves of sleep disorders and alopecia areata were plotted via the Kaplan–Meier method, and statistical significance was examined by the log-rank test. Univariate and multivariate logistic regression analyses were undertaken to examine the associations among sleep disorders, alopecia areata, and comorbidities. We introduced in the multivariate model all variables

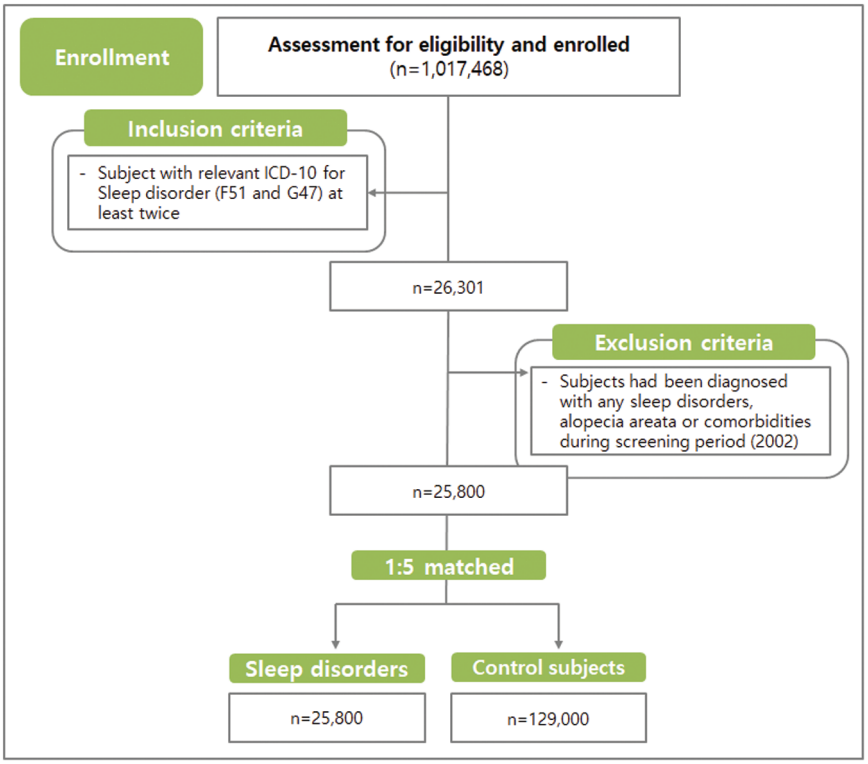

Figure 1. Study flowchart.

with a p value of <0.10 in the univariate model, followed by backward elimination to retain the final significant predictors in the model. Differences were considered to be statistically significant when the p value was less than 0.05. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline and clinical characteristics of patients with sleep disorders and of control subjects

From January 2003 to December 2013, we identified a total of 25,800 patients with sleep disorders and 129,000 1:5 matched control subjects without a sleep disorder. Of the patients with a sleep disorder, there were more females (female:male = 59.13:40.87). The age with the highest prevalence of sleep disorders was among 45 to 64 years (37.89%), followed by 24 to 44 years (29.94%). The demographic and clinical characteristics of the study population are summarized in Table 1.

Incidence of alopecia areata in patients with a sleep disorder

The risk for alopecia areata per 1000 person-years in patients with sleep disorders was significantly higher than that of control subjects (crude HR 1.610 [95% CI 1.350–1.919]). The significance was maintained after adjusting for age, sex, location, income, and comorbidities, including solid-organ cancers, hematologic malignancies, Graves' disease, Hashimoto thyroiditis, vitiligo, lupus erythematosus, and rheumatoid arthritis (adjusted HR 1.651 [95% CI 1.382–1.974]) (Table 2). Sensitivity analyses for the main outcome (alopecia areata) did not alter the significance of the HRs.

The Kaplan–Meier and negative-log estimated survivor function curves for alopecia areata between the patients with sleep disorders and control subjects are plotted in Figure 2. The cumulative incidence rate of alopecia areata in patients with sleep disorders was significantly higher than in control subjects (log-rank $p < 0.001$).

Subgroup analyses by age group and sex

The incidence of alopecia areata was higher in 0–24 years old (2.67 per 1000 person-years, adjusted HR 2.605 [95% CI 1.699–3.992]) and 25–44 years old (1.99 per 1000 person-years, adjusted HR 1.765 [95% CI 11.357–2.295]) than observed in the corresponding age bands in the control subjects. The incidence of alopecia areata in older age groups (45–64 and ≥65 years) did not significantly differ from the corresponding age bands in the control subjects (Table 2). Similarly, only in younger age groups (0–24 and 25–44 years), the cumulative incidence rates of alopecia areata were significantly higher than control subjects (log-rank $p < 0.001$) (Figure 3, A–D).

In the subgroup analysis by sex, the incidence rates of alopecia areata in females and males were 1.42 and 1.00 per 1000 person-years, respectively, and the incidence rates were significantly higher when compared with the control subjects (adjusted HR 1.532 [95% CI 1.112–2.111] for males; adjusted HR 1.695 [95% CI 1.367–2.101] for females). In the both sexes, the cumulative incidence rates of alopecia areata were also significantly higher than in control subjects (log-rank $p = 0.006$ for males; log-rank $p < 0.001$ for females) (Figure 3, E and F).

Table 1. Demographic and clinical characteristics of the study population

Characteristics	Patients with sleep disorders (*n* = 25,800)	Control subjects (*n* = 129,000)	*P* value
Age, *n* (%)			1.000
0–24	2,829 (10.97)	14,145 (10.97)	
25–44	7,724 (29.94)	38,620 (29.94)	
45–64	9,775 (37.89)	48,875 (37.89)	
≥65	5,472 (21.21)	27,360 (21.21)	
Sex, *n* (%)			1.000
Male	10,544 (40.87)	52,720 (40.87)	
Female	15,256 (59.13)	76,280 (59.13)	
Urban location, *n* (%)	12,566 (48.71)	75,903 (58.84)	<0.001
Income, *n* (%)			<0.001
0%–20%	4,274 (16.57)	32,457 (25.16)	
20%–40%	3,635 (14.09)	20,353 (15.78)	
40%–60%	4,371 (16.94)	21,694 (16.82)	
60%–80%	5,435 (21.07)	23,913 (18.54)	
80%–100%	8,085 (31.34)	30,583 (23.71)	
Comorbidities			
Solid-organ cancers	2,420 (9.38)	11,096 (8.60)	<0.001
Hematologic malignancies	88 (0.34)	427 (0.33)	0.813
Graves' disease	614 (2.38)	1,705 (1.32)	<0.001
Hashimoto thyroiditis	245 (0.95)	663 (0.51)	<0.001
Vitiligo	111 (0.43)	326 (0.25)	<0.001
Lupus erythematosus	36 (0.14)	131 (0.10)	0.010
Rheumatoid arthritis	1,678 (6.50)	4,527 (3.51)	<0.001

Table 2. The incidence rates of alopecia areata per 1000 person-years in patients with a sleep disorders when compared with control subjects

	Event	Person-years of follow-up	Incidence rate per 1000 person-years	Crude HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Alopecia areata							
Control subjects	1,013	1,263,942.4	0.80	Reference		Reference	
Patients with sleep disorders	151	120,368.7	1.25	1.610 (1.350–1.919)	<0.001	1.651 (1.382–1.974)	<0.001
Sensitivity test 1†							
Control subjects	1,561	1,260,766.2	1.24	Reference		Reference	
Patients with sleep disorders	268	119,536.0	2.24	1.797 (1.573–2.054)	<0.001	1.839 (1.606–2.107)	<0.001
Sensitivity test 2‡							
Control subjects	733	1,265,533.7	0.58	Reference		Reference	
Patients with sleep disorders	108	120,755.1	0.90	1.629 (1.323–2.005)	<0.001	1.697 (1.374–2.096)	<0.001
Subgroup analysis							
Age (0–24 years)							
Control subjects	171	154,196.5	1.11	Reference		Reference	
Patients with sleep disorders	29	10,879.4	2.67	2.899 (1.908–4.405)	<0.001	2.605(1.699–3.992)	<0.001
Age (25–44 years)							
Control subjects	462	411,402.9	1.12	Reference		Reference	
Patients with sleep disorders	72	36,118.9	1.99	1.777 (1.376–2.295)	<0.001	1.765 (1.357–2.295)	<0.001
Age (45–64 years)							
Control subjects	344	492,584.8	0.70	Reference		Reference	
Patients with sleep disorders	43	47,828.6	0.90	1.247 (0.903–1.723)	0.181	1.187 (0.858–1.642)	0.302
Age (≥65 years)							
Control subjects	36	205,758.2	0.17	Reference		Reference	
Patients with sleep disorders	7	25,541.8	0.27	1.622 (0.709–3.709)	0.252	1.519 (0.652–3.539)	0.333
Male							
Control subjects	323	486,458.5	0.66	Reference		Reference	
Patients with sleep disorders	47	47,167.7	1.00	1.544 (1.128–2.113)	0.007	1.532 (1.112–2.111)	0.009
Female							
Control subjects	690	777,483.9	0.89	Reference		Reference	
Patients with sleep disorders	104	73,201.0	1.42	1.641 (1.328–2.029)	<0.001	1.695 (1.367–2.101)	<0.001

*Multivariate analysis adjusted by age, sex, location, income, and comorbidities including solid-organ cancers, hematologic malignancies, Graves' disease, Hashimoto thyroiditis, vitiligo, lupus erythematosus, and rheumatoid arthritis.

†The patients with alopecia areata who had at least one principal diagnostic code.

‡The patients with alopecia areata who had at least three principal diagnostic codes.

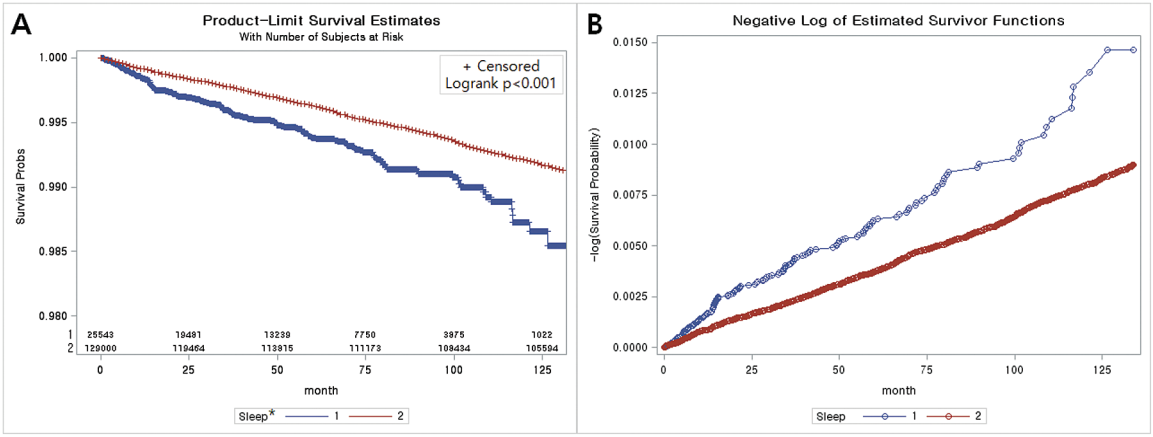

Figure 2. Kaplan–Meier estimates (A) and negative log–estimated survivor functions (B) were plotted to show the survival probabilities of alopecia areata in patients with sleep disorders and control subjects from 2003 to 2013. *(1) Patients with a sleep disorder; (2) Control participants.

Association of sleep disorders with alopecia areata and comorbidities

To evaluate the association of sleep disorders with alopecia areata and comorbidities, univariate and multivariate logistic analyses were performed (Table 3). In the multivariate analyses, patients with sleep disorders were observed to have an increased risk of alopecia areata (OR 1.913 [95% CI 1.717–2.171]), solid-organ cancers (OR 1.099 [95% CI 1.049–1.151]), Graves' disease (OR 1.717 [95% CI 1.562–1.886]), Hashimoto thyroiditis (OR 1.641 [95% CI 1.413–1.905]), vitiligo (OR 1.539 [95% CI 1.236–1.917]), and rheumatoid arthritis (OR 1.886 [95% CI 1.780–1.998]). In univariate analysis, there was a positive trend between lupus erythematosus and sleep disorders (OR 1.375 [95% CI 0.951–1.989], p=0.091), but the significance disappeared after adjusting the variables (p = 0.526). The association between hematologic malignancy and sleep disorders was not significant when compared with control subjects.

Discussion

We performed a retrospective cohort study on 25,800 patients with sleep disorders and 129,000 matched control subjects to investigate the risk of alopecia areata in patients with a sleep disorder. The analysis demonstrated two important findings. First, the patients with sleep disorders were at significantly increased risk of alopecia areata when compared with control participants, especially in younger age groups (0–24 and 25–44 years). Second, sleep disorders were significantly associated with alopecia areata and various comorbidities, including solid-organ cancers, Graves' disease, Hashimoto thyroiditis, vitiligo, and rheumatoid arthritis.

A close relationship between sleep, hypothalamic–pituitary–adrenal (HPA) axis, and immune response is well known [1]. Sleep deprivation is stressful, resulting in increased adrenocorticotropic hormone and corticosterone plasma levels [20]. Palma et al. had shown that increased antinuclear autoantibody production was observed in sleep-deprived NZB/NZWF1 mice, suggesting that increased autoantibody production was mediated by altered HPA function [21]. A study of genome-wide associations in alopecia areata had revealed several genomic regions in common with other autoimmune diseases, including Crohn's disease, lupus erythematosus, Graves' disease, multiple sclerosis, psoriasis, type 1 diabetes mellitus, ulcerative colitis, and vitiligo. In particular, these genomic associations included CTLA4, IL-2/IL-21, IL-2RA, and genes critical to Treg maintenance [22]. Therefore, we propose that the mechanism by which sleep disturbance affects alopecia areata is shared with other autoimmune diseases.

Our study showed an increased risk of alopecia areata in patients with a sleep disorder, and we also found that patients with sleep disorders have a higher prevalence for alopecia areata, solid-organ cancers, Graves' disease, Hashimoto thyroiditis, vitiligo, and rheumatoid arthritis compared with control participants. Hsiao et al. had previously reported increased risks of autoimmune diseases, including ankylosing spondylitis, Sjögren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus in the patients with sleep disorders [4]. Kok et al. also found that an increased risk for subsequent autoimmune diseases in patients with chronic insomnia requires sleep-inducing pills [5]. Sleep disturbance is a major problem in patients with cancer, and multiple studies have reported that the risk of cancers increases in patients with sleep disturbances [23]. In a meta-analysis of 28 studies, an increased risk of breast cancer was observed in women exposed to shift work and sleep deprivation [24].

This study showed that in the age groups of 45 years or older, patients with sleep disorders showed no significant increase in the risk of alopecia areata when compared with control subjects. A previous study on the association between aging and autoantibodies had reported that rheumatoid factor, antinuclear antibodies, and anticardiolipin antibodies were more prevalent in healthy individuals over 80 years old when compared with a nonelderly population [25]. The mechanisms and the significance of autoimmunity during aging are not clear, but the increase in autoantibodies was thought to be the result of high exposure to apoptotic cells and damaged tissue rather than an autoimmune response [26]. In contrast to the high prevalence of autoantibodies, autoimmune disease is rare in the elderly [27]. In a previous report, the incidence of late onset systemic lupus erythematosus had accounted for 12%–18% of all cases, and the course of the disease was found to be milder [28]. Skin manifestations, arthritis, photosensitivity, and nephritis occur rarely in elderly

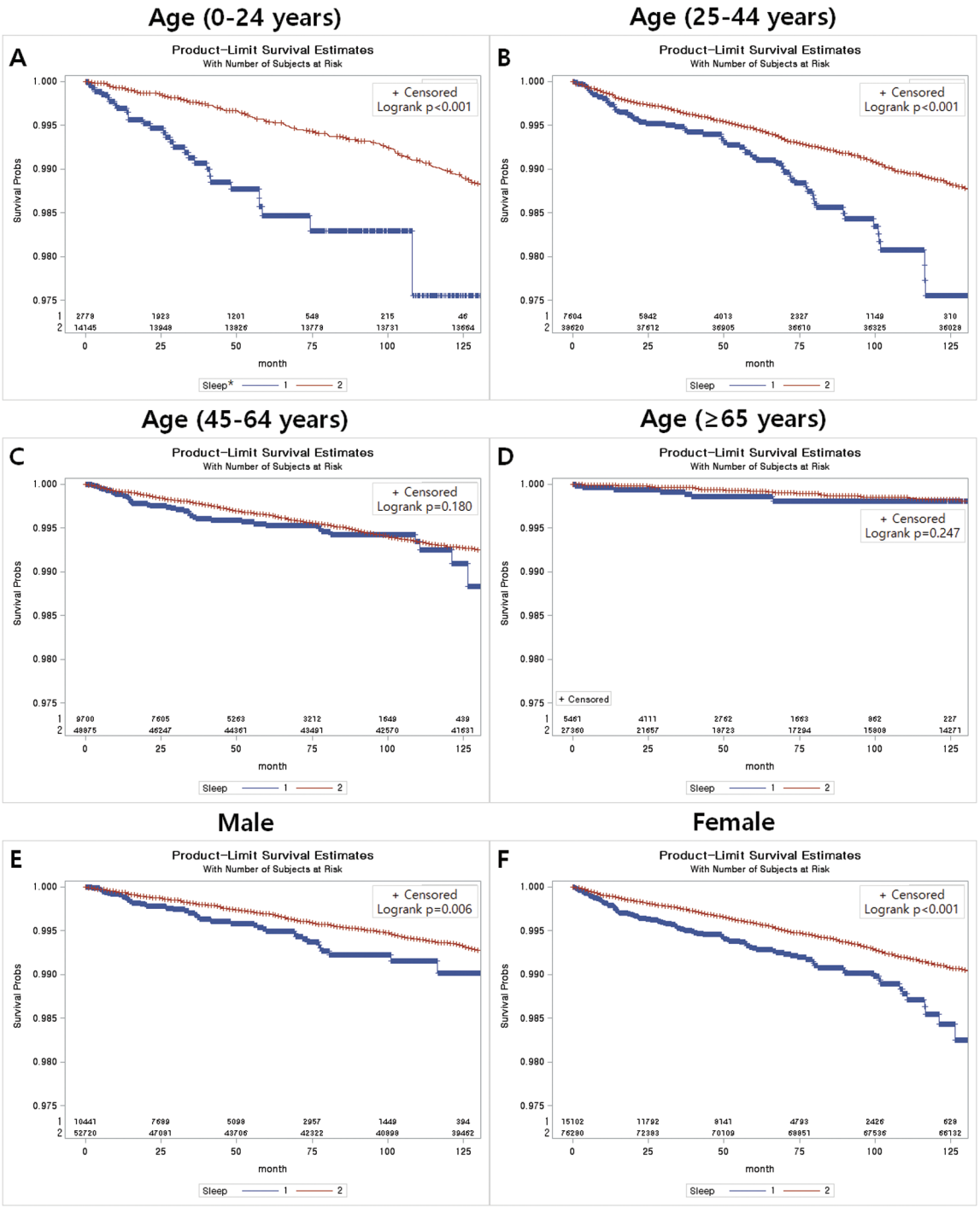

Figure 3. Subgroup analysis by age groups (A–D) and sex (E, F) of Kaplan–Meier estimates and log-rank tests.

patients with late onset of disease. A possible hypothesis for higher autoimmunity, but lower or milder autoimmune disease, is the expansion of many protective regulatory mechanisms characteristic of the elderly. In addition, Dejaco et al. had shown that there is an age-related increase of peripheral $CD4^+$ $CD25^{high}FoxP3^+$ T-regulatory cells, although it remains unclear whether it is a defensive response [29].

Our study has some limitations. First, the diagnosis of sleep disorders, alopecia areata, and comorbidities was identified based on the NHIS claims database without reviewing the detailed clinical charts. However, we thought that the coding error probabilities would be identical between patients with sleep disorders and control subjects; thus, no significant bias would have been introduced. Second, it raises the concern that a substantial portion of patients with sleep disorders can be undiagnosed and may be incorrectly included in the control group. Control group may contain substantial portion of patients with undiagnosed sleep disorders, but the statistical results then go to the null hypothesis. The results show that HR is statistically significant in spite of its limitations, and then we thought it

Table 3. Logistic regression analysis for alopecia areata and comorbidities in patients with sleep disorders when compared with control subjects

	Univariate analysis		Multivariate analysis*	
	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Alopecia areata				
Control subjects	Reference		Reference	
Patients with sleep disorders	**1.975 (1.757–2.219)**	**<0.001**	**1.913 (1.717–2.171)**	**<0.001**
Solid-organ cancers				
Control subjects	Reference		Reference	
Patients with sleep disorders	**1.100 (1.050–1.152)**	**<0.001**	**1.099 (1.049–1.151)**	**<0.001**
Hematologic malignancies				
Control subjects	Reference		–	
Patients with sleep disorders	1.031 (0.819–1.297)	0.796		
Graves' disease				
Control subjects	Reference		Reference	
Patients with sleep disorders	**1.820 (1.658–1.998)**	**<0.001**	**1.717 (1.562–1.886)**	**<0.001**
Hashimoto thyroiditis				
Control subjects	Reference		Reference	
Patients with sleep disorders	**1.856 (1.602–2.150)**	**<0.001**	**1.641 (1.413–1.905)**	**<0.001**
Vitiligo				
Control subjects	Reference		Reference	
Patients with sleep disorders	**1.709 (1.378–2.121)**	**<0.001**	**1.539 (1.236–1.917)**	**<0.001**
Lupus erythematosus				
Control subjects	Reference		Reference	
Patients with sleep disorders	1.375 (0.951–1.989)	0.091	1.129 (0.777–1.641)	0.526
Rheumatoid arthritis				
Control subjects	Reference		Reference	
Patients with sleep disorders	**1.913 (1.805–2.026)**	**<0.001**	**1.886 (1.780–1.998)**	**<0.001**

OR = odds ratio.
*Adjusted by the variables with a *p*-value of <0.10 in the univariate model.

did not compromise the robustness of the results. In 2009, Cho et al. conducted a population-based telephone interview study and they found that more than one-fifth (22.8%) of the 5,000 participants had symptoms of insomnia [30]. Other study with a health survey among 881 participants aged 60 years or older showed that the prevalence of insomnia disorder was 32.8 per cent [31]. In a recent survey of 2740 participants, the prevalence of obstructive sleep apnea was reported to be 15.8 per cent [32]. Third, sleep disorders are complex and heterogeneous, but sleep disturbance is a major feature. Future studies are needed to clarify the effects of sleep characteristics such as sleep apnea, sleep duration, sleep depth, sleep timing, and degree of sleep disturbance on individuals with alopecia areata. The strength of our findings is that this study was the first to report the association of sleep disorders with alopecia areata from the population-based NHIS-NSC database.

In conclusion, our retrospective cohort study found that individuals with sleep disorders have a significantly increased risk of alopecia areata, especially under the age of 45 years old. We also demonstrated that sleep disorders were not only associated with alopecia areata, but also with other comorbid diseases including solid-organ cancers, autoimmune thyroiditis, vitiligo, and rheumatoid arthritis.

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Notes

Conflict of interest statement. None declared.

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