Sleep and Breathing (2018) 22:1083–1091
https://doi.org/10.1007/s11325-018-1639-1

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Sleep disorders associated with risk of rheumatoid arthritis

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Received: 7 November 2017 / Revised: 30 January 2018 / Accepted: 1 February 2018 / Published online: 10 February 2018

Abstract

Background Immune disorders impair sleep quality and sleep disorders (SDs) may derange immune function.

Purpose The study evaluated the incidence and risk of rheumatoid arthritis (RA) in patients with SDs using a nationwide cohort.

Methods We recognized the patients with SDs from 1998 to 2002 by using the Taiwan National Health Insurance Research Database. One control patient for each SD patient was randomly selected and matched based on the proportion of age, sex, and index year. We calculated the person years of follow-up for each participant from the index date to RA diagnosis, censoring, or until December 31, 2011. The risk of RA was estimated by using Cox models incorporating demographics and comorbidities.

Results We enrolled 65,754 patients with SDs and 65,753 controls and followed for 637,906 and 662,514 person-years, respectively. The patients with SDs exhibited a 1.49-fold greater risk of RA development compared with the comparison cohort when we adjusted for covariates. The patients with sleep apnea (SA) showed the greatest incidence density rate of RA, followed by those with non-apnea SDs and the non-SD cohort (4.11, 3.29, and 2.15 per 10,000 person-years, respectively). The SA cohort had a 2.56-fold adjusted hazard ratio (aHR) of RA (95% confidence interval [CI] = 1.11–5.91) and the non-apnea SD cohort had a 1.47-fold aHR of RA (95% CI = 1.18–1.84) compared with the non-SD cohort. Women with SDs presented a considerable risk of developing RA.

Conclusions This nationwide cohort study indicates that SDs are associated with the risk of RA development.

Keywords Sleep disorders · Rheumatoid arthritis · Cohort study

Key message
1. Sleep disorders (SDs) carried a 1.49-fold risk of RA development.
2. The adjusted hazard ratio of RA was 2.56 higher in the sleep apnea cohort and 1.47 higher in the non-apnea SD cohort than that in the comparison cohort.
3. Women with SDs exhibited a considerably higher risk of RA.

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Introduction

Sleep plays a pivotal function in life. The 24-h sleep and wake rhythm is related to certain circadian patterns of immune responses [1, 2]. Sleep is reciprocally related to immune system [3]. Sleep disorders (SDs) may alter immune function, and immune disorders eventually impair sleep quality [4–7].

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease, which causes articular demolition and protean systemic presentation [8, 9]. Most reports have focused on the treatment of RA and improvement for quality of life [10–13]. Studies investigating the risk factors for developing RA are scant.

Cross-sectional studies have indicated that patients with poor control of RA exhibit a reduction in sleep quality [7, 14]. Inadequate sleep may exacerbate pain severity, fatigue, and depression in patients with RA, potentially limiting their daily activity [15]. Whether sleep problems cause or are an independent risk factor of RA remains unclear in these cross-sectional

studies. Therefore, we conducted a longitudinal cohort study to investigate the effect of SDs on the risk of developing RA.

Methods

Data source

This current study involved analyzing data sets in the Taiwan National Health Insurance Research Database (NHIRD). The government initiated the National Health Insurance (NHI) program, which is a single-payer system on March 1, 1995 and covers approximately 99% of the residents in Taiwan [16]. The National Health Insurance Administration (NHIA) managed and maintained the NHIRD. We used the Longitudinal Health Insurance Database (LHID), which contains claims data of 1,000,000 people randomly selected insured people for the period of 1996–2011 in the NHIRD. All study participants were anonymous and deidentified by the NHIA before release of claim data for public research. The Institutional Review Board of China Medical University and Hospital in Taiwan approved this study (CMU-REC-101-012).

Sampled patients

For the study cohorts, patients diagnosed with SDs (N = 67,455) between 1998 and 2002 were divided into two cohorts: those with sleep apnea (SA) syndrome (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 780.51 indicating insomnia with SA, 780.53 indicating hypersomnia with SA, and 780.57 indicating unspecified SA) and non-apnea SDs (ICD-9-CM codes 307.4 comprising non-organic SDs, insomnia, parasomnia, and circadian rhythm SDs, and 780.5 indicating sleep disturbance, except 780.51, 780.53, and 780.57). The index date was defined as the first date of SD diagnosis. We excluded patients with a prior history of RA (ICD-9-CM code 714) (N = 134) or aged < 20 years (N = 1567). We selected four non-SD patients for each SD patient from the LHID randomly by frequency-matched with age (every 5-year interval), sex, and the year of index date to conduct the comparison cohort (N = 64,350). Both cohorts used the same exclusion criteria.

Outcome

We identified patients with RA in the LHID and confirmed the diagnoses from the Registry of Catastrophic Illness Database (RCIPD) between 1998 and 2011 as the study end point. In Taiwan, the NHIA can issue a catastrophic illness card for a patient with RA who fulfills four or more diagnostic criteria according to the American College of Rheumatology criteria for RA diagnosis [17] through a scrutinized peer review process. RA patients with a catastrophic illness card can receive medical therapy without copayment. We followed all the patients till the date of diagnosis with RA, censoring, or the end of 2011.

Variables of interest

We categorized age into ≤ 34, 35–49, 50–64, and ≥ 65 years. The patients' monthly income based on insurance premiums were classified into < 15,000, 15,000–19,999, and ≥ 20,000 NTD (1 USD equals approximately 30 NTD). The NHIA report beneficiaries residing in urbanization from level 1 to level 7 (levels 1 and 7 were the highest and lowest levels of urbanization, respectively) [18]. Because few people resided in levels 4–7, we combined the least urbanized populations into level 4. The baseline comorbidity included obesity (ICD-9-CM code 278), stroke (ICD-9-CM codes 430–438), coronary artery disease (CAD; ICD-9-CM codes 410–414), anxiety (ICD-9-CM codes 300.00), depression (ICD-9-CM codes 296.2, 296.3, 300.4, 311), diabetes mellitus (ICD-9-CM code 250), and other rheumatic diseases (ICD-9-CM code 710.0, 710.1, 710.2, 710.3, 710.4, 720).

Statistical analysis

Comparison of the demographics and comorbidities between the SD (SA and non-apnea SD) and comparison cohorts used the chi-squared test for binomial variables and the Student's t test for continuous variables. The follow-up time (person-years) estimated incidence densities according to demographic status, monthly income, urbanization level, and comorbidity for each cohort. Cox proportional hazard regression models compared the risk of developing RA-associated SD in the SD and comparison cohorts presenting hazard ratios (HRs) and 95% confidence intervals (CIs). In addition, adjusted HRs were determined after we controlled for age, sex, monthly income (NTD), urbanization level, and the comorbidities such as obesity, stroke, CAD, anxiety, depression, diabetes mellitus, and other rheumatic diseases. The Cox models were applied to compare the HRs and 95% CIs of RA for the SA cohort with those of the non-apnea SD cohort. We conducted a survival analysis to estimate the cumulative incidence of RA in the SD and non-SD cohorts. The SAS statistical package for Windows (version 9.3, SAS Institute Inc., Cary, NC, USA) was used for analyses. A statistical significance was set by two-tailed P value of < 0.05.

Results

Comparison of demographics and comorbidities in both cohorts

We identified 65,754 newly diagnosed patients with SD (1404 SA patients and 64,350 non-apnea SD patients)

and 65,753 non-SD controls in this study. The patients in both the SD and comparison cohorts were aged ≤ 49 years (50.1%), predominantly women (62.8%), lived in urbanized areas (56.1 vs 58.8%), and had income levels between 15,000 and 19,999 NTD (50.2 vs 48.4%). The SD cohort had a significantly higher proportion of comorbidities, namely, obesity, stroke, CAD, anxiety, depression, diabetes mellitus, and other rheumatic diseases, compared with the comparison cohort (all $P < 0.001$). The patients in the SA cohort were predominantly men (62.5%), whereas those in the non-apnea SD cohort were mostly women (63.4%) (Table 1).

Comparison of incidence densities and risks of rheumatoid arthritis between the patients with and without sleep disorders according to demographic characteristics and comorbidities

The SD cohort showed higher overall incidence densities of RA than did the comparison cohort (3.31 vs 2.15 per 10,000 person-years, respectively). After we controlled for covariates, a 1.49-fold adjusted HR of RA was present in the SD cohort compared with the non-SD cohort (95% CI = 1.19–1.85). The patients aged younger than 49 years in the SD cohort had a 2.27-fold increased risk of RA compared with those in the counterparts (95% CI = 1.57–3.28). The incidence densities of RA were higher for the women than those for the men in both cohorts. The adjusted HR of RA for the SD cohort to comparison cohort was significantly higher in both the women (adjusted HR = 1.44, 95% CI = 1.13–1.82) and men (adjusted HR = 1.87, 95% CI = 1.03–3.40). For the patients with SDs, a monthly income < 15,000 NTD was associated with a significantly increased risk of RA relative to that of the counterparts (adjusted HR = 2.17, 95% CI = 1.29–3.67). The risk of RA for the SD cohort relative to the comparison cohort was significantly higher for those living in regions with the highest and second highest urbanization levels (adjusted HR = 1.94, 95% CI = 1.28–2.92 and adjusted HR = 1.59, 95% CI = 1.04–2.44, respectively). The relative risk of RA for the SD-to-comparison cohort was significantly higher for those who did not have comorbidity (adjusted HR = 1.60, 95% CI = 1.24–2.05) (Table 2).

To compare incidence and risks of rheumatoid arthritis among the SA, non-apnea SD, and non-SD cohorts

The incidence of RA was the highest in the patients with SA, followed by those with non-apnea SD and the comparison cohort (4.11, 3.29, and 2.15 per 10,000 person-years, respectively). Compared with the comparison cohort, the adjusted HR of RA was 2.56 (95% CI = 1.11–5.91) and 1.47 (95% CI = 1.18–1.84) for the apnea SD and non-apnea SD cohorts, respectively. The adjusted HRs of RA for the SA and non-apnea SD cohorts were significantly increased for those aged ≤ 49 years compared with the counterparts. The incidence densities of RA among the three cohorts were higher in the women than in the men. The sex-specific adjusted HR for the SA cohort relative to the comparison cohort was 3.06-fold in the women (95% CI = 1.23–7.61). The risk of RA was higher in the patients with non-apnea SDs than that in the patients without SDs for both the women and men. Regarding monthly income stratification, the risk of RA was significantly higher in the patients with non-apnea SDs than in the patients without SDs for monthly incomes of < 15,000 (adjusted HR = 2.21, 95% CI = 1.31–3.73) and 15,000–19,999 NTD (adjusted HR = 1.39, 95% CI = 1.02–1.89).

The non-apnea SD patients living in the regions with the highest and second highest urbanization levels were related to increased risks of RA (adjusted HR = 1.93, 95% CI = 1.27–2.92 and adjusted HR = 1.58, 95% CI = 1.03–2.43, respectively). In the non-comorbid subgroup, the risk of RA was significantly higher for the non-apnea SD cohort (adjusted HR = 1.60, 95% CI = 1.24–2.05) compared with the comparison cohort (Table 3).

Incidence rates and risks of rheumatoid arthritis in patients with diverse types of non-apnea sleep disorders

We further categorized non-apnea SDs into insomnia, sleep disturbance, and other SDs. Compared with people without SDs, patients with insomnia and sleep disturbance exhibited a substantially elevated incidence of RA with a significantly increased risk of RA development (adjusted HR = 1.47, 95% CI = 1.12–1.94 for insomnia and adjusted HR = 1.55, 95% CI = 1.20–2.00 for sleep disturbance) (Table 4).

Comparison of cumulative incidence of rheumatoid arthritis between the SD and non-SD cohorts

The RA cumulative incidence curve illustrated an increased risk of developing RA in the SD cohort compared with that in the non-SD cohort ($P < 0.001$, log-rank test) (Fig. 1).

Discussion

This longitudinal cohort study revealed that the patients with SDs exhibited a 1.49-fold greater risk compared with the general population after adjustment for covariates through 1,300,420 follow-up person-years. The incidence density of RA was the highest for the patients with SA, followed by those with non-apnea SD and the comparison cohort (4.11, 3.29, and 2.15 per 10,000 person-years, respectively). After we controlled for covariates, the risk of

Table 1 Comparison of demographics and comorbidity between the sleep disorders and comparison cohorts

	Sleep disorder								
	Non-apnea SD ($N = 64,350$)		Apnea SD ($N = 1,404$)		Total ($N = 65,754$)		Control ($N = 65,753$)		
	n	%	*n*	%	*n*	%	*n*	%	*p* value
Age (year)									0.99
≤ 34	11,268	17.5	262	18.7	11,530	17.5	11,530	17.5	
35–49	20,901	32.5	547	39.0	21,448	32.6	21,448	32.6	
50–64	16,808	26.1	378	26.9	17,186	26.1	17,186	26.1	
≥ 65	15,373	23.9	217	15.5	15,590	23.7	15,589	23.7	
Mean (standard deviation)[a]	51.3	16.1	48.6	14.5	51.3	16.1	51.1	16.3	0.01
Gender									
Women	40,781	63.4	526	37.5	41,307	62.8	41,307	62.8	
Men	23,569	36.6	878	62.5	24,447	37.2	24,446	37.2	
Monthly income (NTD)									< 0.001
< 15,000	16,154	25.1	290	20.7	16,444	25.0	16,521	25.1	
15,000–19,999	32,452	50.4	550	39.2	33,002	50.2	31,798	48.4	
≥ 20,000	15,744	24.5	564	40.2	16,308	24.8	17,434	26.5	
Urbanization level[b]									< 0.001
1 (highest)	17,615	27.4	472	33.6	18,087	27.5	19,956	30.4	
2	18,392	28.6	391	27.9	18,783	28.6	18,642	28.4	
3	11,465	17.8	276	19.7	11,741	17.9	11,320	17.2	
4 (lowest)	16,878	26.2	265	18.9	17,143	26.1	15,835	24.0	
Comorbidity									
Obesity	484	0.75	34	2.42	518	0.79	238	0.36	< 0.001
Stroke	2,329	3.62	36	2.56	2,365	3.60	1,643	2.50	< 0.001
CAD	12,971	20.2	295	21.0	13,266	20.2	6,144	9.34	< 0.001
Anxiety	4,096	6.37	86	6.13	4,182	6.36	530	0.81	< 0.001
Depression	4,270	6.64	91	6.48	4,361	6.63	442	0.67	< 0.001
Diabetes mellitus	4,884	7.43	93	6.62	4,791	7.45	3,398	5.17	< 0.001
Other rheumatic disease	1,272	1.93	31	2.21	1,241	1.93	526	0.80	< 0.001

Chi-squared test compared to total SD

SD sleep disorders, *NTD* new Taiwan dollar, *CAD* coronary artery disease

[a] *t* test

[b] The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized and level 4 as the least urbanized

developing RA was 2.56 (95% CI = 1.11–5.91) for the SA cohort and 1.47 (95% CI = 1.18–1.84) for the non-apnea SD cohort when compared with the non-SD cohort.

The biological mechanism of RA development among the patients with SD remains unclear. The immunogenetics of RA discloses a central role for aberrant pathways of T cell activation at initiation and progression [19, 20]. CD4+ T cells link with human leucocyte antigen (HLA) class II molecules and certain costimulatory molecules expressed on the surface of antigen-presenting cells. Furthermore, the cooperation of T cells and B cells results in ongoing destruction of the synovial membrane [20]. In addition, numerous pro-inflammatory cytokines, namely, tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6, and IL-8, play roles in the pathogenesis of RA [21]. Neuroimmunology indicated that sleep regulation in the central nervous system shows reciprocally related to the immune system [22–24]. The natural regulatory T cells follow a sleep-dependent rhythm and sleep can suppress T cell activity [2]. Sleep has been known to enhance immune defense for decades. Sleep impairment may derange immune function, which might perform a role in the risk of infectious diseases and inflammatory disorders [4, 25]. Sleep disturbance impairs T cell regulation and upregulates certain inflammatory cytokines, such as TNF-α, IL-1, and IL-6, as demonstrated in patients with inflammatory bowel disease [26–28].

Table 2 Comparison of incidence densities and hazard ratios of rheumatoid arthritis between the patients with and without sleep disorders according to demographic characteristics and comorbidity

	Sleep disorder							
	No			Yes			Crude HR (95% CI)	Adjusted HR[b] (95% CI)
	Event	PY	Rate[a]	Event	PY	Rate[a]		
All	137	637,906	2.15	219	662,514	3.31	1.54 (1.24, 1.91)***	1.49 (1.19, 1.85)***
Age								
≤ 49	42	337,384	1.24	103	348,139	2.96	2.37 (1.66, 3.40)***	2.27 (1.57, 3.28)***
50–64	73	176,373	4.14	75	178,407	4.20	1.01 (0.74, 1.40)	0.91 (0.65, 1.28)
> 65	22	124,149	1.77	41	135,967	3.02	1.72 (1.02, 2.89)*	1.82 (1.06, 3.10)*
Gender								
Women	119	409,130	2.91	189	426,864	4.43	1.52 (1.21, 1.92)***	1.44 (1.13, 1.82)**
Men	18	228,777	0.79	30	235,650	1.27	1.62 (0.90, 2.90)	1.87 (1.03, 3.40)*
Monthly income (NTD)								
< 15,000	21	148,717	1.41	51	156,595	3.26	2.31 (1.39, 3.83)**	2.17 (1.29, 3.67)**
15,000–19,999	74	308,108	2.40	114	334,606	3.41	1.42 (1.06, 1.90)*	1.41 (1.04, 1.91)*
≥ 20,000	42	181,082	2.32	54	171,312	3.15	1.36 (0.91, 2.03)	1.23 (0.81, 1.87)
Urbanization level[c]								
1 (highest)	37	196,996	1.88	69	184,137	3.75	1.99 (1.34, 2.97)***	1.94 (1.28, 2.92)**
2	36	182,854	1.97	61	190,835	3.20	1.62 (1.08, 2.45)*	1.59 (1.04, 2.44)*
3	22	108,711	2.02	33	117,533	2.81	1.39 (0.81, 2.38)	1.44 (0.83, 2.50)
4 (lowest)	42	149,345	2.81	56	170,010	3.29	1.17 (0.79, 1.75)	1.06 (0.70, 1.61)
Comorbidity[d]								
No	111	554,142	2.00	137	440,470	3.11	1.55 (1.21, 2.00)***	1.60 (1.24, 2.05)***
Yes	26	83,765	3.10	82	222,044	3.69	1.19 (0.77, 1.85)	1.16 (0.74, 1.82)

NTD new Taiwan dollar, *crude HR* relative hazard ratio

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Rate, incidence rate, per 10,000 person-years

[b] Adjusted HR: multivariable analysis including age; sex; monthly income (NTD); urbanization level; and comorbidities of obesity, stroke, CAD, anxiety, depression, diabetes mellitus, and other rheumatic disease

[c] The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized and level 4 as the least urbanized

[d] Comorbidity: only to have one of comorbidities (including obesity, stroke, CAD, anxiety, depression, diabetes mellitus, and other rheumatic disease) classified as the comorbidity group

Chronic intermittent hypoxia may activate systemic inflammation in patients with SA [29]. The proinflammatory cytokines, such as TNF-α and IL-6, and an inflammatory marker, namely, C-reactive protein in circulation, are increased in patients with SA [30, 31]. In addition, SA is strongly linked with obesity [32]. Excess adiposity related to impaired immune function has been reported in previous studies [33, 34]. Furthermore, obesity is associated with a condition of low-grade chronic inflammation and disturbed metabolic hormones [35]. Moreover, obesity may influence specific and unspecific immune responses mediated by cell and humoral mechanisms [36, 37]. Furthermore, SA is associated with TNF-α gene polymorphism [38]. Some of the polymorphism forms extend haplotypes with HLA class I and II alleles, which play a role in T cell immune-regulated diseases [39]. These plausible mechanisms may explain why the patients with SA had a considerable risk of RA development in our study.

The prevalence of anxiety and depression were higher in the SD cohort than in the comparison cohort. These findings are compatible with previous reports [40, 41]. The association of SD and anxiety may be associated with adaptive response to stress [42]. Otherwise, the relationship between sleep disturbance and depression is strongly related. SDs may become core symptoms of depression [42].

The incidence density rates of RA were higher for the women than for the men in both cohorts, which are accordant with previous studies [8, 43]. However, the SD cohort still

Table 3 Comparisons of incidence densities and hazard ratio of rheumatoid arthritis in the sleep apnea, non-apnea sleep disorders, and comparison cohorts

	Control		Apnea SD		Crude HR (95% CI)	Adjusted HR[b] (95% CI)	Non-apnea SD		Crude HR (95% CI)	Adjusted HR[b] (95% CI)
	Case	Rate[a]	Case	Rate[a]			Case	Rate[a]		
All	137	2.15	6	4.11	1.92 (0.85, 4.34)	2.56 (1.11, 5.91)*	213	3.29	1.53 (1.24, 1.90)***	1.47 (1.18, 1.84)***
Age										
≤49	42	1.24	1	1.16	0.93 (0.13, 6.78)	0.98 (0.13, 7.18)	102	3.00	2.41 (1.68, 3.45)***	2.30 (1.59, 3.32)***
50–64	73	4.14	4	10.1	2.43 (0.89, 6.66)	2.19 (0.78, 6.15)	71	4.07	0.98 (0.71, 1.36)	0.89 (0.63, 1.26)
>65	22	1.77	1	4.92	2.85 (0.38, 21.1)	3.07 (0.40, 23.4)	40	2.99	1.70 (1.01, 2.86)*	1.81 (1.06, 3.10)*
Gender										
Women	119	2.91	5	9.11	3.13 (1.28, 7.65)*	3.06 (1.23, 7.61)*	184	4.37	1.50 (1.19, 1.89)***	1.42 (1.12, 1.81)**
Men	18	0.79	1	1.10	1.42 (0.19, 10.6)	1.30 (0.17, 10.1)	29	1.28	1.63 (0.90, 2.93)	1.87 (1.02, 3.41)*
Monthly income (NTD)										
<15,000	21	1.41	0	0.00	–	–	51	2.32	2.35 (1.41, 3.91)**	2.21 (1.31, 3.73)**
15,000–19,999	74	2.40	4	7.03	2.93 (1.07, 8.00)*	3.03 (1.08, 8.47)*	110	3.34	1.39 (1.04, 1.87)*	1.39 (1.02, 1.89)*
≥20,000	42	2.32	2	3.35	1.44 (0.035, 5.96)	1.24 (0.29, 5.41)	52	3.14	1.35 (0.90, 2.03)	1.23 (0.81, 1.88)
Urbanization level[d]										
1 (highest)	37	1.88	2	4.06	2.16 (0.52, 8.94)	2.22 (0.52, 9.44)	67	3.74	1.99 (1.33, 2.97)***	1.93 (1.27, 2.92)**
2	36	1.97	2	4.93	2.51 (0.61, 10.4)	2.09 (0.47, 9.22)	59	3.16	1.60 (1.06, 2.43)*	1.58 (1.03, 2.43)*
3	22	2.02	1	3.50	1.74 (0.24, 12.9)	1.75 (0.23, 13.3)	32	2.79	1.38 (0.80, 2.38)	1.44 (0.83, 2.52)
4	42	2.81	1	3.64	1.30 (0.18, 9.44)	1.19 (0.16, 9.03)	55	3.29	1.17 (0.79, 1.75)	1.06 (0.70, 1.62)
Comorbidity[c]										
No	111	2.00	2	2.10	1.05 (0.26, 4.24)	1.54 (0.38, 6.28)	135	3.13	1.57 (1.22, 2.01)***	1.60 (1.24, 2.05)***
Yes	26	3.10	4	7.91	2.56 (0.89, 7.36)	3.51 (1.19, 10.4)*	78	3.59	1.16 (0.74, 1.80)	1.12 (0.71, 1.76)

NTD new Taiwan dollar, *crude HR* relative hazard ratio

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Rate, incidence rate, per 10,000 person-years

[b] Adjusted HR: multivariable analysis including age; sex; monthly income (NTD); urbanization level; and comorbidities of obesity, stroke, CAD, anxiety, depression, diabetes mellitus, and other rheumatic disease

[c] Comorbidity: only to have one of comorbidities (including obesity, stroke, CAD, anxiety, depression, diabetes mellitus, and other rheumatic disease) classified as the comorbidity group

[d] The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized and level 4 as the least urbanized

Table 4 Incidence rates and hazard ratios of rheumatoid arthritis in patients with diverse types of non-apnea sleep disorders

Variables	Case	PY	Rate[a]	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
Without SD	137	637,907	2.15	1 (reference)	1 (reference)
Non-apnea SD					
Insomnia	87	257,796	3.37	1.57 (1.20, 2.06)**	1.47 (1.12, 1.94)**
Sleep disturbance	114	337,627	3.38	1.57 (1.23, 2.02)***	1.55 (1.20, 2.00)***
Other sleep disorders	18	67,091	2.68	1.25 (0.76, 2.04)	1.19 (0.73, 1.96)

Crude HR relative hazard ratio

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Rate, incidence rate, per 10,000 person-years

[b] Adjusted HR: multivariable analysis including age; sex; monthly income; urbanization level; and comorbidities of obesity, stroke, CAD, anxiety, depression, diabetes mellitus, and other rheumatic disease

exhibited a substantial risk of developing RA compared with the comparison cohort in both sexes (adjusted HR = 1.87, 95% CI = 1.03–3.40 for the men and adjusted HR = 1.44, 95% CI = 1.13–1.82 for the women). Although the incidence density rates of RA development were higher in the SD cohort than in the comparison cohort, the patients aged 49 years and younger exhibited a considerably higher risk of RA in age-stratified analysis. This result suggested that the effect of SDs on the RA risk was the greatest in younger adults.

The risk of RA for the SD cohort relative to the comparison cohort was significantly higher for those living in regions with the highest and second highest urbanization levels. Numerous studies have indicated that the individuals living in the urban areas are more apt to access medical services than those in the rural areas [44, 45]. For the patients with SDs, a monthly income of < 15,000 NTD was associated with a significantly increased risk of RA relative to that of the patients without SDs. The association of low socioeconomic status and higher risk of RA in this study was consistent with a previous study [46].

The strength of this large sample sized cohort study lies that it provides data on the risk of RA in people with SDs. We could trace the patients throughout the whole study period because the NHI is mandatory in Taiwan and each beneficiary was allocated a personal identification number. Furthermore, RA diagnosis was confirmed in the RCIPD, enhancing a high reliability for our analyses.

However, certain limitations exist when interpreting these findings. First, the NHIRD provides no family history for the patients. Second, patients with SDs may have been

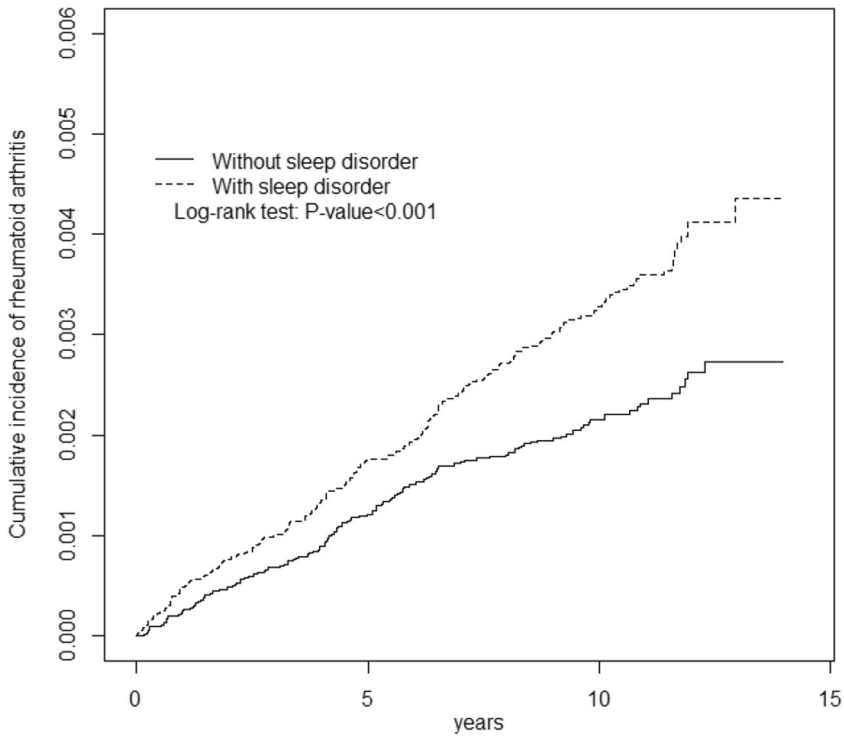

Fig. 1 Kaplan-Meier method determined cumulative incidence of rheumatoid arthritis between sleep disorder cohorts and comparisons without sleep disorder

underrepresented because patients may rarely visit a clinician to discuss sleep problems [47]. The current study did not elaborate the risk of RA in different types of non-apnea SDs and diverse severity of SA because the result of polysomnography was not available in the NHIRD.

In summary, this longitudinal cohort study of 65,754 SD patients with 662,514 follow-up person-years demonstrated that the patients with SDs had a 49% increased risk of developing RA compared with the comparison cohort. Although the causal relationship between SDs and RA development is modest, a bidirectional relationship exists between SDs and RA. The findings remind the clinicians of being awareness of potential derangement of immune function and an increased RA risk in patients with SDs.

Acknowledgments This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002). The funders did not involve in study design, data collection and analysis, decision to publish, and preparation of the manuscript.

Author contributions All authors have substantially contributed to the research and manuscript: preparation. Conception of design: Wei-Sheng Chung, data collection: all authors, data analysis and interpretation: all authors, manuscript writing: all authors, and final approval of manuscript: Wei-Sheng Chung and Cheng-Li Lin.

Compliance with ethical standards

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

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