Observational Study

Medicine®

OPEN

Non-apnea sleep disorder and its risk for all kinds of injuries

A 14-year follow-up for a nationwide population-based retrospective study

Zhu Wei Lim, MD[a], I-Duo Wang, MD[g], Feng-Cheng Liu, MD, PhD[b], Chi-Hsiang Chung, PhD[c,d], Je-Ming Hu, MD[e], Pei-Yi Tsai, MS[f], Wu-Chien Chien, PhD[c,d,h,*]

Abstract

Non-apnea sleep disorder (NASD) increases the risk of motor vehicle accidents. However, systemic review of NASD and its risk for all causes of injury is lacking. The aim of the present study was to provide a detailed demographic data on NASD and all causes of injury in a 14-year follow up.

Our study utilized outpatient and inpatient data from the Longitudinal Health Insurance Database between 2000 and 2013 in Taiwan. We enrolled 989,753 individuals aged ≥20 years who were diagnosed with NASD as outpatients ≥3 times or inpatients ≥1 time. We matched the study cohort with a comparison cohort by age, index date and comorbidities at a ratio of 1:4. We used Cox proportional hazards regression to analyze the association of NASD and the cause of injury.

In this 14-year follow up study, patients with NASD had 12.96% increased risk of injury compared to that of the control cohort. Fall was the first place of the cause of injury with 670.26 per 10^5 PYs. In the stratified age group, patients aged ≧65 years had the highest risk of injury (adjusted HR=1.381; $P<.001$). Kaplan–Meier analysis showed that the incidence of injury between the with- and without-NASD cohorts started from the first year and persisted until the end of the follow-up.

Our study demonstrates that NASD patients were associated with higher risk of all causes of injuries, with falling being the most prevalent diagnosis. The general public should be more aware of this neglected issue of NASD.

Abbreviations: HPA = hypothalamic- pituitary-adrenal, ICD-9-CM = International Classification of Diseases Ninth Revision, Clinical Modification, NASD = Non-apnea sleep disorder, NHIRD = National Health Insurance Research Database, SDs = Sleep disorders.

Keywords: injury, longitudinal health insurance database, national health insurance research database, non-apnea sleep disorder

1. Introduction

Sleep disorders (SDs) are prevalent among the worldwide general population. They are a group of diseases characterized by disturbances in the amount, quality or behaviors of physiological conditions associated with sleep.[1] According to the International Classification of Sleep Disorders (ICSD-3) (American Academy of Sleep Medicine [AASM], 2014), SDs can be divided into 7 categories: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep disorders, parasomnias, sleep-related movement disorders, and other sleep disorders.[1]

Editor: Mohammed Nader Shalaby.

ZWL and I-DW contribute equally in this article.

This study was supported by the Tri-Service General Hospital Research Foundation (TSGH-B-110012), and the sponsor has no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are publicly available.

[a] Department of Obstetrics and Gynecology, Changhua Christian Hospital, Changhua, [b] Division of Rheumatology/Immunology and Allergy, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei 114, [c] Department of Medical Research, Tri-Service General Hospital, [d] School of Public Health, National Defense Medical Center, Taipei, [e] Division of Colorectal Surgery, Department of Surgery, [f] Department of Radiation Oncology, [g] Department of Internal Medicine, Tri-Service General Hospital, [h] Graduate Institute of Life Sciences, National Defense Medical Center, Taipei 114, Taiwan.

[*] Correspondence: Wu-Chien Chien, Department of Medical Research, Tri-Service General Hospital, National Defense Medical Center, No. 325, Section 2, Cheng-Kung Road, Neihu District, Taipei City 11490, Taiwan (e-mail: chienwu@ndmctsgh.edu.tw).

How to cite this article: Lim ZW, Wang ID, Liu FC, Chung CH, Hu JM, Tsai PY, Chien WC. Non-apnea sleep disorder and its risk for all kinds of injuries: a 14-year follow-up for a nationwide population-based retrospective study. Medicine 2021;100:8(e24766).

Received: 12 October 2020 / Received in final form: 22 January 2021 / Accepted: 26 January 2021

http://dx.doi.org/10.1097/MD.0000000000024766

Sleep disorders affect physical activity and psychosocial and performance status.[2] Several studies have shown that SDs are associated with daytime fatigue or chronic fatigue syndrome and may lead to an increased risk of motor vehicle accidents.[2] Among the categories of SDs, sleep-breathing disorders, or the so-called obstructive sleep apnea syndrome, have been related to an increased risk of traffic accidents.[3,4] Nonetheless, studies regarding SDs and their correlation with injuries are rare, especially in non-apnea sleep disorder (NASD) patients. Smolensky et al[2] pointed out that a longitudinal study is needed to study the risk of injuries in patients with different SDs. One article, written by Lin et al,[5] showed an increasing risk of injuries in patients with sleep disorders. However, they did not show the demographic features of the injuries in NASD patients. Therefore, we utilized the Taiwan National Health Insurance Research Database (NHIRD) to perform a longitudinal study of data obtained over 14 years studying the type of injuries in NASD patients with detailed demographic features and common comorbidities, including age, sex, hypertension, type 2 diabetes, hyperlipidemia, coronary disease, etc.

2. Methods

2.1. Data sources

This study used Taiwan's National Health Insurance Research Database (NHIRD), which started in 1995. Taiwan administers its insurance-based health care system, which is characterized by good accessibility, high efficiency, comprehensive population coverage (99% of the 23.74 million residents in Taiwan), relatively low costs and short waiting times. [6,7] The NHIRD contains many health registration records from the general population in Taiwan from healthcare sectors including outpatient, inpatient and emergency departments. Physicians encode clinical diagnoses according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD has demonstrated its high accuracy and validity of diagnoses in previous articles.[6,8] Therefore, it has been used as a source of representative data in medical and health care-related research fields. Our study design was approved by the Institutional Review Board of Tri-Service General Hospital (TSGHIRB No. 1-106-05-169).

2.2. Study population

We enrolled 989,753 outpatients and inpatients from the Longitudinal Health Insurance Database between 2000 and 2013. We included patients 20 years old and above who were diagnosed with NASD as outpatients ≥3 times or were admitted as inpatients with NASD. We defined the index date as the time NASD was diagnosed, and 7671 patients were included. We excluded patients with NASD who were diagnosed before the index date, had injuries before tracking, were <20 years old and had unknown gender, and 6648 participants remained as the study cohort. They were matched by age, gender, index date, and comorbidities to a comparison cohort at a ratio of 1:4. We compared the baseline comorbidities between the study and comparison cohorts, including Type 2 diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular disease, stroke, obesity, anxiety and depression. In addition, we included categories of injury according to the ICD-9 diagnosis, such as fracture, dislocation, sprains and strains, intracranial/internal injury, open wound, injury to blood vessels, superficial injury/contusion, crushing, foreign body entering through orifice, burn, injury to nerve and spinal cord, poisoning, and other injuries. Moreover, we listed the mechanisms of injuries in Table S3, http://links.lww.com/MD/F809: traffic, poisoning (drugs/medicaments/biologicals), poisoning (solid and liquid substances/gases/vapors), surgical/medical care, abnormal reaction to medical procedure, falls, burns, and fires, environment, drowning, suffocation, other unintentional injuries, late effects, adverse drug reaction, suicide and homicide/abuse. Both our study and comparison cohorts were tracked until the end of 2013.12.31.

2.3. Statistical analysis

The comparison of demographic features and comorbidities in both cohorts was performed with the Chi-Squared test. Continuous data, such as the mean age, years of follow-up and years to injury, were compared by Student t test. We calculated the incidence (per 10^5 person-years) of NASD according to age, sex and concomitant comorbidities and used multivariable analysis for the adjustment. Multivariable Cox proportional hazards regression models were used to calculate the adjusted hazard ratios and the 95% confidence intervals. We evaluated the cumulative risk of injury and year of follow-up by using Kaplan–Meier analysis and the log-rank test. SPSS 22.0 software was used for all analyses. We considered a two-sided P value to be statistically significant at $P < .05$.

3. Results

The study included 6648 patients with newly diagnosed NASD and 26,592 patients in the control cohort during the period between 2000 and 2013. The mean follow-up time was 10.78 ± 11.17 years in the NASD cohort and 11.78 ± 11.12 years in the control cohort (see Supplemental Digital Content Table 1 which showed years of follow up in both cohorts, http://links.lww.com/MD/F809). The mean number of years to injury was 4.40 ± 3.88 years in the NASD population and 5.03 ± 3.96 years in the control cohort (see Supplemental Digital Content Table 1 which showed years to injuries in patients with NASD, http://links.lww.com/MD/F809). At the end of follow-up, 2446 participants in the NASD cohort had injuries compared with 6738 participants in the control cohort (Fig. 1).

Table 1 shows the baseline characteristics of the study, with the results of follow-up shown in Table 2. The average ages were 68.14 ± 19.25 and 69.03 ± 20.11 years for the study and comparison cohorts, respectively (Table 2). In the age-stratified NASD group, patients aged ≥65 years had the highest injury rate (49.37%) compared to non-NASD group, followed by patients aged 45 to 64 years (35.05%) (Table 2). Table 2 shows the results after 14 years of follow-up, and we found a higher incidence of injury in the NASD groups with comorbidities of diabetes mellitus, hypertension, cerebrovascular disease, anxiety and depression. Kaplan–Meier analysis showed that the incidence of injury started to branch off in the first year in the NASD cohort and persisted until the end of the follow-up (log-rank; $P < .001$; Fig. 2).

NASD patients had a 32.8% increased risk of injury compared with the control cohort (crude HR = 1.328 [95% CI, 1.238–1.391]; $P < .001$; Table 3). After adjusting for age and other concomitant comorbidities, the HR of injury in patients with NASD decreased to 1.296 (95% CI = 1.236–1.358; $P < .001$;

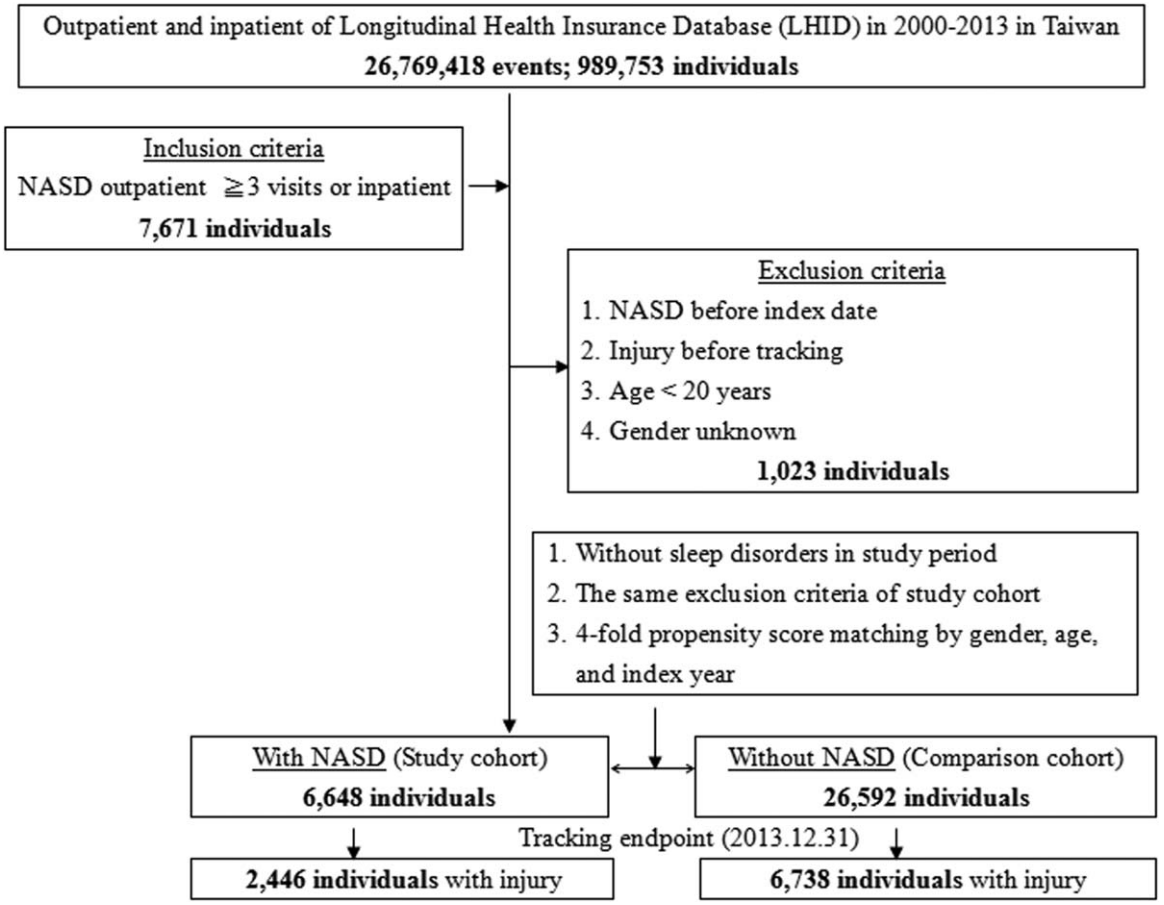

Figure 1. Flowchart of study group selection from the National Health Insurance Research Database in Taiwan.

Table 3). Females were predominant in our study (53.6%, Table 2); however, when adjusted for age and other comorbidities, males had a 12% higher risk of injury than females (adjusted HR = 1.120 [95% CI, 1.074–1.168]; $P < .001$; Table 3). We further stratified common comorbidities and the age groups by using the Cox regression model and studied the impact of NASD on injuries in the study group and the control group (Table 4). The incidence of injuries in the NASD and non-NASD groups were 3122.76 and 2351.34 per 10^5 person-years, respectively (Table 4). When stratified into gender groups, in patients with NASD, male patients had an incidence of 3466.14 injuries per 10^5 person-years, while the incidence was 2784.65 per 10^5 person-years in female patients. Moreover, male patients with NASD had a 39.7% increased risk of injury compared to those who did not, and women with NASD had a 20.4% increased risk of injury than the control group. When stratified into age groups, patients in the 20 to 44-year group had the highest incidence of injury at 4191.61 per 10^5 person-years, whereas patients aged ≥65 years had the lowest incidence rate at 2943.54 per 10^5 person-years. However, NASD had the greatest impact on patients aged ≥65 years, with an adjusted HR of 1.381 (95% CI = 1.318–1.448; $P < .001$), followed by those aged 45 to 64 years (adjusted HR = 1.265), then aged 20 to 44 years (adjusted HR = 1.207), compared to non-NASD patients. In patients with NASD, the spring and summer seasons had the highest risk of injuries (adjusted HR = 1.311 and 1.326, respectively) (Table 4).

In our study, we analyzed injury diagnosis and mechanisms of injury according to the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) list (see Supplemental Digital Content Table 2 which showed injury diagnosis and mechanisms of injury according to the ICD-9-CM list, http://links.lww.com/MD/F809). We further stratified the patients into male and female and studied their associated risk of injury. In the categories of "total causes of injuries," falls had the highest incidence with 670.26 injuries per 10^5 person-years, followed by traffic, with an incidence of 434.07 per 10^5 person-years. In NASD patients, drowning had the highest risk of injury (adjusted HR = 4.760 [95% CI, 4.540–5.012]; $P < .001$), followed by suicide (adjusted HR = 3.184 [95% CI, 3.037–3.339]; $P < .001$) (see Supplemental Digital Content Table 3 for adjusted HR in each injury diagnosis when having NASD, http://links.lww.com/MD/F809). The incidence of injury in male patients with NASD was 3466.14 per 10^5 person-years and 2784.65 per 10^5 person-years in female patients (Table 4). In male patients with NASD, falls and traffic had the highest incidence, 643.31 and 488.91 per 10^5 person-years, respectively. We also ranked the cause of injury in *Table S4*, http://links.lww.com/MD/F809.

However, in regard to the risk of injury, suicide was the highest, with an adjusted HR of 3.198 (95% CI, 3.050–3.352; $P < .001$), followed by accidental poisoning by other solid and liquid substances, gases, and vapors (adjusted HR = 3.000 [95% CI, 2.908–3.199]; $P < .001$; Table S3, http://links.lww.com/MD/

Table 1

Study characteristics at baseline.

	NASD						
	Total		With		Without		
Variables	n	%	n	%	n	%	*P*
Total	33,240		6648	20.00	26,592	80.00	
Gender							
Male	15,425	46.40	3085	46.40	12,340	46.40	.999
Female	17,815	53.60	3563	53.60	14,252	53.60	
Age (years)	57.27 ± 17.64		57.36 ± 17.74		57.25 ± 17.61		.649
Age group (years)							
20–44	6410	19.28	1282	19.28	5128	19.28	.999
45–64	12,370	37.21	2474	37.21	9896	37.21	
≥65	14,460	43.50	2892	43.50	11,568	43.50	
DM							
Without	28,475	85.66	5614	84.45	22,861	85.97	.002
With	4765	14.34	1034	15.55	3731	14.03	
HTN							
Without	27,027	81.31	5121	77.03	21,906	82.38	<.001
With	6213	18.69	1527	22.97	4686	17.62	
Hyperlipidemia							
Without	32,216	96.92	6355	95.59	25,861	97.25	<.001
With	1024	3.08	293	4.41	731	2.75	
CVD							
Without	30,062	90.44	6008	90.37	24,054	90.46	.835
With	3178	9.56	640	9.63	2538	9.54	
Stroke							
Without	30,290	91.13	5996	90.19	24,294	91.36	.003
With	2950	8.87	652	9.81	2298	8.64	
Obesity							
Without	33,216	99.93	6636	99.82	26,580	99.95	.001
With	24	0.07	12	0.18	12	0.05	
Anxiety							
Without	32,895	98.96	6398	96.24	26,497	99.64	<.001
With	345	1.04	250	3.76	95	0.36	
Depression							
Without	32,872	98.89	6,425	96.65	26,447	99.45	<.001
With	368	1.11	223	3.35	145	0.55	
Season							
Spring	9048	27.22	1892	28.46	7,156	26.91	<.001
Summer	7598	22.86	1363	20.50	6235	23.45	
Autumn	6962	20.94	1221	18.37	5741	21.59	
Winter	9632	28.98	2172	32.67	7460	28.05	
Location							
Northern Taiwan	12,769	38.41	1852	27.86	10,917	41.05	<.001
Middle Taiwan	9912	29.82	2538	38.18	7374	27.73	
Southern Taiwan	8433	25.37	1759	26.46	6674	25.10	
Eastern Taiwan	1994	6.00	468	7.04	1526	5.74	
Outlet islands	132	0.40	31	0.47	101	0.38	
Urbanization level							
1 (highest)	11,064	33.29	1746	26.26	9318	35.04	<.001
2	14,111	42.45	2567	38.61	11,544	43.41	
3	2830	8.51	910	13.69	1,920	7.22	
4 (lowest)	5235	15.75	1425	21.44	3810	14.33	
Level of care							
Hospital center	10,800	32.49	1379	20.74	9421	35.43	<.001
Regional hospital	11,596	34.89	2347	35.30	9249	34.78	
Local hospital	10,844	32.62	2922	43.95	7922	29.79	

P = Chi-Squared/Fisher exact test on category variables and *t*-test on continuous variables.

Data are from Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW).

F809). In female patients with NASD, the highest risk of injury was for suicide (adjusted HR = 3.210 [95% CI, 3.016–3.365]; $P < .001$; see Supplemental Digital Content Table 3 for adjusted HR in each injury diagnosis when having NASD, http://links.lww.com/MD/F809), which was the same as in male patients, followed by accidental poisoning by other solid and liquid substances, gases, and vapors (adjusted HR = 3.009 [95% CI, 2.836–3.154]; $P < .001$; see Supplemental Digital Content

Table 2

Study characteristics at the endpoint.

	NASD						
	Total		With		Without		
Variables	n	%	n	%	n	%	*P*
Total	33,240		6648	20.00	26,592	80.00	
Injury							
Without	24,056	72.37	4202	63.21	19,854	74.66	<.001
With	9,184	27.63	2446	36.79	6738	25.34	
Gender							
Male	15,425	46.40	3085	46.40	12,340	46.40	.999
Female	17,815	53.60	3563	53.60	14,252	53.60	
Age (years)	68.85 ± 19.94		68.14 ± 19.25		69.03 ± 20.11		.001
Age group (years)							
20–44	6170	18.56	1036	15.58	5134	19.31	<.001
45–64	11,242	33.82	2,330	35.05	8912	33.51	
≧65	15,828	47.62	3,282	49.37	12,546	47.18	
DM							
Without	27,969	84.14	5496	82.67	22,473	84.51	<.001
With	5271	15.86	1152	17.33	4119	15.49	
HTN							
Without	27,505	82.75	5401	81.24	22,104	83.12	<.001
With	5735	17.25	1247	18.76	4488	16.88	
Hyperlipidemia							
Without	32,562	97.96	6498	97.74	26,064	98.01	.174
With	678	2.04	150	2.26	528	1.99	
CVD							
Without	30,433	91.56	6016	90.49	24,417	91.82	.001
With	2807	8.44	632	9.51	2175	8.18	
Stroke							
Without	30,526	91.84	6104	91.82	24,422	91.84	.962
With	2714	8.16	544	8.18	2170	8.16	
Obesity							
Without	33,219	99.94	6641	99.89	26,578	99.95	.166
With	21	0.06	7	0.11	14	0.05	
Anxiety							
Without	33,018	99.33	6524	98.13	26,494	99.63	<.001
With	222	0.67	124	1.87	98	0.37	
Depression							
Without	32,865	98.87	6441	96.89	26,424	99.37	<.001
With	375	1.13	207	3.11	168	0.63	
Season							
Spring	8168	24.57	1624	24.43	6544	24.61	.072
Summer	8279	24.91	1636	24.61	6643	24.98	
Autumn	8659	26.05	1812	27.26	6847	25.75	
Winter	8134	24.47	1576	23.71	6558	24.66	
Location							
Northern Taiwan	12,750	38.36	1976	29.72	10,774	40.52	<.001
Middle Taiwan	9904	29.80	2401	36.12	7503	28.22	
Southern Taiwan	8459	25.45	1786	26.87	6673	25.09	
Eastern Taiwan	1991	5.99	452	6.80	1539	5.79	
Outlet islands	136	0.41	33	0.50	103	0.39	
Urbanization level							
1 (highest)	10,743	32.32	1841	27.69	8902	33.48	<.001
2	14,429	43.41	2767	41.62	11,662	43.86	
3	2641	7.95	708	10.65	1933	7.27	
4 (lowest)	5427	16.33	1332	20.04	4095	15.40	
Level of care							
Hospital center	11,201	33.70	1764	26.53	9437	35.49	<.001
Regional hospital	12,866	38.71	2720	40.91	10,146	38.15	
Local hospital	9173	27.60	2164	32.55	7009	26.36	

P = Chi-Squared/Fisher exact test on category variables and *t*-test on continuous variables.

Data are from Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW).

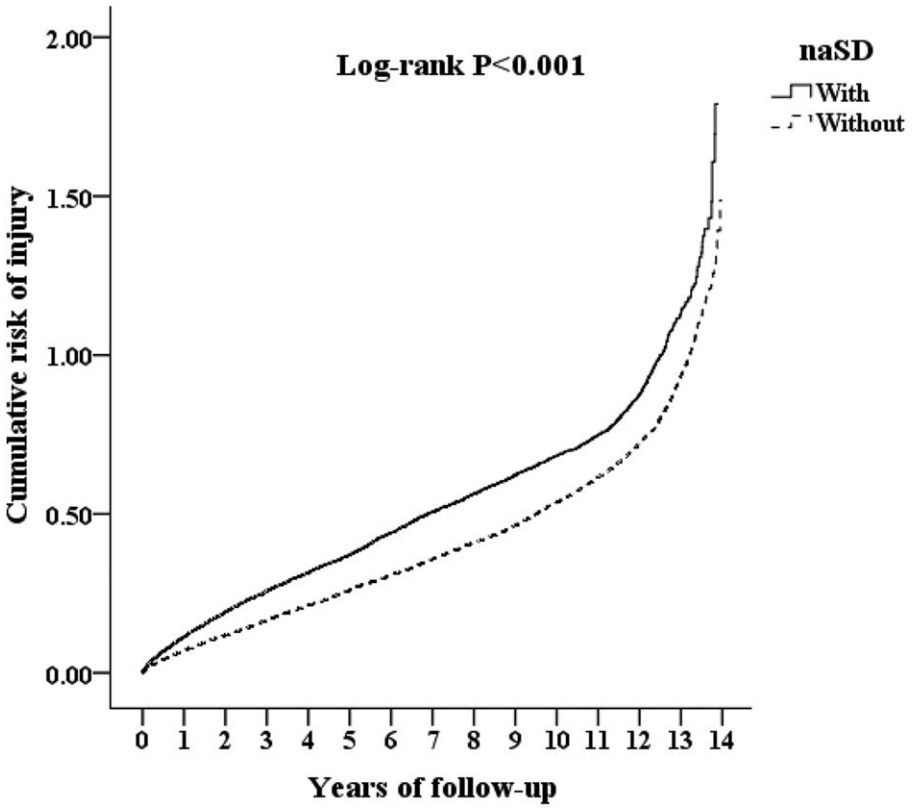

Figure 2. The Kaplan–Meier analysis for cumulative risk of injury in aged 20 years and older between with- and without-non-apnea sleep disorders (NASD) with log-rank test.

Table 3 for adjusted HR in each injury diagnosis when having NASD, http://links.lww.com/MD/F809).

4. Discussion

Our study is the largest and the longest longitudinal cohort to date discussing the association between NASD and factors of all injuries by analyzing the ICD-9-CM code. The mean follow-up time in the NASD group was 10.78 ± 11.17 years. Previous studies only focused on the association between sleep disorders and motor vehicle accidents[2]. Uehli et al[9] published a meta-analysis article about workers with sleep problems, and the results showed a 62% increased risk of injuries compared to workers without sleep problems. However, there was no article to date demonstrating NASD and all causes of injury.

Autumn had the highest percentage of injuries (27.26%), followed by summer (24.61%) (Table 2). However, in patients with NASD, the spring and summer seasons had the highest risk of injury (adjusted HR= 1.311 and 1.326, respectively) (Table 4). Our results are similar to those in the United States, when more injuries occurred during the summer months and less reported in winter.[10]

In our study, falls and traffic had the highest incidence of 670.26 and 434.07 per 10^5 person-years, respectively. In the NASD patients, the highest risk for injuries was drowning (adjusted HR = 4.760 [95% CI, 4.540–5.012]; $P < .001$), followed by suicide (adjusted HR = 3.184 [95% CI, 3.037–3.339]; $P < .001$) (Table S3, http://links.lww.com/MD/F809).[11–15] Scientists have demonstrated that unintentional gun injuries occur while playing with, handling, loading, unloading, cleaning and firing a gun. It may occur in rural areas without parental supervision or permission and while hunting.[16–23] In addition, scientists have concluded that firearm-related homicide and suicide are associated with the use of crack cocaine and binge drinking, changes in the lethality and types of firearms, and urban poverty in the United States.[16,23,24] However, because firearms are not available in Taiwan, the different patterns of injuries may reflect sociocultural preferences and socioeconomic differences between the 2 regions.[25] We suggest that personal medical problems and mental status may be possible reasons for intentional suicide and homicide in Taiwan.[26] Therefore, we need a more thorough investigation of this explanation for further studies.

The 5 leading causes of nonfatal injuries in the United States are unintentional fall, unintentional stuck by/against, unintentional overexertion, unintentional motor vehicles occupant and unintentional cut/pierce, which unintentional injury are more than intentional injury. Traffic is the most prevalence unintentional injury in Taiwan. This is because of the distracted driving with cellphones, such as sending text messages and email, chatting, and playing mobile games while driving.[27,28] In addition, playing with cell phones right before sleep may cause NASD and increase the risk of injuries during the daytime.

The injuries from accidental poisoning by other solid and liquid substances, gases, and vapors in our study, were similar to those in the United States in *2017 and* were among the high-risk injuries among male and female patients with NASD. These substances included alcohol, cleansing and polishing agents, disinfectants, paints and varnishes,

Table 3

Injury factors by using Cox regression.

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
NASD								
Without	Reference				Reference			
With	1.328	1.268	1.391	<.001	1.296	1.236	1.358	<.001
Gender								
Male	1.094	1.049	1.140	<.001	1.120	1.074	1.168	<.001
Female	Reference				Reference			
Age group (years)								
20–44	Reference				Reference			
45–64	1.001	0.956	1.047	.657	1.081	1.010	1.157	.025
≧65	1.014	0.953	1.080	.986	1.125	1.054	1.202	<.001
DM								
Without	Reference				Reference			
With	1.028	0.881	1.297	.725	1.015	0.961	1.073	.586
HTN								
Without	Reference				Reference			
With	1.766	1.737	1.817	<.001	1.845	1.800	1.892	<.001
Hyperlipidemia								
Without	Reference				Reference			
With	1.310	1.250	1.384	<.001	1.382	1.308	1.474	<.001
CVD								
Without	Reference				Reference			
With	1.614	1.509	1.697	<.001	1.714	1.656	1.776	<.001
Stroke								
Without	Reference				Reference			
With	1.725	1.668	1.788	<.001	1.755	1.694	1.821	<.001
Obesity								
Without	Reference				Reference			
With	0.619	0.258	1.488	.284	0.629	0.261	1.513	.300
Anxiety								
Without	Reference				Reference			
With	1.001	0.772	1.299	.991	1.071	0.748	1.261	.826
Depression								
Without	Reference				Reference			
With	1.196	1.016	1.408	.031	1.160	0.984	1.367	.076
Season								
Spring	Reference				Reference			
Summer	0.941	0.888	0.998	.041	0.953	0.899	1.010	.105
Autumn	0.821	0.775	0.870	<.001	0.818	0.771	0.867	<.001
Winter	0.961	0.906	1.019	.186	0.965	0.910	1.024	.238
Location								
Northern Taiwan	Reference					Multicollinearity with urbanization level		
Middle Taiwan	1.272	1.210	1.338	<.001		Multicollinearity with urbanization level		
Southern Taiwan	1.235	1.171	1.302	<.001		Multicollinearity with urbanization level		
Eastern Taiwan	1.305	1.200	1.418	<.001		Multicollinearity with urbanization level		
Outlet islands	1.066	0.711	1.475	.698		Multicollinearity with urbanization level		
Urbanization level								
1 (highest)	1.128	0.686	1.508	.602	1.155	0.800	1.319	.554
2	1.071	0.769	1.373	.585	1.020	0.869	1.175	.801
3	1.007	0.931	1.090	.853	1.008	0.931	1.091	.849
4 (lowest)	Reference				Reference			
Level of care								
Hospital center	0.619	0.587	0.653	<.001	0.684	0.644	0.726	<.001
Regional hospital	0.683	0.651	0.717	<.001	0.701	0.668	0.737	<.001
Local hospital	Reference				Reference			

Adjusted HR = adjusted variables listed in the table, CI = confidence interval, HR = hazard ratio.
Data are from Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW).

petroleum products, other solvents and their vapors, agricultural and horticultural chemical and pharmaceutical preparations other than plant foods and fertilizers, corrosives and caustics, foodstuffs and poisonous plants, gas distributed by pipeline, and other utility gas and other carbon monoxide (ICD code E860-E869).

Adverse drug effects and accidental poisoning by drugs and medicinal and biological substances are other causes of injuries in Taiwan and the United States due to the inappropriate prescribing for elderly patients without knowing the drug-drug interactions.[2] In contrast, for teenagers and young adults, accidental poisoning by narcotics and hallucinogen overdoses are

Table 4

Injury factors stratified by variables listed in the table by using Cox regression.

	NASD										
	With			Without			With *vs.* Without				
Stratified	Event	PYs	Rate (per 10^5 PYs)	Event	PYs	Rate (per 10^5 PYs)	Ratio	Adjusted HR	95% CI	95% CI	*P*
Total	2446	78,328.06	3,122.76	6738	286,559.40	2351.34	1.328	1.296	1.236	1.358	<.001
Gender											
Male	1347	38,861.68	3,466.14	3991	164,836.85	2421.18	1.432	1.397	1.332	1.464	<.001
Female	1099	39,466.38	2,784.65	2747	121,722.55	2256.77	1.234	1.204	1.148	1.262	<.001
Age group (years)											
20–44	383	9137.29	4,191.61	1349	39,799.81	3389.46	1.237	1.207	1.151	1.265	<.001
45–64	815	26,792.87	3,041.85	2162	91,483.77	2363.26	1.287	1.265	1.198	1.316	<.001
≧65	1248	42,397.90	2,943.54	3227	155,275.82	2078.24	1.416	1.381	1.318	1.448	<.001
DM											
Without	2041	64,358.45	3,171.30	5537	230,527.98	2401.88	1.320	1.288	1.224	1.350	<.001
With	405	13,969.61	2,899.15	1201	56,031.42	2143.44	1.353	1.320	1.259	1.383	<.001
HTN											
Without	1963	60,054.40	3,268.70	5390	218,142.85	2470.86	1.323	1.291	1.231	1.351	<.001
With	483	18,273.66	2,643.15	1348	68,416.55	1970.28	1.342	1.309	1.249	1.372	<.001
Hyperlipidemia											
Without	2424	76,375.69	3,173.78	6672	278,014.05	2399.88	1.322	1.291	1.230	1.342	<.001
With	22	1952.37	1,126.84	66	8545.35	772.35	1.459	1.424	1.358	1.492	<.001
CVD											
Without	2,295	71,075.07	3,228.98	6339	258,441.28	2452.78	1.316	1.284	1.221	1.346	<.001
With	151	7252.99	2,081.90	399	28,118.12	1419.01	1.467	1.432	1.365	1.501	<.001
Stroke											
Without	2282	71,756.39	3,180.20	6280	261,087.73	2405.32	1.322	1.290	1.230	1.351	<.001
With	164	6571.67	2,495.56	458	25,471.67	1798.08	1.388	1.354	1.292	1.491	<.001
Obesity											
Without	2445	78,178.29	3,127.47	6734	286,396.96	2351.28	1.330	1.299	1.238	1.364	<.001
With	1	149.77	667.69	4	162.44	2462.45	0.271	0.304	0.201	0.472	.001
Anxiety											
Without	2410	77,349.34	3,115.73	6,717	285,334.27	2,354.08	1.324	1.292	1.224	1.353	<.001
With	36	978.72	3,678.27	21	1,225.13	1,714.10	2.146	2.094	1.997	2.198	<.001
Depression											
Without	2358	76,101.87	3,098.48	6679	283,937.31	2352.28	1.317	1.284	1.226	1.347	<.001
With	88	2226.19	3,952.94	59	2,622.09	2250.11	1.757	1.726	1.635	1.799	<.001
Season											
Spring	617	18,635.02	3,310.97	1607	65,216.09	2464.12	1.344	1.311	1.251	1.374	<.001
Summer	618	19,172.81	3,223.31	1718	72,435.96	2371.75	1.359	1.326	1.265	1.392	<.001
Autumn	635	22,652.02	2,803.28	1739	80,829.34	2151.45	1.303	1.272	1.213	1.332	<.001
Winter	576	17,868.21	3,223.60	1674	68,078.01	2458.94	1.311	1.279	1.220	1.341	<.001
Urbanization level											
1 (highest)	622	21,755.55	2,859.04	1871	88,777.04	2107.53	1.357	1.324	1.267	1.389	<.001
2	1001	32,454.11	3,084.36	2911	127,062.36	2291.00	1.346	1.314	1.253	1.377	<.001
3	281	7,683.45	3,657.21	598	21,842.45	2737.79	1.336	1.304	1.243	1.360	<.001
4 (lowest)	542	16,434.95	3,297.85	1358	48,877.55	2778.37	1.187	1.158	1.105	1.214	<.001
Level of care											
Hospital center	524	21,643.70	2,421.03	1988	97,040.37	2048.63	1.182	1.153	1.100	1.209	<.001
Regional hospital	1005	35,027.74	2,869.15	2657	122,357.80	2171.50	1.321	1.288	1.230	1.350	<.001
Local hospital	917	21,656.62	4,234.27	2093	67,161.23	3116.38	1.359	1.327	1.267	1.398	<.001

Adjusted HR = adjusted hazard ratio: adjusted for the variables listed in Table 3, CI = confidence interval, PYs = person-years.
Data are from Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW).

the most concerning problems to the public, as they may experience lifelong addiction from these drugs.[29]

There are several possibilities for why NASD were associated with high risk of injuries. First, elderly individuals undergo changes in brain morphology. These changes result in more and shorter REM episodes and less total REM sleep, which result in poor quality of sleep and lower tolerance and threshold to fatigue.[30] Second, compared to elderly people, younger patients have less experience with driving exposure and lower accident rates.[2] Third, elderly people have many comorbidities and more concomitant medications than younger people. Abad et al[31] demonstrated that arthritis-related symptoms and chronic painful physical ailments are the leading causes of sleep problems, such as difficulty in initiating sleep, maintaining sleep continuity, early morning awakenings and non-restorative sleep in individuals aged ≥55 years in the United States. Smolensky et al[2] demonstrated certain classes of drugs and sleep disorders as risk factors for driving incidents. However, non-prescription medications and other medical conditions may also be potential risk factors in road crashes, especially for at-fault drivers ≥65 years of

age. Scientists have demonstrated a list of drugs that are associated with an increased risk for injurious motor vehicle collisions: non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors, antihypertensive drugs, antidepressants,[32] opioid analgesics, benzodiazepines, antihistamines, psychoactive drugs, hypnotics, anxiolytics, beta agonists, and sleep medications.[33–41] However, the neglecting and complexity of the potential adverse effects, doses and drug-drug interactions of the above drugs lead to an increased drowsy-driving risk that the public needs to recognize.

The mechanism of NASD and its association with different types of injuries remain unknown. Scientists have demonstrated that NASD is a disorder associated with the activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis. In addition to melatonin acting as an important sleep-regulating hormone, several regulatory neurotransmitters, such as acetylcholine, serotonin and norepinephrine, control our sleep cycles and daily activities.[42] The changes in the neural activation of sympathetic tone disrupt the daytime and nighttime activity and thus increase the occurrence of various types of injury, as shown in Table S3, http://links.lww.com/MD/F809. In addition, NASD may also be responsible for the dysregulation of mood and even suicide, homicide or abuse, as both mood and sleep cycles are derived from the same monoamine neurotransmitters in brain.[43]

NASD and chronic insomnia may cause dysregulation of the HPA axis because of the frequent negative feedback of stress hormones to the hypothalamus and pituitary gland.[44] Cortisol is an important stress hormone that has wide-ranging effects, such as influencing immunologic status, inflammatory reactions, and arousal and increasing the catabolic properties of proinflammatory cytokines, glucocorticoids and stress peptides.[45] The increased levels of stress hormone in NSAD that are involved in the inflammatory and oxidative pathways affect endothelial function and coagulability in the cardiovascular system, causing delayed healing of wounds and late effects of accidental injury, accidental poisoning and accidental fall.[46,47]

The possible mechanism of NASD and drug metabolism is the cumulative cortisol burden, which can influence the development of metabolic disorders and the catabolic reaction of drugs.[45] Liver cytochrome P450 (CYP) is the key enzyme in the metabolism of xenobiotics and other drugs.[48] Cortisol is a type of human glucocorticoid that also acts as an enzyme inhibitor of hepatic metabolism in xenobiotics.[49] Monostory et al[50] demonstrated that NR3C1, a transcription factor mediates glucocorticoid-responsive genes within regulatory DNA regions and modulates the induction of CYP1A1 and CYP1A2 according to the physiological levels of glucocorticoids in human and rodent cells. Therefore, NASD, which leads to a dysfunctional HPA axis and the production of cortisol, may participate in drug metabolism and cause accidental poisoning by drugs, medicines, biological substances, and other solid and liquid substances, gases, and vapors.

Our study has several limitations. First, the NHIRD database lacks laboratory data, clinical images and information about the lifestyles of the patients. Second, there were no objective measurements of NASD in this study. Therefore, we cannot connect the severity of NASD to the different kinds of injuries. Third, our study only identified patients with sleep disorders who visited the OPD or were hospitalized. However, there are moderate numbers of people who have sleep problems and do not seek medical help. They may have had injuries and added some bias to our study. In conclusion, our study is the largest retrospective study to date discussing the association of NASD with all kinds of injuries by using the NHIRD, which has a large sample size and is capable of longitudinal tracking. NASD has a higher prevalence than obstructive sleep apnea syndrome in the general population, especially in the elderly population. Therefore, the general public should be more aware of this neglected issue of NASD, and healthcare providers should do more to prevent the possibility of all kinds of injuries.

Author contributions

Conceptualization: Feng-Cheng Liu, Je-Ming Hu, I-Duo Wang.
Data curation: Chi-Hsiang Chung, Pei-Yi Tsai, I-Duo Wang, Wu-Chien Chien.
Formal analysis: Zhu Wei Lim, Feng-Cheng Liu, Pei-Yi Tsai, I-Duo Wang, Wu-Chien Chien.
Funding acquisition: Chi-Hsiang Chung, Wu-Chien Chien.
Investigation: Zhu Wei Lim, I-Duo Wang, Wu-Chien Chien.
Methodology: Feng-Cheng Liu, Chi-Hsiang Chung, Je-Ming Hu, Pei-Yi Tsai, Wu-Chien Chien.
Project administration: Zhu Wei Lim, Feng-Cheng Liu, Wu-Chien Chien.
Resources: Wu-Chien Chien.
Software: Chi-Hsiang Chung, Pei-Yi Tsai, Wu-Chien Chien.
Supervision: I-Duo Wang, Wu-Chien Chien.
Validation: Chi-Hsiang Chung, Je-Ming Hu, Pei-Yi Tsai, I-Duo Wang, Wu-Chien Chien.
Visualization: I-Duo Wang.
Writing – original draft: Zhu Wei Lim.
Writing – review & editing: I-Duo Wang, Wu-Chien Chien.

References

[1] Armaou M, Schumacher L, Grunfeld E. Cancer survivors' social context in the return to work process: narrative accounts of social support and social comparison information. J Occup Rehabil 2018;28:504–12.
[2] Smolensky MH, Di Milia L, Ohayon MM, et al. Sleep disorders, medical conditions, and road accident risk. Accid Anal Prev 2011;43:533–48.
[3] Tregear S, Reston J, Schoelles K, et al. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. J Clin Sleep Med 2009;5:573–81.
[4] Sanna A. Obstructive sleep apnoea, motor vehicle accidents, and work performance. Chron Respir Dis 2013;10:29–33.
[5] Lin C-L, Chung C-H, Tsai Y-H, et al. Association between sleep disorders and injury: a nationwide population-based retrospective cohort study. Injury Prevention 2016;22:342–6.
[6] Cheng T-M. Taiwan's National Health Insurance system: high value for the dollar. Six Countries, Six Reform Models: The Health Reform Experience of Israel, the Netherlands, New Zealand, Singapore, Switzerland and Taiwan. Hackensack, NJ: World Scientific; 2009. 171-204.
[7] Wang ID, Chien WC, Chen KJ, et al. Taiwan's health-care system and administration are independent of China. Lancet 2019;394:1515.
[8] Cheng CL, Kao YHY, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20:236–42.
[9] Uehli K, Mehta AJ, Miedinger D, et al. Sleep problems and work injuries: a systematic review and meta-analysis. Sleep Med Rev 2014;18:61–73.
[10] Pierce B. The Seasonal Timing of Work-Related Injuries October 2013.
[11] Cunningham RM, Walton MA, Harrison SR, et al. Past-year intentional and unintentional injury among teens treated in an inner-city emergency department. J Emerg Med 2011;41:418–26.
[12] Cherpitel CJ, Ye Y, Bond J. Attributable risk of injury associated with alcohol use: cross-national data from the emergency room collaborative alcohol analysis project. Am J Public Health 2005;95:266–72.
[13] Swahn MH, Simon TR, Hammig BJ, et al. Alcohol-consumption behaviors and risk for physical fighting and injuries among adolescent drinkers. Addict Behav 2004;29:959–63.

[14] Donovan JE, Jessor R, Costa FM. Syndrome of problem behavior in adolescence: a replication. J Consult Clin Psychol 1988;56:762.
[15] Pickett W, Craig W, Harel Y, et al. Cross-national study of fighting and weapon carrying as determinants of adolescent injury. Pediatrics 2005;116:e855–63.
[16] Frattaroli S, Webster DW, Teret SP. Unintentional gun injuries, firearm design, and prevention: what we know, what we need to know, and what can be done. J Urban Health 2002;79:49–59.
[17] Rushforth NB, Hirsch CS, Ford AB, et al. Accidental firearm fatalities in a metropolitan county (1958-1973). Am J Epidemiol 1974;100: 499–505.
[18] Sinauer N, Annest JL, Mercy JA. Unintentional, nonfatal firearm-related injuries: a preventable public health burden. JAMA 1996;275:1740–3.
[19] Copeland A. Childhood firearms fatalities: the Metropolitan Dade County experience. South Med J 1991;84:175–8.
[20] Carter GL. Accidental firearms fatalities and injuries among recreational hunters. Ann Emerg Med 1989;18:406–9.
[21] Cina SJ, Lariscy CD, McGown ST, et al. Firearm-related hunting fatalities in North Carolina: impact of the'Hunter Orange'Law. Southern Med J 1996;89:395–6.
[22] Cole TB, Patetta MJ. Hunting firearm injuries, North Carolina. Am J Public Health 1988;78:1585–6.
[23] Fingerhut LA, Ingram DD, Feldman JJ. Firearm and nonfirearm homicide among persons 15 through 19 years of age: differences by level of urbanization, United States, 1979 through 1989. JAMA 1992;267:3048–53.
[24] Grossman DC. The history of injury control and the epidemiology of child and adolescent injuries. Future Child 2000;23–52.
[25] Ni H, Barnes P, Hardy A. Recreational injury and its relation to socioeconomic status among school aged children in the US. Injury Prevention 2002;8:60–5.
[26] Liu C-L, Peng L-N, Chen Y-T, et al. Potentially inappropriate prescribing (IP) for elderly medical inpatients in Taiwan: a hospital-based study. Arch Gerontol Geriatr 2012;55:148–51.
[27] Lee LK, Mannix R. Increasing fatality rates from preventable deaths in teenagers and young adults. JAMA 2018;320:543–4.
[28] Hersman DA, Rosekind MR. The road to zero deaths from motor vehicle crashes. JAMA Intern Med 2017;177:1717–8.
[29] Control CfD, Prevention. Prescription opioid overdose data. Injury prevention and control Available at: https://www.cdc.gov/drugoverdose/data/overdose.html Accessed January. 2017; 24.
[30] Tori Hudson N, Bradley Bush N. The Role of Cortisol in Sleep. 2010. in press.
[31] Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. Sleep Med Rev 2008;12:211–28.
[32] Verster JC, Ramaekers JG. Antidepressants and traffic safety. Drugs, Driving Traffic Safety Springer 2009;307–13.
[33] McGwin G, Sims RV, Pulley L, et al. Relations among chronic medical conditions, medications, and automobile crashes in the elderly: a population-based case-control study. Am J Epidemiol 2000;152:424–31.
[34] Coupland C, Hill T, Morriss R, et al. Antidepressant use and risk of adverse outcomes in people aged 20-64 years: cohort study using a primary care database. BMC Med 2018;16:36.
[35] Rudisill TM, Zhu M, Kelley GA, et al. Medication use and the risk of motor vehicle collisions among licensed drivers: a systematic review. Accid Anal Prev 2016;96:255–70.
[36] Borgeat A. Do opioids affect the ability to drive safely? J Pain Palliat Care Pharmacother 2010;24:167–9.
[37] Leung SY. Benzodiazepines, opioids and driving: an overview of the experimental research. Drug Alcohol Rev 2011;30:281–6.
[38] Popescu F-D. H1 antihistamines and driving. J Med Life 2008;1:262–8.
[39] Verster JC, Mets MA. Psychoactive medication and traffic safety. Int J Environ Res Public Health 2009;6:1041–54.
[40] Verster JC, Veldhuijzen DS, Patat A, et al. Hypnotics and driving safety: meta-analyses of randomized controlled trials applying the on-the-road driving test. Curr Drug Saf 2006;1:63–71.
[41] Gunja N. In the Zzz zone: the effects of Z-drugs on human performance and driving. Med Toxicol 2013;9:163–71.
[42] Buysse DJ, Soehner A, Abbott S, et al. Sleep and Sleep–Wake Disorders. Psychiatry 2015;1:1264–310.
[43] Thase ME. Depression and sleep: pathophysiology and treatment. Dialogues Clin Neuroscience 2006;8:217.
[44] Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010;14:19–31.
[45] Stephens MAC, Wand G. Stress and the HPA axi: Role of glucocorticoids in alcohol dependence. Alcohol Res 2012.
[46] Li C-H, Huang K-Y, Chen W-C, et al. Sleep disorders in individuals without sleep apnea increase the risk of peripheral arterial disorder: a nationwide population-based retrospective cohort study. Sleep Med 2015;16:966–70.
[47] Spiegelhalder K, Scholtes C, Riemann D. The association between insomnia and cardiovascular diseases. Nat Sci Sleep 2010;2:71–8.
[48] McDonnell AM, Dang CH. Basic review of the cytochrome p450 system. J Adv Pract Oncol 2013;4:263–8.
[49] Gibson GG, Skett P. Factors affecting drug metabolism: internal factors. In: Introduction to Drug Metabolism Boston, MA: Springer US; 1986. 113-146.
[50] Monostory K, Pascussi J-M, Kóbori L, et al. Hormonal regulation of CYP1A expression. Drug Metab Rev 2009;41:547–72.