Non-apnea sleep disorder and its risk for all kinds of injuries
A 14-year follow-up for a nationwide population-based retrospective study

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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 105 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]
Sleep disorders affect physical activity and psychosocial and performance status. 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. 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. Nonetheless, studies regarding SDs and their correlation with injuries are rare, especially in non-apnea sleep disorder (NASD) patients. Smolensky et al 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, 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. 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 clinical diagnoses according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). 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. 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/brain 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;
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/
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 1

**Study characteristics at baseline.**

| Variables                  | With | Without | Total | With | Without | Total | P   |
|----------------------------|------|---------|-------|------|---------|-------|-----|
| **Gender**                 |      |         |       |      |         |       |     |
| Male                       | 15,425 | 46.40 | 3085 | 46.40 | 12,340 | 46.40 | .999|
| Female                     | 17,815 | 53.60 | 3563 | 53.60 | 14,522 | 53.60 |     |
| **Age (years)**            | 57.27 ± 17.64 | 57.36 ± 17.74 | 57.25 ± 17.61 | .649|
| 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 | 6308 | 96.24 | 26,497 | 99.64 | <.001|
| With                       | 345 | 1.04 | 250 | 3.76 | 95 | 0.36 |     |
| **Depression**             |      |         |       |      |         |       |     |
| Without                    | 32,872 | 98.89 | 6425 | 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 | 7156 | 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 | 28.38 | 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 | 1920 | 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             | 10,644 | 32.62 | 2022 | 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).
Table 2
Study characteristics at the endpoint.

| Variables | Total n | % | With n | % | Without 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 | 6,738     | 25.34 |   |
| Gender    |         |   |        |      |           |    |   |
| Male      | 15,425  | 46.40 | 3085   | 46.40 | 12,340    | 46.40 | .999 |
| Female    | 17,815  | 53.60 | 3,241  | 46.40 | 14,575    | 53.60 |   |
| Age (years) | 68.85 ± 19.94 | | 68.14 ± 19.25 | | 69.03 ± 20.11 | | .001 |
| Age group (years) |   | |     | |   |    |   |
| 20–44     | 6,170   | 18.56 | 1,036  | 15.58 | 5,134     | 19.31 | <.001 |
| 45–64     | 11,242  | 33.82 | 2,330  | 35.05 | 8,912     | 33.51 |   |
| ≥65       | 15,828  | 47.62 | 3,282  | 49.37 | 12,546    | 47.18 |   |
| DM        |         |   |        |      |           |    |   |
| Without   | 27,969  | 84.14 | 5,496  | 82.67 | 22,473    | 84.51 | <.001 |
| With      | 5,271   | 15.86 | 1,152  | 17.33 | 4,119     | 15.49 |   |
| HTN       |         |   |        |      |           |    |   |
| Without   | 27,505  | 82.75 | 5,401  | 81.24 | 22,104    | 83.12 | <.001 |
| With      | 7,424   | 17.25 | 1,247  | 18.76 | 6,177     | 16.88 |   |
| Hyperlipidemia |   | |     | |   |    |   |
| Without   | 32,562  | 97.96 | 6,498  | 97.74 | 26,064    | 98.01 | .174 |
| With      | 678     | 2.04  | 150    | 2.26  | 528       | 1.99  |   |
| CVD       |         |   |        |      |           |    |   |
| Without   | 30,433  | 91.56 | 6,016  | 90.49 | 24,417    | 91.82 | .001 |
| With      | 2,807   | 8.44  | 632    | 9.51  | 2,175     | 8.18  |   |
| Stroke    |         |   |        |      |           |    |   |
| Without   | 30,526  | 91.84 | 6,104  | 91.82 | 24,422    | 91.84 | .062 |
| With      | 2,714   | 8.16  | 544    | 8.18  | 2,170     | 8.16  |   |
| Obesity   |         |   |        |      |           |    |   |
| Without   | 33,219  | 99.94 | 6,641  | 99.89 | 26,578    | 99.95 | .166 |
| With      | 21      | 0.06  | 7      | 0.11  | 14        | 0.05  |   |
| Anxiety   |         |   |        |      |           |    |   |
| Without   | 33,018  | 99.33 | 6,524  | 98.13 | 26,494    | 99.63 | <.001 |
| With      | 222     | 0.67  | 124    | 1.87  | 98        | 0.37  |   |
| Depression|         |   |        |      |           |    |   |
| Without   | 32,865  | 98.87 | 6,441  | 96.89 | 26,424    | 99.37 | <.001 |
| With      | 375     | 1.13  | 207    | 3.11  | 168       | 0.63  |   |
| Season    |         |   |        |      |           |    |   |
| Spring    | 8,168   | 24.57 | 1,624  | 24.43 | 6,544     | 24.61 | .072 |
| Summer    | 8,279   | 24.91 | 1,636  | 24.61 | 6,643     | 24.98 |   |
| Autumn    | 8,659   | 26.05 | 1,812  | 27.26 | 6,847     | 25.75 |   |
| Winter    | 8,134   | 24.47 | 1,576  | 23.71 | 6,558     | 24.66 |   |
| Location  |         |   |        |      |           |    |   |
| Northern Taiwan | 12,750 | 38.36 | 1,976  | 36.42 | 10,774    | 38.02 | <.001 |
| Middle Taiwan | 9,904  | 29.80 | 2,401  | 36.12 | 7,503     | 28.22 |   |
| Southern Taiwan | 8,459  | 25.45 | 1,786  | 26.87 | 6,673     | 25.09 |   |
| Eastern Taiwan | 1,991  | 5.99  | 452    | 6.80  | 1,539     | 5.79  |   |
| Outlet islands | 1,36   | 0.41  | 33     | 0.50  | 103       | 0.39  |   |
| Urbanization level |   | |     | |   |    |   |
| 1 (highest) | 10,743 | 32.32 | 1,841  | 27.69 | 8,902     | 32.48 | <.001 |
| 2         | 14,429  | 43.41 | 2,767  | 41.62 | 11,662    | 43.86 |   |
| 3         | 2,641   | 7.95  | 708    | 10.65 | 1,933     | 7.27  |   |
| 4 (lowest) | 5,427  | 16.33 | 1,332  | 20.04 | 4,095     | 15.40 |   |
| Level of care |   | |     | |   |    |   |
| Hospital center | 11,201 | 33.70 | 1,764  | 26.53 | 9,437     | 35.49 | <.001 |
| Regional hospital | 12,866 | 38.71 | 2,720  | 40.91 | 10,146    | 38.15 |   |
| Local hospital | 9,173  | 27.60 | 2,164  | 32.55 | 7,009     | 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).
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. Uehli et al. 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.

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). 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. 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. However, because firearms are not available in Taiwan, the different patterns of injuries may reflect sociocultural preferences and socioeconomic differences between the 2 regions. We suggest that personal medical problems and mental status may be possible reasons for intentional suicide and homicide in Taiwan. 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 struck 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. 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,
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...
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. Second, compared to elderly people, younger patients have less experience with driving exposure and lower accident rates. 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 ≥65 years in the United States. Smolensky et al[29] 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.

### Table 4
Injury factors stratified by variables listed in the table by using Cox regression.

| Stratified | With | Without | With vs. Without |
|------------|------|---------|-----------------|
| Total      | 2446 | 78,328.06 | 2351.34 | 1.328 | 1.296 | 1.236 | 1.358 |
| Gender     |      |          |        |        |        |        |        |
| Male       | 1347 | 38,861.68 | 3,466.14 | 2421.18 | 1.432 | 1.397 | 1.332 | 1.464 |
| Female     | 1099 | 39,466.38 | 2,784.65 | 2256.77 | 1.234 | 1.204 | 1.148 | 1.262 |
| Age group (years) |      |          |        |        |        |        |        |
| 20–44      | 383  | 91,379.29 | 4,191.61 | 3389.46 | 1.237 | 1.207 | 1.151 | 1.265 |
| 45–64      | 815  | 26,792.87 | 3,041.85 | 2363.26 | 1.287 | 1.265 | 1.198 | 1.316 |
| ≥65        | 1248 | 42,397.90 | 2,943.54 | 2078.24 | 1.416 | 1.381 | 1.318 | 1.448 |
| DM         |      |          |        |        |        |        |        |
| Without    | 2041 | 64,358.45 | 3,171.30 | 2401.88 | 1.353 | 1.320 | 1.259 | 1.383 |
| With       | 405  | 13,969.61 | 2,899.15 | 2143.44 | 1.353 | 1.320 | 1.259 | 1.383 |
| HTN        |      |          |        |        |        |        |        |
| Without    | 1963 | 60,054.40 | 3,268.70 | 2470.86 | 1.323 | 1.291 | 1.231 | 1.351 |
| With       | 483  | 18,273.66 | 2,643.15 | 1970.28 | 1.349 | 1.319 | 1.249 | 1.372 |
| Hyperlipidemia |      |          |        |        |        |        |        |
| Without    | 2424 | 76,375.69 | 3,173.78 | 2399.88 | 1.322 | 1.291 | 1.230 | 1.342 |
| With       | 22   | 1952.37   | 1,126.84 | 772.35  | 1.459 | 1.424 | 1.358 | 1.492 |
| Stroke     |      |          |        |        |        |        |        |
| Without    | 2282 | 71,756.39 | 3,180.20 | 2911    | 1.357 | 1.324 | 1.265 | 1.392 |
| With       | 149  | 2226.19   | 3,952.94 | 2291.00 | 1.757 | 1.726 | 1.635 | 1.799 |
| Obesity    |      |          |        |        |        |        |        |
| Without    | 2445 | 76,101.87 | 3,175.30 | 2399.88 | 1.322 | 1.291 | 1.230 | 1.342 |
| With       | 1    | 149.77    | 667.69  | 1419.01 | 1.467 | 1.432 | 1.365 | 1.501 |
| Anxiety    |      |          |        |        |        |        |        |
| Without    | 2410 | 77,349.34 | 3,115.73 | 2354.08 | 1.324 | 1.292 | 1.224 | 1.353 |
| With       | 36   | 978.72    | 3,678.27 | 2146    | 2.146 | 2.094 | 1.997 | 2.198 |
| Depression |      |          |        |        |        |        |        |
| Without    | 2358 | 76,101.87 | 3,098.48 | 2352.28 | 1.317 | 1.284 | 1.226 | 1.347 |
| With       | 88   | 2226.19   | 3,952.94 | 2291.00 | 1.757 | 1.726 | 1.635 | 1.799 |
| Season     |      |          |        |        |        |        |        |
| Spring     | 617  | 18,635.02 | 3,310.97 | 2464.12 | 1.344 | 1.311 | 1.251 | 1.374 |
| Summer     | 618  | 19,172.81 | 3,223.31 | 2371.75 | 1.359 | 1.326 | 1.265 | 1.392 |
| Autumn     | 635  | 22,652.02 | 2,803.28 | 2151.45 | 1.303 | 1.272 | 1.213 | 1.332 |
| Winter     | 576  | 17,868.21 | 3,223.60 | 2458.94 | 1.311 | 1.279 | 1.220 | 1.341 |
| Urbanization level |      |          |        |        |        |        |        |
| 1 (highest) | 622  | 21,755.56 | 2,859.04 | 2107.53 | 1.357 | 1.324 | 1.267 | 1.389 |
| 2          | 1001 | 32,454.11 | 3,084.11 | 2291.00 | 1.346 | 1.314 | 1.253 | 1.377 |
| 3          | 281  | 7,683.45  | 3,657.21 | 2737.79 | 1.336 | 1.304 | 1.243 | 1.360 |
| 4 (lowest) | 542  | 14,434.96 | 3,297.85 | 2778.37 | 1.187 | 1.158 | 1.105 | 1.214 |
| Level of care |      |          |        |        |        |        |        |
| Hospital center | 524  | 21,643.70 | 2,421.03 | 2048.63 | 1.182 | 1.153 | 1.100 | 1.209 |
| Regional hospital | 1005 | 35,027.74 | 2,869.15 | 2171.50 | 1.321 | 1.288 | 1.230 | 1.350 |
| Local hospital | 917  | 21,656.62 | 4,234.27 | 3161.38 | 1.359 | 1.327 | 1.267 | 1.398 |

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).
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,[10–12] opioid analgesics, benzodiazepines, antihistamines, psychoactive drugs, hypnotics, anxiolytics, beta agonists, and sleep medications. However, the neglecting and complexity of the potential adverse effects, doses and 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 immunomodulatory status, inflammatory reactions, and arousing and increasing the catabolic properties of proinflammatory cytokines, glucocorticoids and stress peptides.[45] The increased levels of stress hormone in NASD 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.

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