

SCIENTIFIC INVESTIGATIONS

Narcolepsy and risk of traumatic injury: a population-based matched cohort study

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Study Objectives: We evaluated the risk of traumatic injury in patients with narcolepsy compared to the general population.

Methods: We conducted a population-based matched cohort study using a Japanese health insurance claims database. For each patient with narcolepsy, up to 5 individuals from the general population without narcolepsy were matched by variables such as sex, age, and cohort entry month. The primary outcome was traumatic injury, and the secondary outcome was fracture. The study population was followed for up to 5 years from the cohort entry date. We estimated crude incidence rates, adjusted incidence rate differences, adjusted hazard ratios, and their 95% confidence intervals (CIs) for study outcomes using crude and multivariable Poisson and Cox regression models.

Results: We included 2,451 patients with narcolepsy (mean age, 30.3 years; male, 58.0%) and 10,591 matched individuals (mean age, 30.6 years; male, 58.4%). Crude incidence rate of traumatic injury was 11.4 per 100 person-years for patients with narcolepsy compared with 6.2 per 100 person-years for matched individuals (adjusted incidence rate difference, 6.2 excess events per 100 person-years [95% CI, 4.9–7.4]; adjusted hazard ratio, 1.8 [95% CI, 1.5–2.2]). Crude incidence rate of fracture was 2.3 per 100 person-years for patients with narcolepsy compared with 1.3 per 100 person-years for matched individuals (adjusted incidence rate difference, 1.2 excess events per 100 person-years [95% CI, 0.7–1.7]; adjusted hazard ratio, 1.7 [95% CI, 1.4–2.1]).

Conclusions: Narcolepsy was associated with increased risk of traumatic injury. For patients with narcolepsy, optimized approaches to injury prevention should be considered.

Keywords: narcolepsy, traumatic injury, fracture

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous studies suggested injuries are more frequent in patients with narcolepsy despite shortcomings of limited sample sizes, left truncation bias, and selection bias. We designed a matched cohort study to address the concerns and brought direct evidence of injury risk associated with narcolepsy in the Japanese population.

Study Impact: Our study addressed methodological biases in previous studies and demonstrated the risk of traumatic injury is higher in patients with narcolepsy than in the general population. Optimized approaches to injury prevention in patients with narcolepsy are needed.

INTRODUCTION

Narcolepsy is a rare, chronic neurological disorder characterized by excessive daytime sleepiness (EDS), cataplexy, hallucinations, sleep paralysis, and disturbed nighttime sleep.^{1,2} The estimated prevalence of narcolepsy is highest in Japan, at 1,600 per million, compared with 200–500 per million in Europe and North America,² but exact numbers remain unknown due to differences in methodologies and disease definitions across studies. Age at onset exhibits a bimodal pattern, peaking in adolescence and again in the 30s.³

Traumatic injuries, sometimes fatal, are more frequent in patients with narcolepsy than in the general population, possibly due to EDS or cataplexy. These findings, mainly from Danish and US descriptive studies,^{4–7} have also recently been observed in two Taiwanese cohort studies that adjusted for confounding.^{8,9}

However, the Taiwanese studies had 4 shortcomings: (1) the relatively small number of patients with narcolepsy, at less than 500; (2) limitation of outcomes to motor vehicle accident injuries and fractures; (3) introduction of left truncation bias in patients with narcolepsy due to the setting of cohort entry as the date of the third visit for narcolepsy^{8,10}; and (4) selection bias from differential loss to follow-up due to the restriction of patients with narcolepsy to those with multiple medical visits after cohort entry, vs no such restriction for general population comparators.^{9,11}

Here, to better understand the risk of traumatic injury in patients with narcolepsy compared to the general population, we compared the risk of all types of traumatic injury requiring medical visits in 2,451 patients with narcolepsy and 10,591 matched general population comparators in Japan, which has the highest prevalence of narcolepsy worldwide, while addressing the aforementioned biases.

METHODS

Study design and data source

In this matched cohort study,¹² we used a Japanese health insurance claims database maintained by JMDC Inc., from January 1, 2005, through October 31, 2021.^{13–16} This database compiles claims data from health insurance societies for company employees and their dependents aged <75 years in Japan.¹³ As of March 2021, the database covered approximately 12 million individuals, which is about 10% of the entire population in Japan.¹⁷ The database contains anonymized information on demographics, diagnoses, medical procedures, and pharmacy dispensing. The study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (No. R3431). Informed consent from patients was not deemed necessary because the study used anonymized data.

Study population

Patients with narcolepsy were defined as having ≥ 2 medical claims for narcolepsy. The date of first diagnosis of narcolepsy was set as the cohort entry date and was required to be between April 1, 2012, and May 4, 2021 (180 days before October 31, 2021). Entry after April 1, 2012, was set because claims data in the national health insurance reimbursement scheme in Japan lacked information on dates before March 31, 2012. Eligible patients were required to have at least 180 days of continuous enrollment in the database before cohort entry. We excluded patients with a history of traumatic injury, intentional self-harm, mental retardation, dementia, and mental and behavioral disorders due to psychoactive substance use within 180 days prior to cohort entry, or a secondary malignant neoplasm of bone and bone marrow prior to cohort entry or during follow-up. Details of the inclusion and exclusion criteria are shown in **Table S1** in the supplemental material.

For each patient with narcolepsy, up to 5 individuals without narcolepsy were randomly selected from the general population and matched with replacement by sex, age, cohort entry month,

number of beds in the medical facility visited at the cohort entry date, and number of outpatient visits within 180 days before the cohort entry date. The number of beds in the facility visited is indicative of the facility size and reflects the severity and complexity of the patient conditions. Matched individuals from the general population were required to be enrolled in the database at least until the date of the second claim for narcolepsy for their corresponding patient with narcolepsy to avoid selection bias from differential loss to follow-up.¹¹ Matched individuals were subject to the same exclusion criteria as patients with narcolepsy.

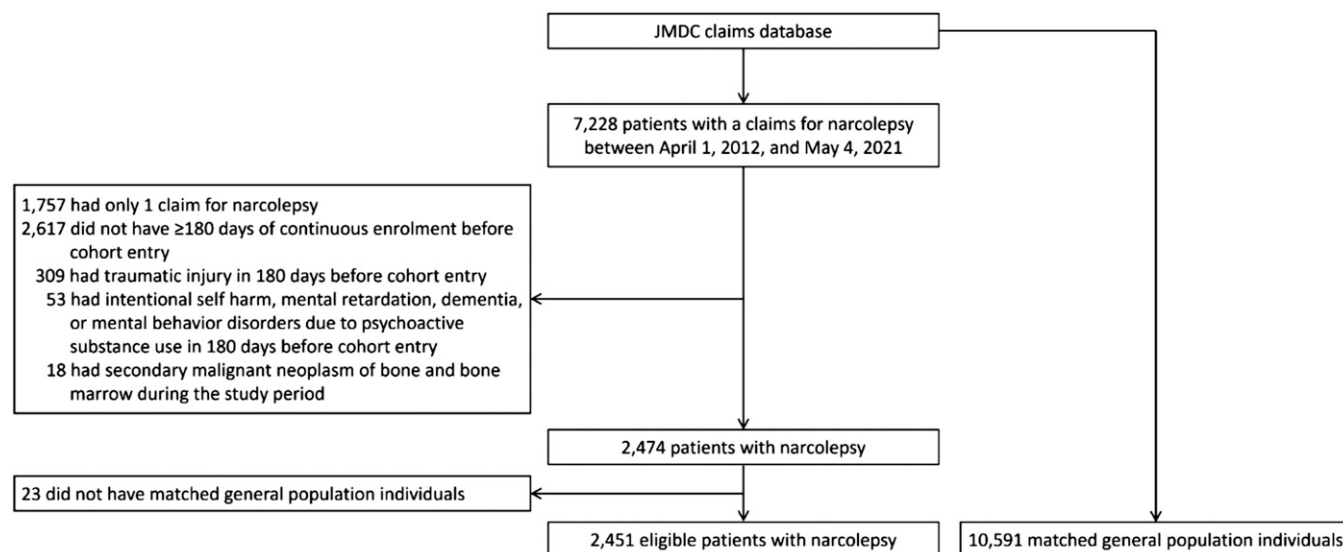
Outcomes and follow-up

The primary outcome was traumatic injury, and the secondary outcome was fracture (**Table S2** in the supplemental material).¹⁸ Fracture was defined by claims with a combination of *International Classification of Diseases, 10th revision* (ICD-10) codes and radiographic examination codes. Traumatic injuries other than fractures were defined by claims with only ICD-10 codes. Study population individuals were followed for up to 5 years from their cohort entry date until occurrence of the study outcome, death, disenrollment, or end of the study period (October 31, 2021), whichever occurred first. Separate follow-up was conducted for primary and secondary outcomes.

Patients' characteristics

Baseline patients' characteristics included (1) demographics (age and sex); (2) number of beds in the medical facility visited at cohort entry date; (3) number of outpatient visits as a proxy for intensity of care, overall disease state, and surveillance; (4) comorbidities (attention-deficit/hyperactivity disorder, autism spectrum disorder, depression, insomnia, anxiety disorder, schizophrenia, hypertension, diabetes); and (5) medication use considered to be associated with fall-related injuries (antidepressants, hypnotics, anxiolytics, antipsychotics, antiepileptics) (**Table S3** in the supplemental material).^{8,19,20}

Figure 1—Flowchart of data collection in the study.



Statistical analysis

Covariate imbalance at baseline between patients with narcolepsy and matched general population individuals was assessed using standardized mean differences, with values >0.2 considered significantly different. We estimated crude incidence rates, adjusted incidence rate differences (aIRDs), adjusted hazard ratios (aHRs), and their 95% confidence intervals (CIs) for study outcomes using Poisson and Cox regression models. Further, we estimated direct adjusted cumulative incidence curves with Cox regression models.²¹ The adjusted models included the matching factors and covariates (attention-deficit/hyperactivity disorder and medication use of antidepressants, hypnotics, anxiolytics, antipsychotics, and antiepileptics).^{8,19,22,23} Comorbidities that are relevant to the comedication use were not included in models to avoid overadjustment.

The robustness of the primary findings was examined with a sensitivity analysis that used a more specific definition of narcolepsy, namely the inclusion of at least 1 claim for polysomnography or multiple sleep latency testing for patients with narcolepsy in addition to the eligibility criteria above (Table S1).²⁴

All statistical analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, North Carolina) and R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

We included 2,451 patients with narcolepsy (mean age, 30.3 years; male, 58.0%) and 10,591 matched individuals from the general population (mean age, 30.6 years; male, 58.4%) (Figure 1 and Table 1). Median follow-up for the primary outcome was 1.9 years (interquartile range, 0.9–3.5) for patients with narcolepsy and 2.5 years (interquartile range, 1.3–4.3) for matched individuals (Table S4 in the supplemental material). The following characteristics were more prevalent in the patients than in the matched individuals: attention-deficit/hyperactivity disorder (7.8% vs 1.6%), depression (37.4% vs 9.3%), insomnia (30.2% vs 9.7%), anxiety disorder (10.5% vs 4.1%), schizophrenia (10.1% vs 3.6%), medication use of antidepressants (23.1% vs 7.3%),

Table 1—Baseline characteristics of patients with narcolepsy and matched individuals.

Characteristics	Narcolepsy (n = 2,451)	General Population (n = 10,591)	SMD
Male, n (%)	1,421 (58.0%)	6,189 (58.4%)	0.009
Age (years), mean (SD)	30.3 (13.8)	30.6 (13.8)	0.024
No. of beds in the medical facility visited at cohort entry date, n (%)			0.023
0–19	1,618 (66.0%)	7,103 (67.1%)	
20–99	28 (1.1%)	121 (1.1%)	
100–199	139 (5.7%)	594 (5.6%)	
200–299	102 (4.2%)	422 (4.0%)	
300–499	182 (7.4%)	757 (7.1%)	
500+	382 (15.6%)	1,594 (15.1%)	
No. of outpatient visits, mean (SD)	7.4 (6.6)	7.5 (6.8)	0.021
Comorbidities, n (%)			
ADHD	192 (7.8%)	172 (1.6%)	0.296
ASD	83 (3.4%)	200 (1.9%)	0.094
Depression	917 (37.4%)	982 (9.3%)	0.705
Insomnia	741 (30.2%)	1,026 (9.7%)	0.532
Anxiety disorder	258 (10.5%)	437 (4.1%)	0.247
Schizophrenia	247 (10.1%)	380 (3.6%)	0.259
Hypertension	141 (5.8%)	910 (8.6%)	0.110
Diabetes	43 (1.8%)	393 (3.7%)	0.120
Medication use, n (%)			
Antidepressants	565 (23.1%)	770 (7.3%)	0.451
Hypnotics	642 (26.2%)	955 (9.0%)	0.463
Anxiolytics	488 (19.9%)	1,005 (9.5%)	0.298
Antipsychotics	467 (19.1%)	665 (6.3%)	0.391
Antiepileptics	264 (10.8%)	522 (4.9%)	0.219

ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, SD = standard deviation, SMD = standardized mean difference.

hypnotics (26.2% vs 9.0%), anxiolytics (19.9% vs 9.5%), antipsychotics (19.1% vs 6.3%), and antiepileptics (10.8% vs 4.9%).

Risk of traumatic injury

A total of 627 patients with narcolepsy experienced a traumatic injury (11.4 events per 100 person-years), compared with 1,789 matched general population individuals (6.2 events per 100 person-years) (aIRD, 6.2 excess events per 100 person-years [95% CI, 4.9–7.4]; aHR, 1.8 [95% CI, 1.5–2.2]; **Table 2**). A total of 155 patients with narcolepsy had a fracture (2.3 events per 100 person-years) compared with 417 matched individuals (1.3 events per 100 person-years) (aIRD, 1.2 excess events per 100 person-years [95% CI, 0.7–1.7]; aHR, 1.7 [95% CI, 1.4–2.1]). The time courses of traumatic injury and fracture are shown in **Figure 2**.

Sensitivity analysis

When the definition was changed to narcolepsy with at least 1 claim for polysomnography or multiple sleep latency testing, the baseline characteristics were similar to the results in the main analysis (**Table S5** in the supplemental material). A total of 354 out of 1,377 patients with narcolepsy experienced a traumatic injury (11.2 events per 100 person-years), compared with 974 among 5,898 matched general population individuals (6.0 events per 100 person-years) (aIRD, 6.1 excess events per 100 person-years [95% CI, 4.2–7.9]; aHR, 1.8 [95% CI, 1.6–2.1]; **Table 2**). In addition, 77 patients with narcolepsy had a fracture (2.1 events per 100 person-years) compared with 219 matched individuals (1.2 events per 100 person-years) (aIRD, 1.1 excess events per 100 person-years [95% CI, 0.3–1.9]; aHR, 1.6 [95% CI, 1.2–2.1]). The time courses of traumatic injury and fracture

were similar to the results in the main analysis (**Figure S1** in the supplemental material).

DISCUSSION

In this population-based matched cohort study, patients with narcolepsy had an increase in absolute risk of 6.2 and 1.2 for excess traumatic injury and fracture events per 100 person-years compared to matched individuals from a general population. The findings were shown to be robust in a sensitivity analysis with a more rigorous definition of narcolepsy.

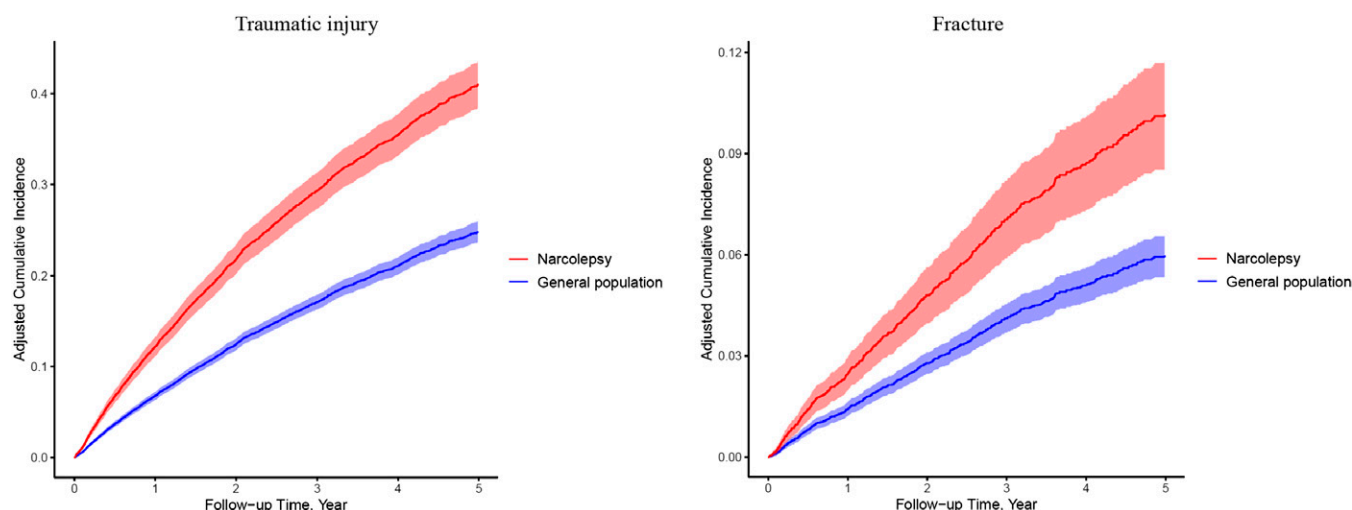
The prevalence of insomnia and the medication use of hypnotics was observed higher in patients with narcolepsy. This is because hypnotics are typically prescribed as second-line treatment for disrupted nighttime sleep in patients with narcolepsy and it is common practice to document insomnia in claims records as associated insurance disease names.^{3,25} This practice likely explains the higher prevalences of insomnia noted in our study, which is consistent with a previous study using claims data.²⁰

EDS and cataplexy are plausible as underlying mechanisms to explain the increased risk of traumatic injury in patients with narcolepsy. EDS, as the main clinical manifestation of narcolepsy, impairs a patient's wakefulness and cognitive attention during the daytime.² Cataplexy is a pathognomonic symptom of narcolepsy type 1, characterized by sudden loss of muscle tone while maintaining consciousness.² These findings of elevated risk of traumatic injury and fracture events in narcolepsy are consistent with 2 Taiwanese cohort studies.^{10,26} However, our study is likely more robust because (1) it included approximately 5 times more

Table 2—Crude incidence rates, adjusted incidence rate differences, and adjusted hazard ratios for study outcomes.

Analyses	Patients, n	Person-years, n	Events, n	Crude IR per 100 person-years (95% CI)	aIRD per 100 person-years (95% CI)*	aHR per 100 person-years (95% CI)*
Main analysis						
Traumatic injury						
Narcolepsy	2,451	5,490	627	11.4 (10.5–12.4)	6.2 (4.9–7.4)	1.8 (1.5–2.2)
General population	10,591	29,011	1,789	6.2 (5.9–6.5)	Reference	Reference
Fracture						
Narcolepsy	2,451	6,510	155	2.3 (2.0–2.7)	1.2 (0.7–1.7)	1.7 (1.4–2.1)
General population	10,591	31,733	417	1.3 (1.2–1.4)	Reference	Reference
Sensitivity analysis†						
Traumatic injury						
Narcolepsy	1,377	3,162	354	11.2 (10.1–12.4)	6.1 (4.2–7.9)	1.8 (1.6–2.1)
General population	5,898	16,219	974	6.0 (5.6–6.4)	Reference	Reference
Fracture						
Narcolepsy	1,377	3,752	77	2.1 (1.6–2.6)	1.1 (0.3–1.9)	1.6 (1.2–2.1)
General population	5,898	17,689	219	1.2 (1.1–1.4)	Reference	Reference

*Adjusted for matching factors (sex, age, cohort entry month, number of beds in the medical facility visited at the cohort entry date, and number of outpatient visits within 180 days before the cohort entry date); attention-deficit/hyperactivity disorder; and medication use of antiepileptics, antipsychotics, anxiolytics, hypnotics, and antidepressants. †Restricted to patients with narcolepsy with at least 1 claim record for polysomnography or a multiple sleep latency test. aHR = adjusted hazard ratio, aIRD = adjusted incidence rate difference, CI = confidence interval, IR = incidence rate.

Figure 2—Adjusted cumulative incidence of traumatic injury and fracture in patients with narcolepsy and matched individuals.

Adjusted for matching factors (sex, age, cohort entry month, number of beds in the medical facility visited at the cohort entry date, and number of outpatient visits within 180 days before the cohort entry date); attention-deficit/hyperactivity disorder; and medication use of antidepressants, hypnotics, anxiolytics, antipsychotics, and antiepileptics.

patients with narcolepsy than these previous studies, (2) it examined all types of traumatic injury requiring medical visits, and (3) it addressed the left truncation bias and potential selection bias from differential loss to follow-up occurring in the previous studies.¹⁰

In most patients with narcolepsy, optimal control can be achieved only with a combination of pharmacological (eg, stimulants) and nonpharmacological (eg, regular night sleep and scheduled napping) approaches.^{2,3} However, to our knowledge, no studies have yet shown that these treatments reduce traumatic injuries in patients with narcolepsy. Two Taiwanese cohort studies that compared patients with narcolepsy who used stimulants with those who did not suggested that stimulant use may reduce motor vehicle accident injuries and showed lower incidence rates in fractures^{8,9}; however, these studies were hampered by the following factors: (1) Setting time zero in stimulant users before treatment assignment introduced immortal time bias^{10,26} and (2) patient characteristics likely differed between stimulant users and nonusers.²⁷ We are currently conducting a self-controlled case series study to examine the impact of stimulant use on the frequency of traumatic injuries that addresses these biases.^{28,29}

Our study has 4 limitations. First, potential misclassification of narcolepsy may have occurred due to the reliance on ICD-10 codes in the claims data. However, we improved the specificity of the disease definition by restricting the main analysis to patients with at least 2 claims for narcolepsy and further restricted the sensitivity analysis to patients with at least 1 claim for polysomnography or multiple sleep latency testing.⁹ In claims databases, polysomnography or multiple sleep latency testing is confirmed by the claim of medical procedure rather than detailed test results in medical records. Second, the 2 subtypes of narcolepsy, type 1 and type 2, share most of the same EDS symptoms, but cataplexy occurs only in narcolepsy type 1.² The ICD-10-based diagnosis did not differentiate between narcolepsy subtypes, which prevents further subgroup

analysis. These limitations are acknowledged in previous studies using claims databases.^{8,9,24} Despite these limitations, we believe our study contributes valuable insights into the long-term consequences of patients with narcolepsy considering the limited available evidence nowadays due to the rarity of the disease. Third, despite our efforts to adjust for a rich set of covariates, we cannot preclude the possibility of unmeasured confounding factors, such as lifestyle, physical activity, and socioeconomic status. Finally, the results of this Japanese study may not be transportable to other populations due to differences in health care systems, cultural practices, genetic factors, and lifestyle choices.

CONCLUSIONS

We found an increased risk of traumatic injury, including fractures, in patients with narcolepsy compared with the general population. Development of an optimized approach to injury prevention in patients with narcolepsy is desirable.

ABBREVIATIONS

aHR, adjusted hazard ratio
aIRD, adjusted incidence rate difference
CI, confidence interval
EDS, excessive daytime sleepiness
ICD, *International Classification of Diseases*

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DISCLOSURE STATEMENT

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