SLEEP DISORDERS AND INCREASED RISK OF AUTOIMMUNE DISEASES

Sleep Disorders and Increased Risk of Autoimmune Diseases in Individuals without Sleep Apnea

Yi-Han Hsiao, MD[1,2,*]; Yung-Tai Chen, MD[3,5,*]; Ching-Min Tseng, MD[1,2,12]; Li-An Wu, MD[6]; Wei-Chen Lin, MD[7]; Vincent Yi-Fong Su, MD[1,2]; Diahn-Warng Perng, MD, PhD[2,8]; Shi-Chuan Chang, MD, PhD[1,2,9]; Yuh-Min Chen, MD, PhD[2,8]; Tzeng-Ji Chen, MD, PhD[4,10]; Yu-Chin Lee, MD[2,8]; Kun-Ta Chou, MD[1,2,8,11]

*[1]Center of Sleep Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [2]Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [3]Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [5]Department of Medicine, Taipei City Hospital Heping Fuyou Branch, Taipei, Taiwan; [6]Department of Radiology, Taipei City Hospital Heping Fuyou Branch, Taipei, Taiwan; [7]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan; [8]Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan; [9]Institute of Emergency and Critical Care Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan; [10]Institute of Hospital and Health Care Administration, School of Medicine, National Yang-Ming University, Taipei, Taiwan; [11]Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan; [12]Section of Respiratory Therapy, Department of Internal Medicine, Cheng Hsin General Hospital, Taipei, Taiwan; *co-first authors*

Study Objectives: To explore the association between the non-apnea sleep disorder (NSD) and autoimmune diseases.
Design: Cohort study.
Setting: Nationwide database research.
Participants: 84,996 adult patients with NSD diagnoses recorded in the Taiwan National Health Insurance Research Database between 2000 and 2003, after excluding those with antecedent autoimmune diseases. A comparison cohort of 84,996 participants was formed by age-, gender-, income-, and urbanization-matched controls.
Interventions: None.
Measurements and Results: The two cohorts were followed up for occurrence of autoimmune diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and systemic sclerosis (SSc). A Cox proportional hazards regression model was used for muti-variate adjustment. In patients with NSD, the overall risk for incident autoimmune diseases was significantly higher than in controls (adjusted hazard ratio [HR] = 1.47, 95% confidence interval [CI] = 1.41–1.53). With regard to individual diseases, the risks for SLE, RA, AS and SS among NSD patients were also significantly higher than in controls (HR [95% CI] for SLE, RA, AS, and SS were 1.81 [1.50–2.18], 1.45 [1.36–1.54], 1.53 [1.38–1.70], and 1.51 [1.43–1.60], respectively), whereas the increased risk for SSc did not reach statistical significance (HR: 1.36 [0.82–2.26]).
Conclusion: Patients with non-apnea sleep disorder were associated with a higher risk for developing autoimmune diseases.
Keywords: sleep disorder, non-apnea sleep disorder, autoimmune disease, autoimmunity
Citation: Hsiao YH, Chen YT, Tseng CM, Wu LA, Lin WC, Su VY, Perng DW, Chang SC, Chen YM, Chen TJ, Lee YC, Chou KT. Sleep disorders and increased risk of autoimmune diseases in individuals without sleep apnea. *SLEEP* 2015;38(4):581–586.

INTRODUCTION

Sleep has a vital and widespread impact on human immunity.[1] Several animal and human studies have shown insufficient sleep may enhance the susceptibility to infection.[2,3] However, the deranged immunity caused by sleep deprivation may not only be restricted to the dampened response against pathogens, but may also involve breakdown of immunologic self-tolerance, thereby driving development of autoimmune diseases.[4]

In a murine model of systemic lupus erythematosus (SLE), sleep deprivation contributed to an earlier onset of the disease.[4] Epidemiologic evidence evaluating the influence of sleep disorders on the susceptibility of autoimmune diseases is limited to sleep apnea,[5] whereas other sleep disorders were not thoroughly studied, for example, insomnia, the most common sleep disorder. We hypothesized sleep disorders other than sleep apnea—non-apnea sleep disorders (NSD)—would predispose occurrence of autoimmune diseases. We thus conducted this cohort study to explore their relationship by utilizing a nationwide database.

Submitted for publication May, 2014
Submitted in final revised form September, 2014
Accepted for publication October, 2014
Address correspondence to: Dr. Kun-Ta Chou, Center of Sleep Medicine, Taipei Veterans General Hospital, 14F, No. 201, Sec. 2, Shi-Pai Rd., Taipei, Taiwan 11217; Tel: 886-2-2871-2121 ext. 2440; Fax: 886-2-2875-2380; Email: hbjoue@vghtpe.gov.tw

MATERIALS AND METHODS

Data Source

The National Health Insurance (NHI) program in Taiwan, which was launched by the government under the principle of mandatory and universal enrollment for more than 23 million people beginning March 1, 1995, provided adequate health care and covered approximately 98.4% of Taiwanese in 2007.[6] The National Health Research Institute (NHRI) organized the entire NHI Research Database (NHIRD) computerized claims data, including demographic data, treatment, and diagnosis by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM),[7] and the database is one of the largest nationwide population-based databases in the world. A consistent encryption procedure was applied to all the cohort data, including each patient's

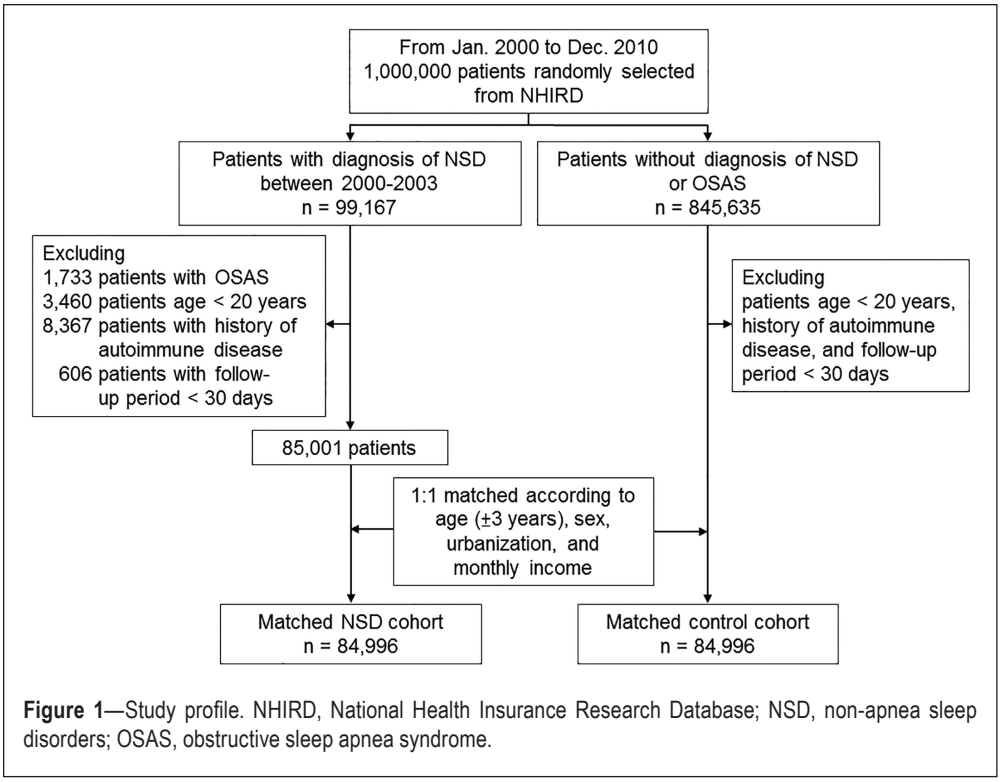

Figure 1—Study profile. NHIRD, National Health Insurance Research Database; NSD, non-apnea sleep disorders; OSAS, obstructive sleep apnea syndrome.

original identification, to protect privacy. In addition, the linkage of claims belonging to the same patient is feasible within the NHIRD datasets. In the current study, we used the Longitudinal Health Insurance Database (LHID) from 1995 to 2010 obtained from the NHIRD. The LHID consisted of one million beneficiaries randomly sampled from the original NHI beneficiaries.

This study was exempt from full review by the Institutional Review Board of Taipei Veterans General Hospital because the datasets consisted of de-identified secondary data released to the public for research purposes.

Study Sample

We performed a nationwide study to assess the association between incidence of NSD and autoimmune disease. Two cohorts, the NSD cohort and matched control cohort, were enrolled (as shown in Figure 1). The NSD cohort comprised all adult patients (age ≥ 20 years) who were newly diagnosed with sleep disorders (ICD-9-CM codes, 307.4 and 780.5x, except for sleep apnea [ICD-9-CM codes, 780.51, 780.53, and 780.57]) from inpatient and outpatient claims data of LHID for the period of January 2000 to December 2003.[8] The control cohort was selected from the remaining participants in the LHID and matched for age (± 3 years), gender, income, and urbanization.

The date of enrollment was defined as the date on which sleep disorders were initially diagnosed. In both cohorts, participants had a past medical history of any autoimmune disease before enrollment (ICD-9-CM code 714.0, 720, 720.0, 710.0, 370.33, 710.2, 710.1, 710.3, 710.4, 710.9, 242, 242.0, 242.00, 242.01, 245.2, 571.42, 696, 696.0, 696.1, 136.1, 556.9, 446.7, 446.5, 446.0, 446.4, 287.0, 713.6, 273.2, and 710.x) were excluded. The participants with a follow-up period less than 30 days were also excluded. Charlson comorbidity index (CCI) scores were calculated to represent global comorbidity severity at baseline.[9]

Outcome

The primary outcome was the occurrence of autoimmune diseases, including rheumatoid arthritis (RA) (ICD-9-CM code 714.0), ankylosing spondylitis (AS) (ICD-9-CM codes 720 or 720.0), and SLE (ICD-9-CM code 710.0), Sjögren's syndrome (SS) (ICD-9-CM codes 370.33 or 710.2), and systemic sclerosis (SSc) (ICD-9-CM codes 710.1). Both cohorts were followed from the date of enrollment until the occurrence of primary outcome, death, or the end of the study (December 31, 2010).

Statistical Analysis

Pearson χ^2 tests were used for comparisons between categorical variables, whereas independent *t*-tests were utilized for parametric continuous variables. The incidences were compared based on the assumption of Poisson distribution with 95% confidence interval (CI) expressed. A Cox regression model was employed for multivariate adjustment, including baseline comorbid diseases and CCI score. The cumulative incidences of overall and individual autoimmune diseases were compared by Kaplan-Meier method and log-rank test.

Microsoft SQL Server 2008 R2 (Microsoft Corp., Redmond, WA, USA) was used for data linkage, processing, and sampling. All statistical analyses were conducted using STATA statistical software (version 12.0; StataCorp, TX, USA). Statistical significance was defined as a P value < 0.05.

RESULTS

Baseline Characteristics of Non-Apnea Sleep Disorders and Comparison Cohort

Table 1 shows the demographic characteristics for all sampled participants, including 84,996 NSD patients and 84,996 controls. NSD included insomnia (ICD-9-CM code 780.52, 41.12%), sleep disturbance (780.5, 780.50, 46.92%), unspecified disruptions of 24-h sleep-wake cycle (780.55, 0.006%), dysfunctions associated with sleep stage or arousal from sleep (780.56, 0.06%), and others (780.59 & 307.4, 11.89%).

The controls were well matched for age, gender, income, and urbanization level (all P > 0.9). The mean age was 48.4 (standard deviation [SD] ± 16.7) years, and the majority of participants in two cohorts were female (60.4%). The follow-up period was 7.77 years on average. Patients with NSD had higher CCI score, more comorbid diseases, and more hypnotics medication use than controls (Table 1).

Higher Incidence of Incident Autoimmune Diseases among Non-Apnea Sleep Disorders Patients

There were 7,731 new autoimmune diseases cases among the NSD cohort and 4,753 among the matched-control cohort during the follow-up of 1,321,281 person-years (Table 2). For NSD patients, the crude and adjusted hazard ratios (HR) for all autoimmune diseases were 1.64 (95% confidence interval [CI], 1.59–1.70; P < 0.001) and 1.47 (95% CI, 1.41–1.53; P < 0.001), respectively (Table 2). With regard to individual types of autoimmune disease, the risks for developing SLE, RA, AS and SS among patients with NSD were also significantly higher than in subjects without NSD (adjusted HR [95% CI] = 1.81 [1.50–2.18] for SLE; 1.45 [1.36–1.54] for RA; 1.53 [1.38–1.70] for AS; 1.51 [1.43–1.60] for SS), whereas the increased risk for SSc did not reach statistical significance (adjusted HR = 1.36 [95% CI: 0.82–2.26], P = 0.234). Kaplan-Meier analyses also revealed NSD patients had a higher risk for autoimmune diseases (log-rank test, P < 0.001, Figure 2). Further association between risk for developing autoimmune diseases and different types of NSD was also examined. The adjusted HRs (95% CI) were 1.49 (1.42–1.57) for acute insomnia; 1.53 (1.42–1.65) for chronic insomnia; 1.52 (1.46–1.59) for sleep disturbance; and 1.57 (1.41–1.75) for other NSD (Table 3).

Table 1—Demographic and clinical characteristics of our study subjects.

Characteristic	NSD	Control	P Value
n	84,996	84,996	
Female, n (%)	51,372 (60.4)	51,372 (60.4)	1.000
Age in years, mean (SD)	48.4 (16.7)	48.4 (16.7)	0.998
Income (NTD)			1.000
Dependent	19,119	19,119	
0–19,100	19,756	19,756	
19,100–42,000	39,708	39,708	
> 42,000	6,413	6,413	
Urbanization			1.000
Level 1	48,133	48,133	
Level 2	29,482	29,482	
Level 3	6,323	6,323	
Level 4	1,058	1,058	
Charlson comorbidity score			< 0.001
0	35,193	50,623	
1	21,936	16,934	
2	12,143	8,135	
3	6,595	4,086	
≥ 4	9,129	5,218	
Comorbid disease			
Hypertension	23,652	16,391	< 0.001
Coronary artery disease	12,364	7,843	< 0.001
Cerebrovascular disease	7,985	4,990	< 0.001
Chronic kidney disease	5,123	3,275	< 0.001
Dyslipidemia	11,984	8,283	< 0.001
Diabetes mellitus	11,756	8,562	< 0.001
Chronic hypnotics medication use			
All drugs	26,442	3,378	< 0.001
BZD	20,298	2,626	< 0.001
Antidepressant	4,700	664	< 0.001
Z medication	8,869	442	< 0.001
Others	1,212	334	< 0.001

NSD, non-apnea sleep disorder; SD, standard deviation; NTD, New Taiwan dollars; BZD, benzodiazepine; Z medications, zolpidem, zopiclone, zaleplon.

DISCUSSION

It has long been known that sleep has a great impact on immune function, although little evidence has been explored and translated to clinical practice. This study is the first to demonstrate the linkage of sleep disorders to subsequent occurrence of autoimmune diseases, including SLE, RA, AS, and SS, by using a large nationwide database. The increased risk of incident SSc did not reach statistical significance, which might be due to the relative lower incidence of SSc in our (Asian) cohorts.[10] Although the etiology of autoimmune diseases is not well understood, our results suggested that disturbed sleep may be a trigger or a risk factor for such diseases.

Published literature has focused on the sleep quality of patients with autoimmune diseases, showing lower sleep quality is common and independently associated with higher disease activity.[11,12] Whether or not individuals with sleep disorders are susceptible to autoimmune diseases remains unanswered. Our data disclosed sleep disorders confer a higher risk for autoimmune diseases, supporting a bidirectional relationship between sleep disorders and autoimmune diseases.

Our conclusion was reinforced by several animal and human studies. In an experimental model of SLE, mice subjected to sleep deprivation exhibited a hastened development of the disease, as reflected by an increased number of antinuclear antibodies.[4] In addition, the function of regulatory T cells (T_{reg}) in patients with autoimmune diseases appeared to be impaired.[13] T_{reg} are the key players to suppress inappropriate immune response, maintaining self-tolerance.[14] Breakdown of self-tolerance is central to the pathogenesis of most autoimmune diseases. In experimentally sleep-deprived healthy persons, the suppressive activity of T_{reg} is reduced, providing a link between sleep disorder and autoimmune diseases.[15]

Furthermore, sleep deprivation resulted in elevation of several proinflammatory cytokines, including IL (interleukin)-1, IL-1β, IL-6, IL-17, and TNF-α. Of note, IL-17 remained elevated despite recovery for 7 days following sleep deprivation, indicating the pivotal role IL-17 played in coordinating the inflammation.[16] IL-17 has been associated with several autoimmune diseases including SLE, RA, inflammatory bowel disease, and multiple sclerosis.[17] Overt production of IL-17 may amplify systemic inflammation through activating autoantibody production and enhancing the immune response at inflammation locations.[18,19] Taken together, disordered sleep may induce systemic inflammation and activate the function of IL-17-secreting (Th17) cells, thereby predisposing to the occurrence of autoimmune diseases.[16,17,20]

One particular strength of this study is its matched-control cohort study design. Since the NHI is a single-payer, mandatory insurance program, the majority of events could be traced with a minimum of referral bias. Also, the large sample size of our studied subjects allowed a powerful conclusion to be drawn.

Table 2—Incidence of autoimmune diseases among patients with non-apnea sleep disorders and controls.

				Crude		Adjusted [b]	
	Number of Events	Person-Years	Incidence Rate [a]	HR (95% CI)	P Value	HR (95% CI)	P Value
All							
NSD	7,731	656,868	117.70	1.64 (1.59–1.70)	< 0.001	1.47 (1.41–1.53)	< 0.001
Control	4,753	664,413	71.54	1		1	
SLE							
NSD	341	689,939	4.94	1.82 (1.52–2.18)	< 0.001	1.81 (1.50–2.18)	< 0.001
Control	186	683,772	2.72	1		1	
RA							
NSD	3,134	676,090	46.36	1.62 (1.53–1.71)	< 0.001	1.45 (1.36–1.54)	< 0.001
Control	1,936	675,858	28.65	1		1	
AS							
NSD	992	686,761	14.45	1.65 (1.49–1.83)	< 0.001	1.53 (1.38–1.70)	< 0.001
Control	596	681,788	8.74	1		1	
Sjögren syndrome							
NSD	3,970	676,295	58.70	1.70 (1.61–1.79)	< 0.001	1.51 (1.43–1.60)	< 0.001
Control	2,329	675,996	34.45	1		1	
Systemic sclerosis							
NSD	40	691,434	0.579	1.42 (0.87–2.30)	0.158	1.36 (0.82–2.26)	0.234
Control	28	684,560	0.409	1		1	

[a] Per 10^4 person-years. [b] Adjusted for Charlson comorbidity index score, coronary artery disease, cerebrovascular disease, hypertension, diabetes mellitus, chronic kidney disease, dyslipidemia, and medication for non-apnea sleep disorders. HR, hazard ratio; CI, confidence interval; NSD, non-apnea sleep disorders; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; AS, ankylosing spondylitis; SS, Sjögren syndrome; SSc, systemic sclerosis.

Table 3—Incidence and hazard ratios of autoimmune diseases in patients with different types of non-apnea sleep disorders.

				Crude		Adjusted [b]	
Variables	Number of Events	Person-Years	Incidence Rate [a]	HR (95% CI)	P Value	HR (95% CI)	P Value
No sleep disorders	4,753	664,413	71.54	1		1	
NSD	7,731	656,868	117.70	1.64 (1.56–1.73)	< 0.001	1.51 (1.46–1.57)	< 0.001
Insomnia	3,692	300,313	122.94	1.71 (1.64–1.79)	< 0.001	1.50 (1.43–1.57)	< 0.001
Chronic [c]	936	69,199	135.26	1.89 (1.76–2.02)	< 0.001	1.53 (1.42–1.65)	< 0.001
Acute	2,756	231,114	119.25	1.66 (1.59–1.74)	< 0.001	1.49 (1.42–1.57)	< 0.001
Sleep disturbance	3,661	326,572	112.10	1.57 (1.50–1.64)	< 0.001	1.52 (1.46–1.59)	< 0.001
Others	378	29,983	126.07	1.75 (1.58–1.95)	< 0.001	1.57 (1.41–1.75)	< 0.001

[a] Per 10^4 person-years. [b] Adjusted for age, sex, urbanization, income, Charlson comorbidity index score, coronary artery disease, cerebrovascular disease, hypertension, diabetes mellitus, chronic kidney disease, dyslipidemia, and medication for non-apnea sleep disorders. [c] According to the International Classification of Sleep Disorders, 3rd edition (ICSD-3) definition as insomnia lasts more than three months. ICD-9-CM codes: Insomnia: 780.52, 307.41, 307.42; Sleep disturbance: 780.5, 780.50; Others: 780.55, 780.56, 780.59, 307.4. HR, hazard ratio; CI, confidence interval; NSD, non-apnea sleep disorders.

Our study has several limitations. Firstly, diagnoses of sleep disorders and autoimmune diseases that rely on administrative claims data could be less accurate than diagnoses made by standardized criteria, which may be an inherent weakness for all database research. Furthermore, our database lacks some personal information, including body mass index, smoking status, alcohol consumption, and family history. Even though the etiology of most autoimmune diseases is largely unknown, cigarette smoking, for instance, has been reported to predispose to the occurrence of RA and SLE.[21] Lastly, sleep disorders are complex and heterogeneous despite disruption of sleep being their main feature. More details regarding evaluation of sleep, such as sleep duration, sleep depth, or the extent of sleep disruption are not included in this study, which may call for further research to elucidate their differential influence on the development of autoimmunity.

CONCLUSION

Patients with NSD were associated with a higher risk of developing autoimmune diseases. Further investigation to elucidate the mechanism underlying this link is required.

ACKNOWLEDGMENTS

Yi-Han Hsiao and Yung-Tai Chen contributed equally to this work. The authors thank the Taiwan National Health Research Institute for providing the insurance claims data.

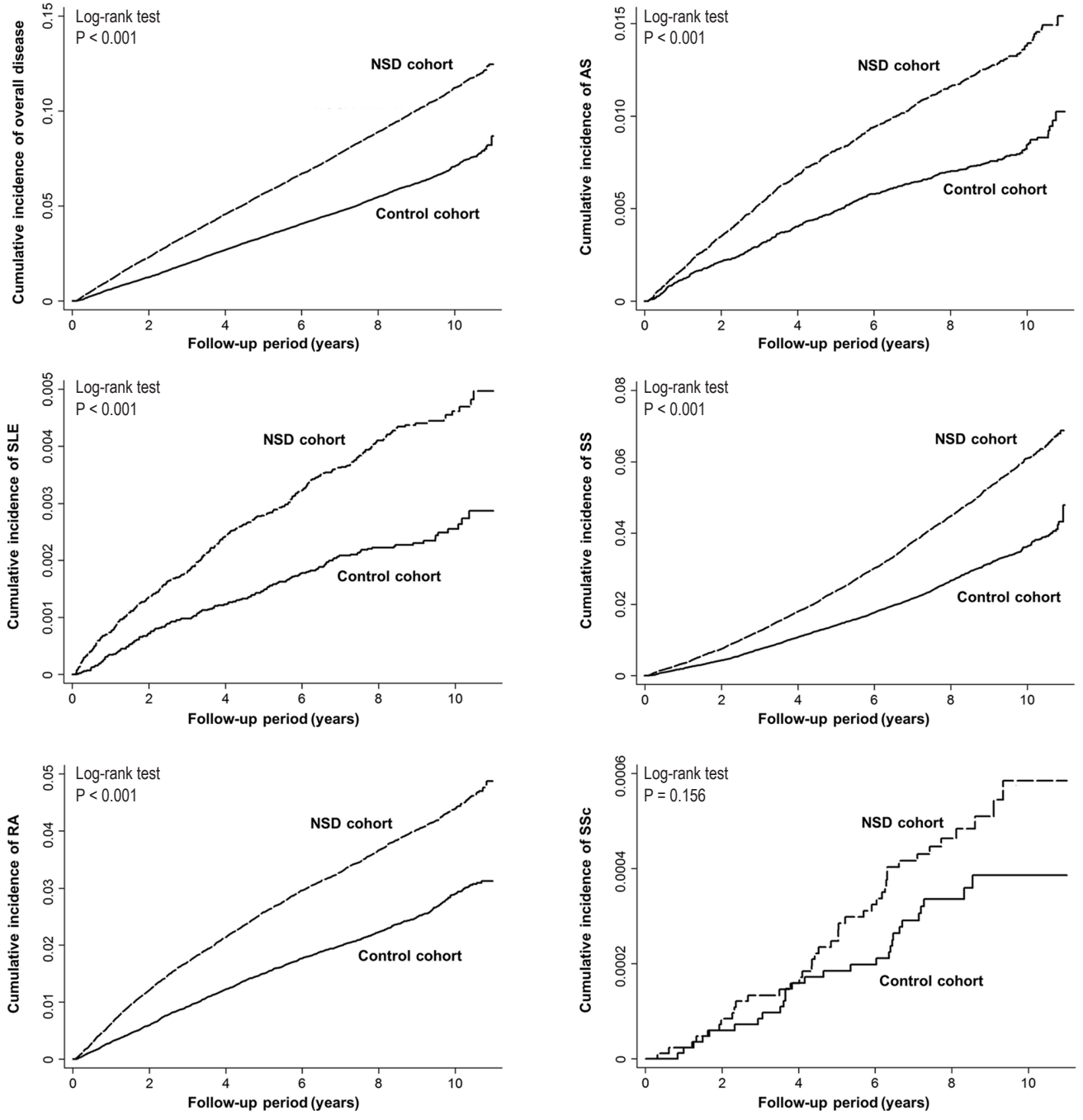

Figure 2—Kaplan-Meier plots of cumulative incidence of autoimmune diseases. NSD, non-apnea sleep disorders; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; AS, ankylosing spondylitis; SS, Sjögren's syndrome; SSc, systemic sclerosis.

Author Contributions: Kun-Ta Chou: study conception and design, data analysis and interpretation, drafting of manuscript; Yi-Han Hsiao: study design, data analysis, drafting of manuscript; Yung-Tai Chen: data acquisition and analysis; Ching-Min Tseng: data analysis and interpretation and statistical analysis; Li-An Wu: data analysis and statistical analysis; Wei-Chen Lin: data analysis and interpretation; Vincent Yi-Fong Su: data analysis and statistical analysis; Diahn-Warng Perng: data analysis and interpretation; Shi-Chuan Chang: data analysis and interpretation; Yuh-Min Chen: data analysis and interpretation, statistical analysis; Tzeng-Ji Chen: acquisition of data and technical support; Yu-Chin Lee: study design, interpretation and statistical analysis, and critical revision of the manuscript for important intellectual content.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. All authors had access to the data and played a role in writing this paper. IRB: Waived by the Institutional Review Board of Taipei Veterans General Hospital.

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