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RESEARCH ARTICLE

The effect of sleep disorders on dementia risk in patients with traumatic brain injury: A large-scale cohort study

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Abstract

Introduction: We investigated the association between sleep disorders (SDs) and incident dementia in adults with traumatic brain injury (TBI).

Methods: Adults with a TBI between 2003 and 2013 were followed until incident dementia. Sleep disorders at TBI were predictors in Cox regression models, controlling for other dementia risks.

Results: Over 52 months, 4.6% of the 712,708 adults (59% male, median age 44, <1% with SD) developed dementia. An SD was associated with a 26% and a 23% of increased risk of dementia in male and female participants (hazard ratio [HR] 1.26, 95% confidence interval [CI] 1.11–1.42 and HR 1.23, 95% CI 1.09–1.40, respectively). In male participants, SD was associated with a 93% increased risk of early-onset dementia (HR 1.93, 95% CI 1.29–2.87); this did not hold in female participants (HR 1.38, 95% CI 0.78–2.44).

Discussion: In a province-wide cohort, SDs at TBI were independently associated with incident dementia. Clinical trials testing sex-specific SD care after TBI for dementia prevention are timely.

KEYWORDS
cognitive decline, comorbidity, concussion, insomnia, parasomnia, sex differences, sleep-related breathing disorder

Highlights

- TBI and sleep disorders are linked to each other, and to dementia.
- It is unclear if sleep disorders pose a sex-specific dementia risk in brain injury.
- In this study, presence of a sleep disorder increased dementia risk in both sexes.
- The risk differed by type of sleep disorder, which differed between the sexes.
- Sleep disorder awareness and care in persons with brain injury is vital for dementia prevention.

1 | BACKGROUND

Traumatic brain injury (TBI) has an extremely high incidence and a vast array of associated pathological brain changes, positioning this injury among the most important causes of neurodegeneration and cognitive impairment.[1] Sleep disorders (SDs) are common in TBI[2] and have long been connected to adverse cognitive outcomes.[3] In the general population, certain categories of SDs, including sleep-related breathing disorders (SRBDs), insomnia disorder, and rapid eye movement sleep behavior disorder, have been implicated as risk factors for dementia.[4] Research on the impact of such SDs in persons with TBI, particularly its potential role in the development of dementia, is inconsistent. Some studies observe an association between SDs and dementia incidence[5–7] and others not,[8,9] bringing into question the existence of a direct association.

Also unclear is whether the potential SD–dementia association in individuals with TBI is relevant to both younger and older persons, and whether the risk applies to both sexes. Because of low dementia incidence in TBI, most studies to date have pooled all severities of TBI, all SDs, and both sexes, to increase statistical power.[5,7–9] This approach can dilute the associations of SDs with incident dementia: for example, certain TBI severities can be more or less susceptible to intermittent hypoxia (as in SRBDs), insufficient sleep duration (as in insomnia disorder), and/or sleep fragmentation (any sleep disorder). In addition, there can be differences between male and female patients in the degree of susceptibility to these disorders: for example, it is recognized that SRBD is more common in males and insomnia in females.[10]

Previous studies exploring the SD–dementia association in TBI have also been limited by inadequate control for other potential dementia risk factors, such as cardiovascular disorders, obesity, and smoking status, among other factors.[5,7–9] Our previous study involving a large cohort of adults with TBI, observed an association between the presence of a SD and incident dementia after controlling for known dementia risks (e.g., cardiovascular pathology, depression, and other risks factors)[6]; however, the results were limited by study of all sleep disorders that posed a risk together and across ages, making it unclear where the risk remains the same in younger and older persons with TBI. Thus there is a need for more robust data analyses to circumvent the issues observed previously, and a more comprehensive approach to the study of the SD–dementia association is warranted in the TBI population, to bolster preventive efforts and resource allocation.

We conducted a population-based cohort study of adult males and females with TBI to examine the association between different categories of SDs at the time of injury and incident dementia (all subtypes), controlling for known dementia risk factors. We hypothesized that intermittent hypoxemia and sleep fragmentation in SRBDs, and insufficient sleep in insomnia disorder, categories of SDs that are disproportionally distributed between the sexes, would be associated with risk of dementia in a sex-specific manner (Figure 1).

RESEARCH IN CONTEXT

1. **Systematic Review**: Research on the link between sleep disorders (SDs) and dementia in persons with traumatic brain injury (TBI) is inconclusive. Many studies do not stratify their results by sex, age, category of SD, or severity of TBI, presenting a significant gap in the research.
2. **Interpretation**: We studied 712,708 adults admitted to a publicly funded health care system with a diagnosis of TBI, of whom less than 1% had a recorded SD diagnosis at the time of injury. We observed that presence of a SD increased the risk of new dementia onset. The risk differed between the sexes and according to category of SD, age at time of injury, and injury severity, when controlling for other known dementia risks.
3. **Future Directions**: Risk stratification of individuals with equal severity of TBI and a SD by sex and age is important for practice addressing sleep health as part of brain health early in the course of TBI recovery.

2 | METHODS

This research study was approved by the institutional review board at University Health Network and reviewed by ICES (https://www.ices.on.ca/About-ICES) Privacy and Legal Office,[11] and was carried out in accordance with Section 45 of Ontario's Personal Health Information Protection Act (PHIPA). The results were reported according to the STrenghthening the Reporting of OBservtional studies in Epidemiology (STROBE) guidelines for observational studies.

2.1 | Data sources

The data used in for this study were obtained from ICES, an independent, non-profit research institute that houses high-quality person-level administrative databases on publicly funded services provided to Ontario residents, Canada.[11] The data sets from the National Ambulatory Care Reporting System and the Discharge Abstract Database databases, which hold all public and private claims for emergency department (ED) and acute care hospital admissions, respectively, were linked at the ICES using unique encoded identifiers (Tables S1–S4). The data from within these databases contained information on patient demographics (e.g., sex, age at entry, and postal code of residency) and primary and associated diagnostic codes from the International Classification of Diseases and Related Health Problems (ICD-10) Canadian Enhancement classification system. The data held at the ICES is regularly checked for quality and completeness.[12]

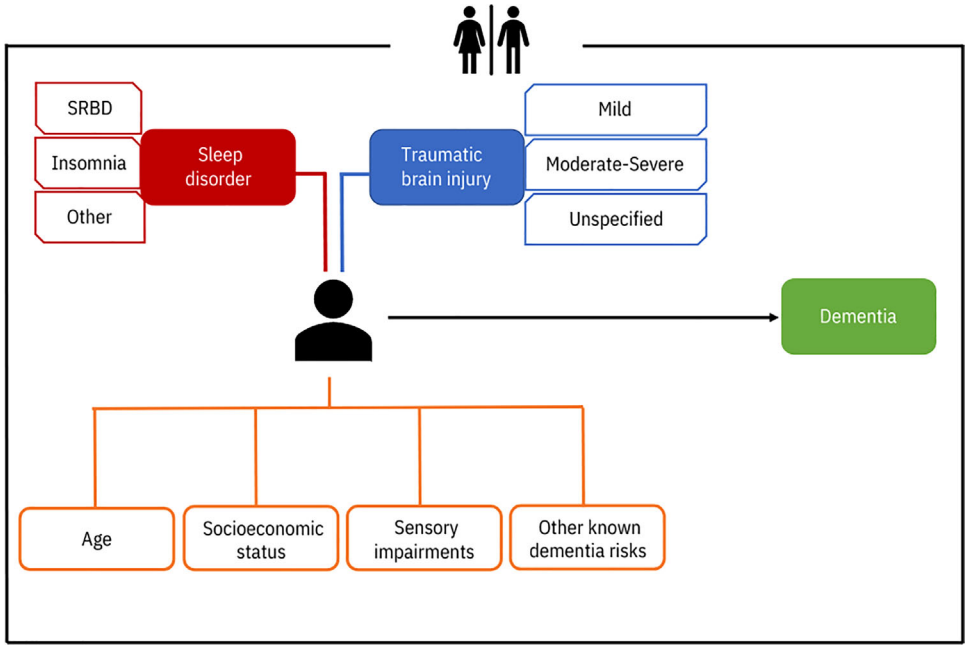

FIGURE 1 A model of the hypothesized relationship between SDs in TBI and dementia. TBI is a recognized risk for the development of dementia. Sleep disorders, age, sex, socioeconomic status, sensory impairments, disorders of circulatory system, and vascular risk factors have also been independently implicated as risks in the development of dementia in the general and TBI populations. Our study investigated whether the presence of a SD at the time of a TBI presented greater risk for dementia than brain injury on its own, with the goal of bringing attention to the potentially compounded impacts of these risks and their implications for TBI management. SD, sleep disorder; SRBD, sleep-related breathing disorder; TBI, traumatic brain injury.

2.2 | Study population

All consecutive adults (≥18 years) who had received a diagnosis of TBI (Table S5) in an ED or acute care unit between April 1, 2002 and March 31, 2016, in Ontario were identified using previously validated criteria from the Centers for Disease Control and Prevention.[13] Patient demographics, main and associated diagnoses (i.e., comorbidities), and injury-related information were recorded for each individual. The date of the first TBI diagnosis following open or closed injury was defined as the index date, marking the beginning of the study period for each individual. Each individual was followed from the TBI index date to the first occurrence of the outcome (i.e., dementia), death, deregistration from the system, or the end of the follow-up period, whichever occurred first. More details on how the cohort was created are provided in Figure S1 and Table S6.

2.2.1 | Injury severity

We previously developed an algorithm for determining injury severity through a composite score[6] that included the Glasgow Coma Scale (GCS) score and the most severe injury, irrespective of anatomic location, based on an Abbreviated Injury Scale (AIS).[14] Individuals with a recorded ICD-10 diagnostic code S06.0 (concussion) in whom the severity of TBI could not be established due to absence of GCS data and/or AIS, were included in a separate cohort—"unspecified injury severity" (Table S7).

2.3 | Variables

2.3.1 | Exposure

We considered any SD diagnosis as the primary exposure, including categories: (i) SRBD; (ii) insomnia disorder; (iii) circadian rhythm sleep-wake disorder (CRSD); (iv) parasomnias; (v) sleep-related movement disorders; and (vi) other SDs.[15] As secondary exposures, we considered two common categories of SDs individually—SRBD and insomnia disorder, combining all other SD categories under "other SDs" (explained further in the 'Results' section). More detail on SD definitions and codes is presented in Table S8.

2.3.2 | Outcome

The primary outcome was time from the TBI index date to incident dementia (any type) (Table S9A,B). Dementia was defined according to validated ICD-10 codes for the diagnosis of dementia in an inpatient setting.[16] Individuals with delirium were excluded to minimize the chance of reverse causality and misdiagnosis.[17]

2.3.3 | Potential confounders

A number of potential confounders and risk factors were considered: age, TBI severity, disorders of the circulatory system (e.g., cerebrovascular disease, ischemic heart disease, peripheral arterial disease, atrial fibrillation, heart failure), vascular risk factors (e.g., obesity, tobacco smoking, hyperlipidemia, and diabetes mellitus), other risk factors (e.g., depression, sensory impairments, spinal cord injury).[18,19] In addition, each individual was assigned a neighborhood income quintile based on their postal code, which was treated as a confounding factor (Table S10).

2.4 | Analyses

Descriptive statistics were used to describe the study population: frequencies and proportions for dichotomous and categorical variables, means (standard deviation) for normally distributed continuous data, and medians (interquartile ranges) for non-normally distributed data. Univariable and multivariable sex-specific Cox cause-specific regressions were used to assess the relationship between the SDs and outcome, controlling for potential confounders; the results were expressed as hazard ratios (HRs) with their associated 95% confidence intervals (CIs). We used restricted cubic-spline transformations for age because non-linearity was observed. The proportional sex-specific hazards assumption for exposure and covariates were tested[20] (Figures S2–S6, Table S11)

2.5 | Unmeasured confounding

Confounding bias is of particular concern in observational studies. The lack of information about the effectiveness of and adherence to SD treatment may bias estimates of the association between SD and incident dementia. We hypothesized that males younger than 65 years of age are more likely to be screened for SRBDs and females for insomnia disorder, and that these patterns would be reflected in the prevalence of these categories of SDs at the injury event. We also hypothesized that insomnia disorder will be more prevalent in milder forms of TBI, and thus in females, whereas SRBDs in more severe injuries, and thus more prevalent in males. To test these hypotheses and to assess the sensitivity of our analysis results, we used the recommended approach for observational studies,[21] which makes assumptions about potential residual confounding and quantifies its effect on the estimated HR for the association between an exposure and the outcome of interest in different subgroups. We first used the model to make statistical inferences about the effect of SDs on early onset-dementia in males and females. We then repeated this analysis in different injury severity subgroups.

2.6 | Sensitivity analyses

We considered death as a competing event in individuals with TBI, which may have precluded the occurrence of dementia in older individuals or those with more severe TBI, or led to selective survivorship in younger individuals with less severe TBI (Figure S2 and Figure S3), and overestimation of incidence by the Cox regressions method. We, therefore, ran the Fine and Gray regression[22] estimating dementia incidence with the cumulative incidence function, which accounts for competing risks and protection factors. All statistical analyses were performed using SAS 9.4.

3 | RESULTS

3.1 | Study population characteristics

Of 1,990,183 individuals considered for inclusion in our study, 712,708 individuals were included in the final cohort (Figure S1): the median age was 44 years and 59% of the cohort composed of male persons. The major causes of TBI included falls ($n = 297,794$, 41.78%), object strikes ($n = 188,301$, 26.42%), and assaults ($n = 76,255$, 10.70%). Object strikes and assaults were more frequent in males compared to females (31.45% vs 19.05% and 14.26% vs 5.58%, respectively). Falls were more frequent in females than in males (56.07% vs 32.04%). Table 1 outlines the baseline characteristics by TBI severity and sex.

3.2 | Exposure

Sleep disorders at the time of injury were present in 4,143 individuals (0.98%) in the included male group and 2,856 individuals (0.99%) in the female group. The most frequent SDs, across the sexes, were SRBDs ($n = 4,153$, 0.58%) and insomnia ($n = 2,522$, 0.35%). Due to low counts, SDs that were not insomnia disorder or SRBDs were combined into a single category of "other SDs" for the purpose of analysis (Table 1 and Figure 2).

3.3 | Outcome characteristics

Over a median follow-up time of 52 months (interquartile range [IQR] 19.22–86.44), 32,864 individuals (4.61%) were diagnosed with dementia, of which 5,983 (18.22%) were diagnosed with Alzheimer's disease (AD), 1,668 (5.08%) with vascular dementia, 108 (0.33%) with frontotemporal dementia, and the rest (24,504, 74.63%) with unspecified dementia type (Table 1). These diagnoses were unevenly distributed among individuals with mild TBI ($n = 19,401$, 4.37%), moderate TBI ($n = 405$, 5.50%), severe TBI ($n = 1,117$, 6.42%), and unspecified TBI severity ($n = 11,921$, 4.87%) (Table 1). Many cases of dementia presented themselves within the first 3 years of the TBI index date in both sexes (Table S12A and Table S12B).

3.4 | The relationship between SD and incident dementia

In univariate analysis, cumulative dementia incidence increased across SD categories (Tables S13A–C). When stratified by sex, the only

TABLE 1 Characteristics of individuals included in the cohort, by sex and TBI severity.

	Total, *n* (%)		With dementia, *n* (%)		Without dementia, *n* (%)		TBI severity, *n* (%)							
							Mild		Moderate		Severe		Unspecified	
Variables	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Total (both sexes)	712,708	32,834	679,874	443,456	7,365	17,390	244,497							
Total, by sex	289,051	423,657	19,492	13,342	269,559	410,315	150,192	293,264	2,445	4,920	5,969	11,421	130,445	114,052
Primary and secondary exposures: sleep disorders														
Any SD	2,856 (0.99)	4,143 (0.98)	254 (1.30)	283 (2.12)	2,602 (0.97)	3,860 (0.94)	1,310 (0.87)	2,508 (0.86)	31 (1.27)	59 (1.20)	73 (1.22)	157 (1.37)	1,442 (1.11)	1,419 (1.24)
SRBD	1,625 (0.56)	2,528 (0.60)	158 (0.81)	172 (1.29)	1,467 (0.54)	2,356 (0.57)	738 (0.49)	1,521 (0.52)	20 (0.82)	33 (0.67)	44 (0.74)	112 (0.98)	823 (0.63)	862 (0.76)
Insomnia disorder	1,073 (0.37)	1,449 (0.34)	87 (0.45)	98 (0.73)	986 (0.37)	1,351 (0.33)	495 (0.33)	878 (0.30)	8 (0.33)	25 (0.51)	25 (0.42)	37 (0.32)	545 (0.42)	509 (0.45)
Other SD[a]	231 (0.08)	288 (0.07)	11 (0.06)	13 (0.09)	149 (0.06)	182 (0.04)	77 (0.05)	120 (0.04)	<6	<6	<6	8 (0.07)	74 (0.06)	67 (0.06)
Confounder: Sociodemographic characteristics														
Age at first TBI	51.00 (28.00–69.00)	40.00 (27.00–60.00)	83.00 (77.00–87.00)	81.00 (75.00–87.00)	49.00 (27.00–64.00)	39.00 (26.00–57.00)	53.00 (28.00–69.00)	39.00 (27.00–59.00)	64.00 (34.00–76.00)	43.00 (29.00–66.00)	68.00 (40.00–79.00)	54.00 (37.00–75.00)	48.00 (28.00–66.00)	39.00 (26.00–61.00)
Income quartile (lowest)	64,674 (22.37)	91,498 (21.60)	4,705 (24.14)	2,981 (22.34)	59,969 (22.25)	88,517 (21.57)	33,126 (22.06)	61,830 (21.08)	539 (22.04)	1,211 (24.61)	1,334 (22.35)	2,556 (22.38)	29,675 (22.75)	25,901 (22.71)
Income quartile (highest)	54,259 (18.77)	79,367 (18.73)	3,424 (17.57)	2,482 (18.60)	50,835 (18.86)	76,885 (18.74)	29,078 (19.36)	56,135 (19.14)	474 (19.39)	855 (17.38)	1,097 (18.38)	1,999 (17.50)	23,610 (18.10)	20,378 (17.87)
Rural residence	38,999 (13.49)	62,347 (14.72)	2,308 (11.84)	1,767 (13.24)	36,691 (13.61)	60,580 (14.76)	21,106 (14.05)	44,819 (15.28)	289 (11.82)	693 (14.09)	747 (12.51)	1,648 (14.43)	16,857 (12.92)	15,187 (13.32)
Confounder: Disorders of circulatory system														
Cerebrovascular disease	8,899 (3.08)	10,308 (2.43)	1,723 (8.84)	1,663 (12.46)	7,176 (2.66)	8,645 (2.11)	3,998 (2.66)	4,956 (1.69)	291 (11.90)	333 (6.77)	1,153 (19.32)	2,004 (17.55)	3,457 (2.65)	3,015 (2.64)
Ischemic heart disease	15,809 (5.47)	20,503 (4.84)	2,749 (14.10)	2,463 (18.46)	13,060 (4.84)	18,040 (4.40)	8,010 (5.33)	12,502 (4.26)	208 (8.51)	319 (6.48)	676 (11.33)	1,251 (10.95)	6,915 (5.30)	6,431 (5.64)
Atrial fibrillation	10,760 (3.72)	11,254 (2.66)	1,999 (10.26)	1,624 (12.17)	8,761 (3.25)	9,630 (2.35)	5,441 (3.62)	6,568 (2.24)	176 (7.20)	184 (3.74)	637 (10.67)	935 (8.19)	4,506 (3.45)	3,567 (3.13)
Heart failure	8,947 (3.10)	8,301 (1.96)	1,619 (8.31)	1,253 (9.39)	7,328 (2.72)	7,048 (1.72)	4,644 (3.09)	4,938 (1.68)	126 (5.15)	132 (2.68)	430 (7.20)	585 (5.12)	3,747 (2.87)	2,646 (2.32)
Confounder: Vascular risk factors														
Obesity	2,533 (0.88)	1,370 (0.32)	166 (0.85)	76 (0.57)	2,367 (0.88)	1,294 (0.32)	1,132 (0.75)	763 (0.26)	17 (0.70)	19 (0.39)	56 (0.94)	71 (0.62)	1,328 (1.02)	517 (0.45)

(Continues)

TABLE 1 (Continued)

Variables	Total, *n* (%)		With dementia, *n* (%)		Without dementia, *n* (%)		TBI severity, *n* (%)							
							Mild		Moderate		Severe		Unspecified	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Hyperlipidemia	5,457 (1.89)	6,855 (1.62)	956 (4.90)	887 (6.65)	4,501 (1.67)	5,968 (1.45)	2,653 (1.77)	4,065 (1.39)	90 (3.68)	115 (2.34)	249 (4.17)	444 (3.89)	2,465 (1.89)	2,231 (1.96)
Diabetes mellitus	23,102 (7.99)	25,036 (5.91)	3,509 (18.00)	3,009 (22.55)	19,593 (7.27)	22,027 (5.37)	11,139 (7.42)	14,652 (5.00)	271 (11.08)	430 (8.74)	785 (13.15)	1,527 (13.37)	10,907 (8.36)	8,427 (7.39)
Other confounders														
Tobacco smoking	327 (0.11)	543 (0.13)	27 (0.14)	24 (0.18)	300 (0.11)	519 (0.13)	NA	327 (0.11)	NA	11 (0.22)	NA	21 (0.18)	NA	184 (0.16)
Depression	13,228 (4.58)	12,518 (2.95)	994 (5.10)	618 (4.63)	12,234 (4.54)	11,900 (2.90)	6,168 (4.11)	7,478 (2.55)	133 (5.44)	210 (4.27)	351 (5.88)	447 (3.91)	6,576 (5.04)	4,383 (3.84)
Visual impairments	4,199 (1.45)	3,431 (0.81)	668 (3.43)	453 (3.40)	3,531 (1.31)	2,978 (0.73)	2,193 (1.46)	2,180 (0.74)	69 (2.82)	51 (1.04)	146 (2.45)	198 (1.73)	1,791 (1.37)	1,002 (0.88)
Hearing loss	700 (0.24)	989 (0.23)	90 (0.46)	78 (0.58)	610 (0.23)	911 (0.22)	331 (0.22)	570 (0.19)	10 (0.41)	18 (0.37)	31 (0.52)	80 (0.70)	328 (0.25)	321 (0.28)
Incidence of														
Dementia	19,492 (6.74)	13,342 (3.15)	19,492 (100.00)	13,342 (100.00)	-	-	10,975 (7.31)	8,426 (2.87)	248 (10.14)	157 (3.19)	526 (8.81)	591 (5.17)	7,743 (5.94)	4,168 (3.65)
Follow-up time, in months														
Time to dementia[b]	25.66 (8.25–52.25)	23.89 (8.08–52.50)	25.66 (8.25–52.25)	23.89 (8.08–52.50)	-	-	25.69 (8.64–52.40)	25.28 (8.67–53.49)	19.63 (4.01–54.70)	21.09 (3.12–45.04)	34.53 (7.77–62.32)	30.55 (7.54–67.71)	25.30 (7.77–50.83)	21.19 (7.43–48.89)

[a]The "Other SD" category combines hypersomnia disorders, circadian rhythm sleep disorders, parasomnias, sleep related movement disorders, and other sleep disorders; some patients might have multiple sleep disorders. SD, sleep disorder.

[b]Reported as median and interquartile range, not *n* (%) as for the rest.

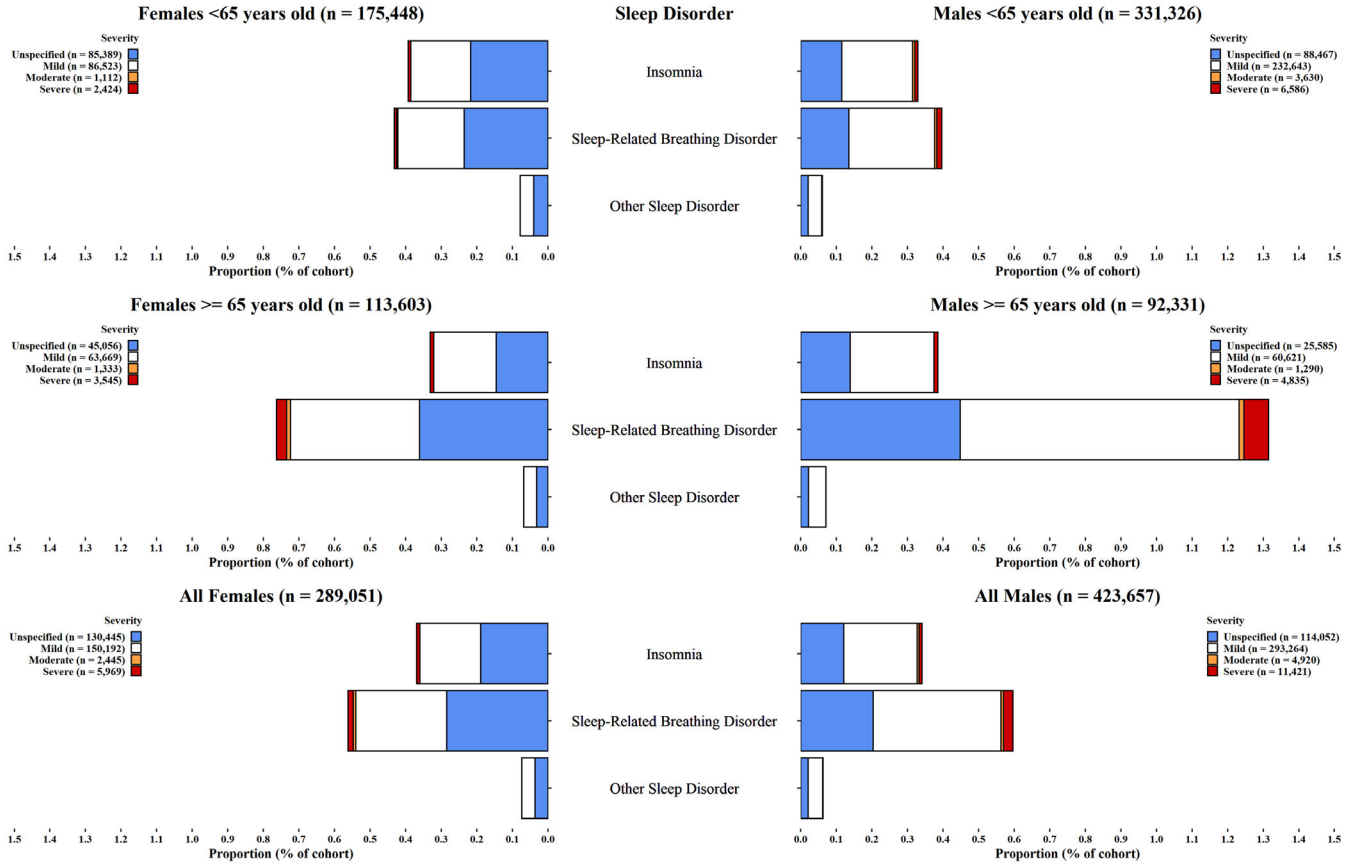

FIGURE 2 Relative frequencies of categories of sleep disorders in males and females with TBI, by injury severity and age. TBI, traumatic brain injury.

relationships that were no longer significant were those between dementia and SRBD in males and dementia and insomnia disorder in females (Table S13A–C). Adjusting for age, income level, TBI severity, and other known clinical dementia risk factors (Figure 1), SD was associated with a 26% increased hazard of dementia in males (HR 1.26, 95% CI 1.11–1.42) and 23% increased hazard in females (HR 1.23, 95% CI 1.09–1.40), as compared with those with no SD (Table 2).

3.4.1 | The relationship between SD and incident dementia by injury severity

Limited by a relatively small sample size and multiple comparisons, we found dementia to be directionally but not in all cases significantly associated with SDs in males and females, respectively, with mild TBI (all HRs >1; for insomnia disorder: HR 1.51, 95% CI 1.17–1.95 and HR 1.10, 95% CI 0.81–1.48; for SRBD: HR 1.06, 95% CI 0.86–1.29 and HR 1.45, 95% CI 1.16–1.82; and other SDs: HR 1.78, 95% CI 1.03–3.09), adjusting for potential confounders and dementia risks. Results for moderate-severe and unspecified injury severity are presented in Table 2 and Figure 3A.

3.4.2 | The relationship between SDs and early-onset dementia

The association between SDs and dementia was significant for males who were diagnosed with early-onset dementia (HR 1.93, 95% CI 1.29–2.87). The relationship was driven largely by insomnia disorder (HR 2.56, 95% CI 1.45–4.49). The association between categories of SDs and early-onset dementia in females was either not significant or not possible to study due to limited power (Table 2 and Figure 3B).

3.4.3 | The relationship between SDs and dementia in individuals 65 years of age and older

The association between dementia and different categories of sleep disorders in males 65 years of age and older are as follows: insomnia disorder (HR 1.48, 95% CI 1.19–1.84); SRBD (HR 1.03, 95% CI 0.88–1.21); and other SDs (HR 1.75, 95% CI 1.10–2.78). In females 65 years of age or older, the overall association between dementia was significant for SRBDs (HR 1.24, 95% CI 1.05–1.46), as was the case for other SDs (HR 1.72, 95% CI 1.10–2.70). The association with insomnia

TABLE 2 Results from multivariate Cox cause-specific regression models on the associations between incident dementia and incident early-onset dementia and the presence of sleep disorder among male and female patients with TBI.

	Dementia Cox regression model			Early-onset dementia Cox regression model		
Variables	**M**	**F**	**Overall**	**M**	**F**	**Overall**
Primary exposure						
Any SD: Yes vs no	1.26 (1.11–1.42)***	1.23 (1.09–1.40)***	1.25 (1.15–1.36)****	1.93 (1.29–2.87)***	1.38 (0.78-2.44)	1.70 (1.23–2.36)***
Secondary exposure						
SRBD: Yes vs no	1.06 (0.91–1.24)	1.28 (1.09–1.50)**	1.16 (1.04–1.30)**	1.33 (0.75–2.38)	1.87 (0.94–3.72)	1.53 (0.98–2.39)
Insomnia disorder: Yes vs no	1.57 (1.28–1.92)***	1.14 (0.92–1.40)	1.33 (1.15–1.54)****	2.56 (1.45–4.49)***	1.04 (0.38–2.83)	1.91 (1.18–3.11)**
Other SD: Yes vs no	1.73 (1.11–2.69)*	1.63 (1.04–2.57)*	1.72 (1.25–2.35)***	1.09 (0.26–4.62)	N/C	0.78 (0.19–3.17)
Covariates						
Age[a]	−0.01/0.05/5.69*	0.02 /0.06/0.14	−0.05 /0.04/1.63	−0.66/0.18/13.2***	−0.12/0.29/0.03	−0.51/0.15/11.88***
Male sex	1	1	1	1	1	1
Female sex	NA	NA	0.876 (0.857–0.896)****	NA	NA	0.884 (0.772–1.01)
Neighborhood income: Highest vs lowest	0.80 (0.75–0.84)****	0.90 (0.86–0.94)****	0.86 (0.83–0.89)****	0.55 (0.42–0.73)****	0.57 (0.42–0.79)****	0.57 (0.46–0.70)****
TBI severity: Unknown vs mild	1.17 (1.13–1.22)****	1.05 (1.02–1.08)***	1.10 (1.07–1.12)****	1.30 (1.09–1.57)	0.93 (0.76–1.14)	1.13 (0.98–1.30)
TBI severity: Moderate vs mild	0.98 (0.84–1.15)	1.23 (1.09–1.40)***	1.12 (1.02–1.24)***	1.00 (0.49–2.03)	0.55 (0.14–2.21)	0.84 (0.45–1.58)
TBI severity: Severe vs mild	0.94 (0.86–1.02)	1.00 (0.92–1.09)	0.97 (0.91–1.03)	1.52 (1.04–2.20)**	1.25 (0.65–2.38)	1.45 (1.05–2.01)*
Comorbid SCI: Yes vs no	1.13 (1.06–1.21)***	1.05 (1.00–1.11)	1.08 (1.03–1.12)***	1.57 (1.15–2.12)**	0.96 (0.60–1.52)	1.33 (1.03–1.71)*
Cerebrovascular disease: Yes vs no	1.45 (1.37–1.53)****	1.40 (1.33–1.48)****	1.43 (1.37–1.48)****	4.20 (3.18–5.55)****	2.45 (1.60–3.75)****	3.49 (2.77–4.40)****

(Continues)

TABLE 2 (Continued)

Variables	Dementia Cox regression model			Early-onset dementia Cox regression model		
	M	F	Overall	M	F	Overall
Ischemic heart disease: Yes vs no	0.85 (0.81–0.90)****	0.94 (0.90–0.98)***	0.90 (0.87–0.93)****	1.29 (0.95–1.73)	0.98 (0.62–1.55)	1.19 (0.93–1.53)
Dx of arteries, capillaries: Yes vs no	1.18 (1.08–1.28)***	1.03 (0.94–1.14)	1.12 (1.05–1.19)***	1.07 (0.61–1.90)	1.39 (0.66–2.93)	1.14 (0.73–1.80)
Atrial fibrillation: Yes vs no	0.93 (0.88–0.99)***	0.95 (0.91–1.00)	0.94 (0.91–0.98)***	1.50 (0.34–1.06)	1.40 (0.69–2.83)	0.81 (0.52–1.25)
Heart failure: Yes vs no	1.20 (1.13–1.28)****	1.13 (1.06–1.19)****	1.16 (1.11–1.21)****	1.51 (0.95–2.40)	1.43 (0.75–2.71)	1.51 (1.03–2.19)*
Obesity: Yes vs no	0.89 (0.70–1.11)	0.99 (0.85–1.16)	0.95 (0.84–1.08)	0.560 (0.27–1.30)	1.02 (0.54–1.90)	0.79 (0.49–1.30)
Tobacco smoking: Yes vs no	1.52 (1.02–2.28)***	2.49 (1.71–3.64)****	1.95 (1.48–2.56)****	1.62 (0.66–3.94)	3.84 (1.41–10.47)**	2.23 (1.15–4.33)*
Hyperlipidemia: Yes vs no	1.10 (1.02–1.18)***	1.00 (0.93–1.07)	1.04 (1.00–1.09)	1.02 (0.68–1.54)	1.20 (0.68–2.12)	1.07 (0.77–1.49)
Diabetes mellitus: Yes vs no	1.49 (1.42–1.55)****	1.44 (1.38–1.49)****	1.46 (1.42–1.50)****	1.86 (1.47–2.35)****	2.23 (1.70–2.97)****	2.01 (1.68–2.41)****
Depression: Yes vs no	2.01 (1.85–2.18)****	1.71 (1.61–1.83)****	1.82 (1.73–1.91)****	3.95 (3.12–5.01)****	2.76 (2.08–3.67)****	3.37 (2.81–4.05)****
Vision impairments: Yes vs no	0.99 (0.91–1.09)	0.92 (0.85–0.99)***	0.95 (0.89–1.00)	1.48 (0.84–2.60)	1.77 (0.88–3.19)	1.54 (1.01–2.35)*
Hearing loss: Yes vs no	1.24 (0.99–1.55)	1.13 (0.91–1.38)	1.18 (1.01–1.37)***	1.96 (0.63–6.11)	<6	1.07 (0.34–3.33)
LRχ2	52654.88****	54048.52****	111134.13****	1719.00****	912.36****	2259.82****
AIC	277549.06	413829.46	735762.68	11616.12	7920.33	21179.85
Degree of freedom	17	17	18	17	17	18

Note: Estimates are presented as adjusted HRs and 95% CIs.

[a]Significant nonlinearity was observed: a restricted cubic spline transformation was used.

Abbreviations: AIC, Akaike information criterion; CI, confidence interval; Dx, disorders; F, female; HR, hazard ratio; LR, likelihood ratio; M, male; NA, not applicable; N/C, not calculated (limited power to study associations); SCI, spinal cord injury; SD, sleep disorder; SRBD, sleep-related breathing disorder; TBI, traumatic brain injury; vs, versus.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

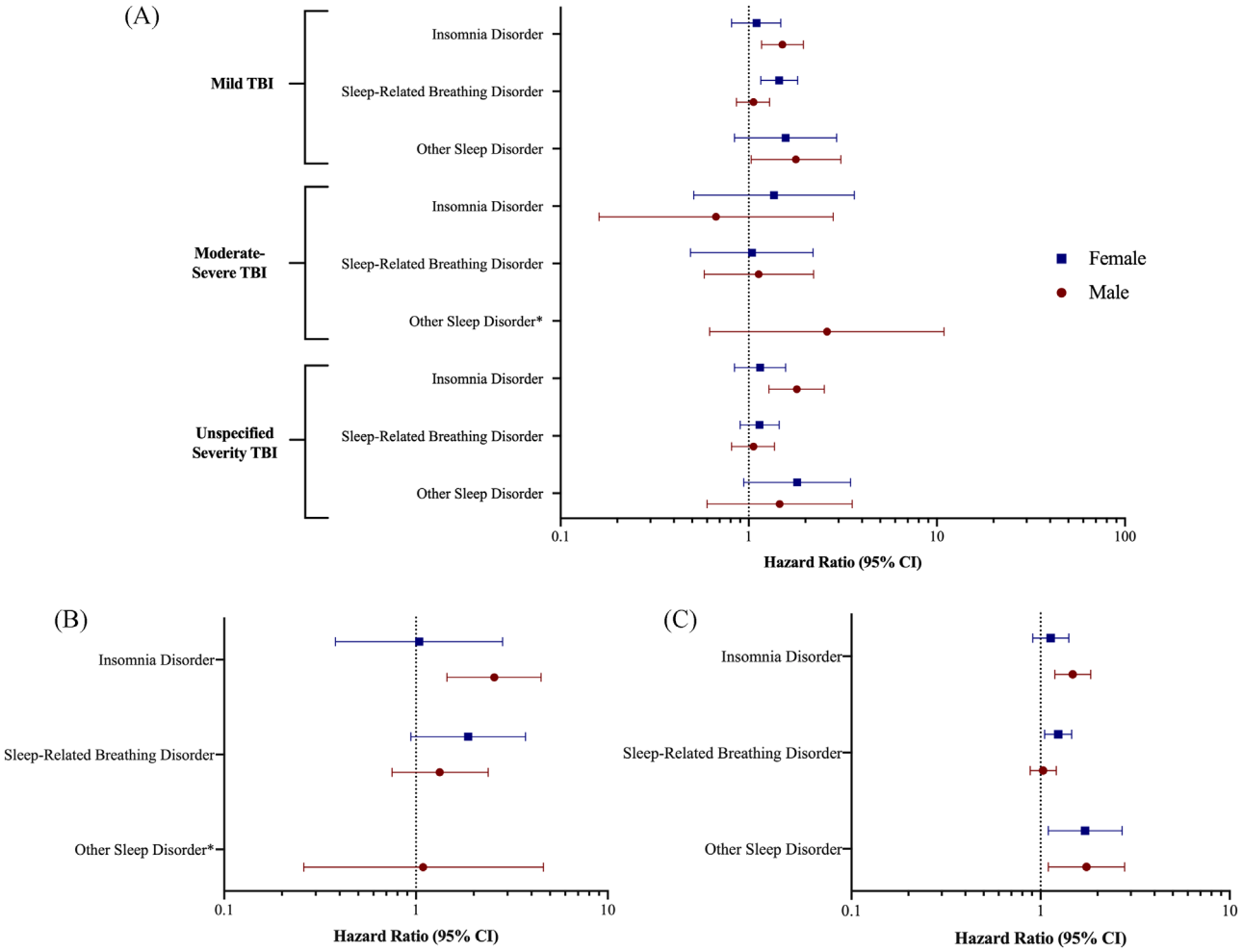

FIGURE 3 (A) Hazard ratios of incident dementia in males and females with TBI and sleep disorder, by injury severity. (B) hazard ratios of incident early-onset dementia (<65 years of age) in male and female patients with TBI and sleep disorder. (C) Hazard ratios of incident late-onset dementia (≥65 years of age) in males and females with TBI and sleep disorder. Figures 3B and 3C are not stratified by injury severity due to low power. TBI, traumatic brain injury.*Hazard ratio calculated for males only as there was not enough power to study the relationship in females.

disorder was not significant (HR 1.13, 95% CI 0.91–1.41) (Table 2 and Figure 3C).

3.5 | Sensitivity analyses

The Fine and Grey regression models fits and effect measures (HR) confirmed the association between SDs and dementia in males and females (HR 1.26/$p < 0.001$ and HR 1.23/$p = 0.002$, respectively), after controlling for potential confounders and dementia risks. For specific categories of SDs, age, and TBI severity subgroups, the estimates for males and females remained similar to those from the Cox regression models (Table S14A and Table S14B).

4 | DISCUSSION

We conducted a population-based study of a province-wide cohort of consecutive individuals diagnosed with TBI in the ED or acute care hospitals, and we found that over a median follow-up of 52 months, almost 5% had developed dementia. In the less than 1% of TBI individuals who had a comorbid SD at the time of injury, there was a greater relative risk of dementia in males and females, independent of TBI severity and other known dementia risk factors. To the best of our knowledge, this is among the first large-scale population-based study to investigate the cognitive sequelae of TBI with comorbid SDs using a comprehensive analytic approach. The effect measures were found to be robust in sensitivity analyses, and, therefore, can be used to alert clinicians to these modified-risk and high-risk groups, and to develop secondary preventive and rehabilitation strategies to deal with SDs in individuals with TBI.

Our findings on the association of specific SDs with dementia incidence align with the results of a recently published meta-analysis.[23] Several studies included in the work reported that insomnia,[24,25] SRBDs,[25,26] and other SDs[27] are associated with incident AD and/or all-cause dementia in a sex-specific manner. The pathophysiological mechanisms of these sex differences are not entirely clear, but it is interesting that SRBD, which is more common in males,[28] posed a

greater risk to females, whereas insomnia disorder, which is more common in females,[29] posed a greater risk of dementia to males in this study. A possible explanation for these unexpected results is that the mechanisms of these SDs differ between males and females and TBI-induced pathophysiological processes are more amenable to interaction with the SD-related processes to trigger dementia. Adherence to treatment also warrants consideration—if males are more often diagnosed with SRBDs, the knowledge of the condition and treatment may be more common among males with TBI and thus potentially more likely to be addressed after the injury, attenuating the risk of dementia. Likewise, females with TBI may have a greater awareness of insomnia, facilitating better management after injury and a lesser risk with respect to dementia as compared to males.[30,31]

4.1 | The relationships between SDs, TBI, and dementia

The link between TBI and dementia has been highlighted in previous studies and has been attributed to a number of pathophysiological mechanisms, triggered by diffuse axonal injury, as in concussion, particularly involving the frontal and temporal lobes, lesions in various regions due to shearing strains,[32–34] as well the secondary cascade of events after TBI that include cerebral hemorrhage, hypotension, hypoperfusion, and immune responses.[35,36] In this study, we examined the association between SDs and incident dementia in persons with TBI of various severities. The results shed light on the significance of specific SD categories in the development of dementia in males and females with TBI at different life stages (e.g., late- vs early-onset). Our results also highlighted that many cases of dementia presented themselves within the first 3 years of the TBI index date in both sexes (Table S12A and Table S12B), potentially suggesting that the SDs present at the time of the TBI may have been a marker of subclinical dementia, or that SD is a proximate cause of the injury itself, and together with TBI expedites progression to dementia.[6]

In the general population, SDs have been linked to the development of neurocognitive disorders and progression of these disorders co-occurred with deficits in behavioral inhibition, self-regulation of affect and arousal, working and contextual memory, and analytical ability.[37–39] In turn, these functional implications have been linked to treatment adherence: the most recent estimates of patients' failure to adhere to treatment recommendations, in general, range from 20% to 40% for acute disease regimens, 20% to 60% for chronic disease regimens, and 50% to 80% for preventive regimens.[40–43] Traditional facilitators to adherence have been categorized into patient-related factors (i.e., targeting attitudes and beliefs, perceived benefits, and lifetime habits), regimen-related factors (i.e., altering the complexity of the regimen and frequency of or duration of treatment), and factors related to health care providers, including their level of knowledge and principles of communication.[44] Since the approval of nasal continuous positive airway pressure therapy for obstructive sleep apnea (i.e., a common form of SRBD) in 1981, numerous studies have been conducted to improve the understanding of patients and providers, and the role of technology in adherence to this therapy, considering that conservative estimates show that 29% to 83% of patients are nonadherent, depending on how nonadherence is defined. Adherence has also been reported to be sex dependent.[45,46] Likewise, adherence to insomnia disorder treatment, both non-pharmacological (e.g., cognitive behavioral therapy) and pharmacological, has been reported to be challenging to implement with continuity.[47,48] Although the discussion is limited, as we did not investigate the topic of adherence, our results bring attention to the impact of SDs, if left untreated or suboptimally treated in patients with TBI and call for serious clinical consideration in light of the dementia risk SDs pose. This point is further supported by the concern that less than 1% of individuals at the time of TBI had a documented SD. This is much lower than what has been reported in clinical samples preceding injury and acute TBI.[49,50] Therefore, the impact of limited inquiry into sleep in the context of the TBI event and recovery and how this can be reflected in adverse outcomes cannot be discarded.[51]

4.2 | The pathophysiological pathways implicated in the relationships uncovered

Sleep disorders are thought to be linked to dementia development and progression through their adverse downstream biochemical consequences, including systemic oxidative stress, inflammation, increased sympathetic nervous system activity, endothelial dysfunction, altered immune response, and disrupted circadian rhythm.[52] Although the conditions by which pathogenic proteins may become entrapped and aggregate in glymphatic channels in male and female persons with TBI and SD are not fully understood and were not the subject of this study, in the conception of the brain's "glymphatic" system, sleep is considered a fundamental tenet of brain homeostasis that is responsible for removal of protein waste via classical cellular protein degradation pathways, autophagy and ubiquitination.[53,54] Intermittent hypoxia and sleep fragmentation in SRBDs may alter this system's function, affecting the spread of protein aggregates by acting on endothelial cells through vascular remodeling and angiogenesis.[55] Intermittent hypoxemia may also influence dementia progression along with systemic or local inflammatory responses and increased levels of reactive oxygen species associated with obstructive sleep apnea (OSA), a common form of SRBD.[56] Insomnia and CRSD, through sleep fragmentation, disruption of melatonin secretion, and/or short sleep duration, may influence cellular protein degradation pathways—autophagy and ubiquitination—and dysregulate DNA repair, impair regulation of the cell cycle, and result in apoptosis.[57] Finally, blunted baroreflex sensitivity and augmented sympathetic neural and reactivity to stress in insomnia disorder and acute and long-term carotid body response to intermittent hypoxia in SRBD may affect amyloid beta ($A\beta$) overexpression, causing progression of neurodegenerative activity through elevated cardiovascular risks.[57] Although we acknowledge that further work will be required to advance our knowledge of these pathways, our findings call for consideration of each category of SD as a dementia risk in TBI in research and practice.

4.3 | Systemic challenges: The limited recognition of sleep disorders in the healthcare system

As a member state of World Health Organization, Canada is governed by its nomenclature regulations. The ICD-10 meets the international standards for reporting diagnoses, symptoms, conditions, problems, complaints, or other reason(s) for an encounter/visit in the health care system. Although the data are continuously checked for quality and completeness, the results of this study call for improved methodologies for capturing ICD codes for SDs, to aid in understanding of the complex interplay of disease processes where SDs are involved, as they present a pervasive and highly consequential health problem. Less than 1% of individuals forming the present study sample had a documented SD at the time of their TBI. This is much lower than what has been reported in clinical samples preceding injury and acute TBI.[49,50] This highlighted the limited inquiry into sleep in the context of a TBI event and recovery and how this gap can reflect in adverse cognitive outcomes.

4.4 | Limitations

One of the main limitations of our study was its observational and retrospective design, utilizing data from ED and acute care hospitals in a publicly funded system, limiting its generalizability to countries with different health care systems and increasing the potential for unmeasured confounding, age-period cohort effects, and surveillance bias despite multiple sensitivity analyses. For example, information on the family history of dementia was not available. The observed HR of SD of 1.26 and 1.23 in male and female persons with TBI, respectively, could be explained by an unmeasured confounder that was associated with both SD and incident dementia. However, we believe it to be unlikely given that this means that an unmeasured confounder would have to be associated with both incident dementia and SD by an relative risk above 1.2-fold each, through pathways independent of age, sex, severity of TBI, socioeconomic status, smoking, and clinical comorbidity indicators, that is, disorders of the circulatory system (i.e., cerebrovascular disease, ischemic heart disease, peripheral arterial disease, atrial fibrillation, heart failure), vascular risk factors (i.e., obesity, tobacco smoking, hyperlipidemia, diabetes mellitus), and other risk factors (i.e., depression, visual impairments, hearing loss) as a time-varying covariate. Given the magnitude, it does not seem plausible. Furthermore, when performing the Fine and Grey competing risk analyses, the associations remained significant and of similar magnitude, thereby confirming our research hypotheses.

Despite reasonable concerns that data from medical records may underestimate the actual incidence of dementia, the calculated risk of dementia in TBI in the present study was similar to other population-based estimates.[6] Also important to note is that we were unable to distinguish between a first TBI event and repeated TBI events (i.e., prior events that may have occurred outside the study window). Assessing the effects of a SD exposure at a TBI event helped us make more sound decisions for methodology based on the temporal ordering of the data. Nonetheless, a limitation in studies in which the exposure and TBI event (Figure 1) are assessed at the same time is that it can be difficult to determine whether an exposure is in fact affected by a previous history of TBI. A historical cohort is needed to guide standards of studying history of repeated TBI and SD risk in dementia.

This feeds into another important point that is the continuity and evolution of SDs from the time of injury to post-injury and how this impacts the risk of dementia, questions we were not able to touch on due to the limited nature of the data that was available. This is perhaps the greatest limitation in this study—that it assumes that the same SD present at the time of injury carries through to the post-injury stages until the development of dementia. Although our control for other known risk factors mitigates this to some extent, it is a weakness that could only be remedied with more complete longitudinal data, leveraging health care data with clinical data for cohort enrichment.

Finally, although ICD-10 codes for SDs are used, they do not allow for the detection of important clinical differences in severity and response to treatment within a single SD category. We, therefore, were unable to account for treatment adherence in the results and determine whether and how this may have shaped the relationships uncovered (e.g., how many of the patients with TBI and SD were successfully treated and did this temper the risk of dementia, relative to those whose SDs were detected but who did not adhere to treatment/whose treatment was otherwise unsuccessful). In addition, given that level of education is not captured in health care data sets, and that education is an important factor potentially related to dementia risk, our inability to explore this relationship is a limitation.

4.5 | Conclusion

Our results highlight that presence of a SD at the time of TBI has implications for the development of dementia after controlling for severity of TBI, socioeconomic status, smoking, and clinical comorbidity indicators. Our results are consistent with prior studies on the mediating effects of SDs in TBI and offer support for the involvement of sleep specialists early in the care individuals with TBI and SDs to evaluate appropriate treatment and facilitate adherence to interventions that may stifle progressive cognitive decline. The sex differences we observed need to be further assessed in a more robust data set that provides the power to study the associations and the significance of time (e.g., continuity and evolution of SDs from time of injury to post-injury), to better grasp the progression of cognitive decline in individuals with comorbid SDs for preventive and management purposes.

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Government of Ontario. The opinions, results, and conclusions reported are those of the authors. No endorsement by ICES or any of its funders or partners is intended or should be inferred. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed herein are those of the author, and not necessarily those of CIHI. We also wish to acknowledge Ms. Shirin Mollayeva for proofreading the final version of the manuscript, visual presentation, and checking the data. The research reported in this presentation was supported by the research grant from the Alzheimer's Association (AARF-16-442937), Canada Research Chair in Neurological Disorders and Brain Health (Grant/Award Number: CRC-2021-00074), Canada Research Chair in Traumatic Brain Injury and Underserved Populations (Grant/Award Number: CRC-2019-00019), and in part by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (Grant/Award Number: 494 R01NS117921). The content is solely the authors' responsibility and does not necessarily represent the official views of the Alzheimer's Association, the Canadian Institutes of Health Research or the National Institutes of Health.

CONFLICT OF INTEREST STATEMENT

The authors (Tatyana Mollayeva, Andrew Tran, Mackenzie Hurst, Michael Escobar, and Angela Colantonio) declare no competing interests or personal relationships that could have appeared to influence the results reported in this paper. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

This study utilized ICES Data & Analytic Services (DAS) and used de-identified data from the ICES Data Repository, which is managed by ICES with support from its funders and partners: Canada's Strategy for Patient-Oriented Research (SPOR), the Ontario SPOR Support Unit, the Canadian Institutes of Health Research, and the Government of Ontario. No humans were directly involved in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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