The Journal of Prevention of Alzheimer's Disease 13 (2026) 100360

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Associations between traumatic brain injury and the prevalence of Alzheimer's disease dementia and behavioral and psychological symptoms of dementia: A retrospective cohort study

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ARTICLE INFO

Keywords:
Alzheimer's disease
Mild cognitive impairment
Traumatic brain injury
Dementia progression
Behavioral and psychological symptoms of dementia

ABSTRACT

Background: Traumatic brain injury is an environmental risk factor that may accelerate the progression of Alzheimer's disease and behavioral and psychological symptoms of dementia in patients with mild cognitive impairment.
Objectives: To investigate whether traumatic brain injury in patients with mild cognitive impairment is associated with an increased risk of progression to Alzheimer's disease dementia and behavioral and psychological symptoms of dementia.
Design: A retrospective cohort study using the Korean National Health Insurance Service database.
Setting: National-level health data covering healthcare utilization, diagnoses, prescriptions, and procedures in South Korea from January 2012 to December 2021.
Participants: Patients diagnosed with mild cognitive impairment between January 1, 2013, and December 31, 2016, were followed until Alzheimer's disease dementia diagnosis, behavioral and psychological symptoms of dementia occurrence, death, or December 31, 2021. These patients were classified into two groups according to the presence of traumatic brain injury during the follow-up period.
Measurements: Age at the time of mild cognitive impairment diagnosis, sex, income level, the presence of several chronic conditions, presence of traumatic brain injury, progression of Alzheimer's disease dementia, and behavioral and psychological symptoms of dementia
Results: We assessed 452,718 patients (mean age: 67.16 years). Traumatic brain injury was significantly associated with an increased risk of Alzheimer's disease dementia progression (hazard ratio = 1.252, 95 % confidence interval: 1.206–1.301), particularly among patients aged <65 years (hazard ratio = 1.560, 95 % confidence interval: 1.391–1.749), and was linked to a higher risk of behavioral and psychological symptoms of dementia following Alzheimer's disease dementia diagnosis (hazard ratio = 1.300, 95 % confidence interval: 1.181–1.431).
Conclusions: Our results underscore the importance of traumatic brain injury prevention in patients with mild cognitive impairment for mitigating the progression and neuropsychiatric complications of Alzheimer's disease.

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https://doi.org/10.1016/j.tjpad.2025.100360
Received 29 May 2025; Received in revised form 24 July 2025; Accepted 20 August 2025
Available online 28 August 2025

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia across all age groups [1]. Its progression is characterized by two core pathologies; an initial accumulation of amyloid-β (Aβ) plaques, followed by the propagation of neurofibrillary tangles (NFTs) of tau [2,3]. Moreover, factors such as neuroinflammation, vascular burden, synaptic dysfunction, and axonal damage contribute to disease progression [4,5] and various risk factors, including genetic and environmental factors, influence the progression of AD [6].

Traumatic brain injury (TBI) is a potent environmental risk factor for the progression of AD. Both repetitive mild TBIs and a single moderate-to-severe TBI increase the risk of future cognitive decline and dementia [7–9]. Following TBI, a range of polypathological changes occur, including Aβ accumulation [10–12], tau hyperphosphorylation [13,14], TDP-43 inclusions [15], neuroinflammation [16], and synucleinopathy [17]. Moreover, repetitive TBIs are associated with pathological alterations characteristic of chronic traumatic encephalopathy (CTE) [18, 19]. CTE shares the hyperphosphorylated tau pathology with AD; however, the deposition sites and pathological features differ [20].

Behavioral and psychological symptoms of dementia (BPSD) can occur with disease progression in most dementia subtypes and are challenging symptoms for caregivers [21–23]. BPSD refers to the spectrum of non-cognitive neuropsychiatric symptoms, such as agitation, delusions, depression, and anxiety, and these symptoms will affect up to 90 % of patients over the course of illness [24]. Similarly, behavioral features are commonly observed in CTE and can be present from the early stages through disease progression [18,19]. Therefore, when TBI overlaps with neurodegenerative diseases, it may exacerbate BPSD.

Mild cognitive impairment (MCI) is a heterogeneous condition and may represent an early stage of neurodegenerative diseases such as AD. A certain proportion of MCI patients, approximately 10 %–15 % per year, progress to clinical dementia, most often AD, whereas others remain stable or revert to normal cognition [25]. Because disease progression can be influenced by interventions or exposure to risk factors, modifying factors may alter its trajectory. In previous studies, a history of TBI was consistently associated with an increased risk of AD not only in cases of mild TBI but also in cases of TBI with loss of consciousness [26,27]. A study has failed to demonstrate an association between TBI and progression from MCI to AD, but they have also shown that TBI is linked to an earlier age at MCI diagnosis [28]. Based on the hypothesis that TBI events accelerate AD-related pathological progression, we used large-scale nationwide cohort data to investigate whether, in patients with MCI, (i) TBI increases the risk of progression to AD dementia, and (ii) TBI increases the subsequent risk of developing BPSD after AD dementia diagnosis.

2. Methods

2.1. Study design and data source

The Korean National Health Insurance Service (NHIS) is a mandatory insurance system in South Korea that covers 97 % of the population through national health insurance and provides medical aid to the remaining 3 % at the lowest income level. This nationwide, population-based cohort study utilized data from the NHIS database, which comprises comprehensive patient information, including demographic records, date of death, and healthcare data such as diagnostic codes, prescription records, medical procedures, treatments, and costs. Data from January 2012 to December 2021 were available for analysis.

2.2. Protocol approval and patient consent

The study protocol was approved by the Institutional Review Board of Wonju Severance Christian Hospital (CR321308) and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was formally waived due to the secondary analytical study design and the use of de-identified data.

2.3. Study population

We included patients newly diagnosed with MCI between January 1, 2013, and December 31, 2016. MCI was defined according to the International Classification of Disease, 10th Revision (ICD-10), using code F067. The exclusion criteria were: (i) diagnosis of MCI in 2012, (ii) prior history of dementia (ICD-10 codes F00-F03, G30-G31), (iii) age below 40 years, (iv) dementia diagnosis within 1 year of the initial MCI diagnosis, (v) stroke diagnosis after MCI diagnosis, and (vi) TBI diagnosis within 1 year of MCI diagnosis. We excluded any patient who sustained a TBI in the year following MCI diagnosis to avoid including cases where an immediate post-MCI trauma could confound the baseline cognitive status. Additional details regarding the cohort selection process can be found in Additional file 1.

2.4. TBI diagnosis

Participants were classified into two groups based on the presence or absence of TBI, identified using the following codes: S01.0-S01.9, S02.0, S02.1, S02.3, S02.7-S02.9, S04.0, S06.0-S06.3, S06.7-S06.9, S07.0, S07.1, S07.8, S07.9, T01.0, T02.0, T04.0, T06.0, T90.1, T90.2, T90.4, T90.5, T90.8, and T90.9 [29–31]. When defining TBI, we excluded epidural, subdural, and subarachnoid hemorrhage (S06.4-S06.6), which may cause direct parenchymal damage. The TBI group consisted of patients who were diagnosed with TBI at least once following the MCI diagnosis. The non-TBI group included individuals without a TBI diagnosis during the study period. To differentiate the severity of TBI, we subdivided the TBI group into those diagnosed only in the outpatient clinic (TBI without admission) and those who required inpatient treatment (TBI with admission).

2.5. Covariates

Covariates included age at the time of MCI diagnosis, sex, income level, and the presence of several chronic conditions, such as hypertension, diabetes mellitus (DM), dyslipidemia, heart failure, chronic kidney disease (CKD), cancer, and chronic obstructive pulmonary disease (COPD). Income levels, initially divided into 20 percentiles using health insurance data, were grouped into three categories: low, middle, and high. Hypertension (I10–I13, I15) and DM (E11–E14) were identified by diagnostic codes from at least one hospital admission or two outpatient visits. Dyslipidemia (E78), heart failure (I50), CKD (N18), and cancer (C00–C97, including rare intractable disease: V193) were defined using diagnostic codes during at least one hospital admission or outpatient visit. COPD was identified using codes J41–J44 from at least one hospital admission. Each of these seven chronic conditions was analyzed as a binary variable, indicating whether the condition was diagnosed within 1 year prior to MCI diagnosis.

2.6. Outcomes

The primary outcome was the development of AD dementia, identified using the diagnostic codes F00 or G30, along with a recorded prescription for dementia medications (rivastigmine, galantamine, donepezil, or memantine). The study population was followed retrospectively from the date of MCI diagnosis until the onset of AD dementia, death, or the conclusion of the study period (December 31, 2021). The secondary outcome measures, which were analyzed in patients who developed AD dementia, were behavioral symptoms identified using ICD-10 codes, such as agitation (R45.1), aggression (R45.6, F91.8), psychosis (R44.1-R44.3, F06.0, F06.2, F23, F24, F28, F29. F32.3, F33.3), delirium (F05), and wandering (Z91.83)[32,33]. To define

incident BPSD, we focused on emergent behavioral disturbances that typically signify neuropsychiatric complications of dementia. We did not include common affective symptoms such as depression or anxiety in our BPSD definition, because these are often present in patients even before dementia onset and are not reliably distinguishable as new 'dementia-related' symptoms in claims data. Our BPSD outcome thus captures mainly the behavioral and psychotic manifestations of dementia.

2.7. Statistical analysis

Baseline characteristics were compared using independent *t*-tests for continuous variables and chi-squared tests with Yates' continuity correction for categorical variables. (i) Cox models for progression from MCI to AD (primary outcome), and (ii) among those who developed AD, Cox models for time from AD diagnosis to BPSD (secondary outcome). The model was adjusted for covariates, including sex, age, income level, hypertension, DM, dyslipidemia, heart failure, CKD, cancer, and COPD. Survival time was defined as the period from MCI diagnosis to the occurrence of dementia, death, or the end of the study period (December 31, 2021). Additionally, we performed additional post hoc subgroup analyses by age, sex, and comorbidities to explore effect modifiers. Kaplan–Meier estimates were used to illustrate the incidence of AD dementia and BPSD, and differences between TBI groups were assessed using log-rank tests. *P*-values of <0.05 were considered statistically significant. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

A total of 452,718 patients with MCI were included in the analysis, with a mean age of 67.16 years (Table 1). Among them, 58,017 (12.7 %) experienced TBI during the follow-up period (mean duration: 2824,960 person-years). The TBI group (66.54 years) had a lower mean age than the non-TBI group (67.25 years) and showed a higher proportion of men (40.5 % vs. 30.5 %, $P < 0.001$). Additionally, the TBI group had a slightly higher prevalence of DM and COPD, whereas hypertension, hyperlipidemia, and cancer were more common in the non-TBI group (All $P < 0.001$). No significant differences were observed in the prevalence of heart failure and CKD.

3.2. AD dementia progression

Progression to AD dementia was observed in 30,503 patients (6.7 %) in overall participatns, 3012 (5.2 %) in the TBI and 27,491 (7.0 %) in the non-TBI group. In the Cox proportional-hazards model adjusted for age, sex, and chronic diseases, the TBI group exhibited a significantly increased risk of AD dementia (hazard ratio [HR] = 1.252, 95 % confidence interval [CI]: 1.206–1.301; Fig. 1A, Table 2). The Harrell's concordance index for this model was 0.7556. Subgroup analysis revealed age-related risk differences (Additional file 4), prompting additional analysis adjusted for age, sex, and chronic diseases. We conducted an ad hoc analysis using age, which showed the greatest difference among these variables. Younger patients (<65 years) exhibited a significantly higher risk for AD dementia (HR = 1.560, 95 %

Table 1
Baseline patient characteristics.

	Total MCI		Non-TBI		TBI		
	n	(%)	n	(%)	n	(%)	*p*-value
Total	452,718	100.0	394,701	87.2	58,017	12.8	
Age, *Mean* (SD)	67.16	10.69	67.25	10.65	66.54	10.95	<0.0001
Age							<0.0001
40~49	25,420	5.6	21,386	5.4	4034	7.0	
50~59	89,369	19.7	77,107	19.5	12,262	21.1	
60~69	136,902	30.2	120,159	30.4	16,743	28.9	
70~79	145,954	32.2	127,642	32.3	18,312	31.6	
80~	55,073	12.2	48,407	12.3	6666	11.5	
Sex							<0.0001
Male	144,051	31.8	120,550	30.5	23,501	40.5	
Female	308,667	68.2	274,151	69.5	34,516	59.5	
Income							<0.0001
Low	114,760	25.3	98,919	25.1	15,841	27.3	
Middle	260,874	57.6	228,335	57.9	32,539	56.1	
High	77,084	17.0	67,447	17.1	9637	16.6	
Hypertension							<0.0001
No	221,152	48.8	192,168	48.7	28,984	50.0	
Yes	231,566	51.2	202,533	51.3	29,033	50.0	
Diabetes mellitus							<0.0001
No	339,008	74.9	296,226	75.1	42,782	73.7	
Yes	113,710	25.1	98,475	24.9	15,235	26.3	
Dyslipidemia							0.0007
No	218,875	48.3	190,442	48.2	28,433	49.0	
Yes	233,843	51.7	204,259	51.8	29,584	51.0	
Heart failure							0.8221
No	434,462	96.0	378,795	96.0	55,667	95.9	
Yes	18,256	4.0	15,906	4.0	2350	4.1	
Chronic kidney disease							0.2759
No	446,315	98.6	389,148	98.6	57,167	98.5	
Yes	6403	1.4	5553	1.4	850	1.5	
Cancer							<0.0001
No	433,031	95.7	377,285	95.6	55,746	96.1	
Yes	19,687	4.3	17,416	4.4	2271	3.9	
COPD							0.0026
No	446,078	98.5	388,994	98.6	57,084	98.4	
Yes	6640	1.5	5707	1.4	933	1.6	

Abbreviations: MCI=mild cognitive impairment; COPD=chronic obstructive pulmonary disease.

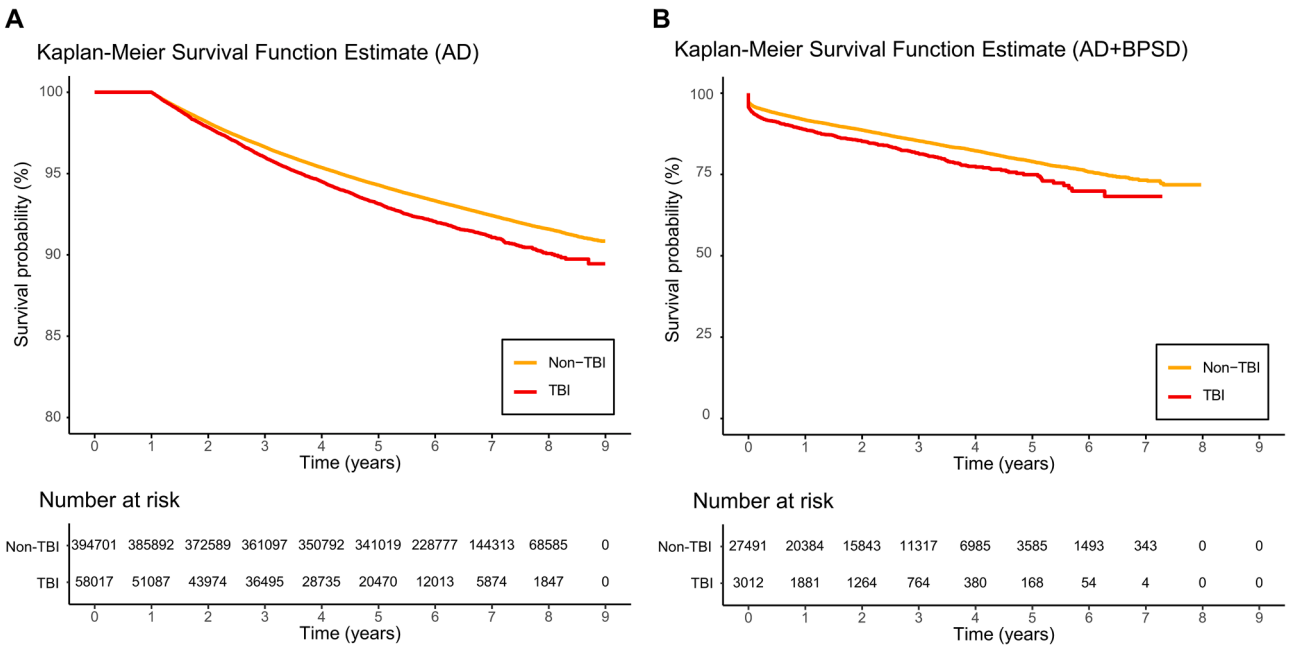

Fig. 1. Kaplan–Meier curves for AD dementia progression and BPSD risk
Kaplan–Meier survival curves illustrating the risk of Alzheimer's disease (AD) dementia progression in the traumatic brain injury (TBI) and non-TBI groups (A) and the risk of behavioral and psychological symptoms of dementia (BPSD) occurrence after AD dementia (B). In both analyses, the TBI group exhibited a higher risk.

Table 2
Cox proportional hazard model for Alzheimer's disease dementia.

	Total	Event		IR	Crude			Model 1			Model 2		
	No.	No.	(%)		HR	95 % CI		HR	95 % CI		HR	95 % CI	
Overall Alzheimer's disease dementia progression													
Non-TBI	394,701	27,491	7.0	11.24	1			1			1		
TBI	58,017	3012	5.2	13.19	1.192	1.148	1.238	1.257	1.210	1.305	1.252	1.206	1.301
Alzheimer's disease dementia progression in young age group (age < 65 years)													
Non-TBI	153,501	2322	1.5	2.27	1			1			1		
TBI	23,958	346	1.4	3.44	1.544	1.378	1.730	1.581	1.410	1.772	1.560	1.391	1.749
Alzheimer's disease dementia progression in old age group (age ≥ 65 years)													
Non-TBI	241,200	25,169	10.4	17.70	1			1			1		
TBI	34,059	2666	7.8	20.88	1.211	1.164	1.261	1.221	1.173	1.271	1.218	1.170	1.267

Model 1 is adjusted for age and sex.
Model 2 is adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, chronic kidney disease, cancer, and chronic obstructive pulmonary disease.
Abbreviations: TBI=traumatic brain injury; IR=incidence ratio; HR=hazard ratio; CI=confidence interval.

CI: 1.391–1.749) than older patients (≥65 years; HR = 1.218, 95 % CI: 1.170–1.267; Table 2). TBI with admission (HR = 1.362, 95 % CI: 1.250–1.484) had a significantly higher hazard ratio than TBI without admission (HR = 1.231, 95 % CI: 1.181–1.283), with the difference being statistically significant ($P = 0.0339$; Additional file 2A, 3).

3.3. Subgroup analysis of AD dementia progression

To further examine the factors influencing the progression from MCI to AD dementia, a subgroup analysis was conducted based on age, sex, income, and the presence of chronic conditions. Regardless of comorbidities, TBIs consistently increased the risk of AD dementia. The effect of TBI was particularly pronounced in younger patients (<65 years), who had a higher risk of AD dementia (HR = 1.475, 95 % CI: 1.315–1.654) than older patients (≥65 years; HR = 1.220, 95 % CI: 1.172–1.270; P for interaction < 0.0001). Additionally, men (HR = 1.296, 95 % CI: 1.216–1.381) demonstrated a slightly higher risk than women (HR = 1.223, 95 % CI: 1.166–1.282; P for interaction = 0.0494). Income level did not significantly modify the association between TBI and AD dementia (P for interaction = 0.2207). Patients without COPD exhibited a higher risk of AD dementia (HR = 1.256, 95 % CI: 1.209–1.305) than those with COPD (HR = 1.080, 95 % CI: 0.837–1.393; P for interaction = 0.0343). The presence of other chronic conditions did not significantly alter the risk of AD dementia progression (Additional file 4).

3.4. AD dementia with BPSD risk

Among patients who converted to AD dementia ($n = 30,503$), BPSD occurred in 471 patients (15.6 %) in the TBI group and in 3965 (14.4 %) in the non-TBI group. The risk of BPSD was significantly higher in the TBI group, as indicated by a Cox proportional hazards model adjusted for age, sex, and chronic diseases (HR = 1.300, 95 % CI: 1.181–1.431; Fig. 1B, Table 3). The Harrell's concordance index for this model was 0.5697. Similarly, the risk for BPSD was higher in younger (HR = 1.489, 95 % CI: 1.113–1.992) than in older patients (HR = 1.278, 95 % CI: 1.154–1.415; Table 3). TBI with admission (HR = 1.325, 95 % CI: 1.066–1.647) showed a higher HR than TBI without admission (HR = 1.295, 95 % CI: 1.116–1.438), but there was no significant difference between the two groups ($P = 0.8507$; Additional file 2B, 3).

Table 3
Cox proportional hazard model for Alzheimer's disease dementia with behavioral and psychologic symptoms of dementia.

	Total	Event		IR	Crude			Model 1			Model 2		
	No.	No.	(%)		HR	95 % CI		HR	95 % CI		HR	95 % CI	
Overall Alzheimer's disease dementia with BPSD													
Non-TBI	27,491	3965	14.4	54.65	1			1			1		
TBI	3012	471	15.6	80.58	1.333	1.211	1.467	1.302	1.183	1.433	1.300	1.181	1.431
Alzheimer's disease dementia with BPSD in young age group (age < 65 years)													
Non-TBI	2322	296	12.7	43.34	1			1			1		
TBI	346	56	16.2	81.76	1.625	1.219	2.165	1.516	1.135	2.025	1.489	1.113	1.992
Alzheimer's disease dementia with BPSD in old age group (age ≥ 65 years)													
Non-TBI	25,169	3669	14.6	55.82	1			1			1		
TBI	2666	415	15.6	80.42	1.308	1.181	1.448	1.277	1.154	1.414	1.278	1.154	1.415

Model 1 is adjusted for age and sex.
Model 2 is adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, chronic kidney disease, cancer, and chronic obstructive pulmonary disease.
Abbreviations: TBI=traumatic brain injury; BPSD= behavioral and psychological symptoms of dementia; IR=incidence ratio; HR=hazard ratio; CI=confidence interval.

3.5. Progression rates from TBI to AD dementia and BPSD after AD dementia diagnosis

The median time from a TBI event to progression to AD dementia was 2.59 years (interquartile range [IQR]: 1.68–3.85) (Fig. 2A, Additional file 5). The cumulative progression rate gradually increased, reaching 34.53 % at 2 years, 59.86 % at 3 years, 76.93 % at 4 years, and 99.8 % at 8 years.

The median time to the onset of BPSD after an AD dementia diagnosis was shorter in the TBI (0.27 years, IQR: 0.00–1.52) than in the non-TBI group (0.83 years, IQR: 0.05–2.36). This suggests a more rapid emergence of neuropsychiatric symptoms following AD dementia onset in patients with TBI. In the TBI group, 66.88 % of patients developed BPSD within the first year, increasing to 80.68 % in year 2 and 90.23 % in year 3. By year 7 post-AD dementia diagnosis, all patients with TBI who eventually developed BPSD had already done so. In contrast, the non-TBI group showed a more gradual progression, with 54.00 % of cases occurring within the first year, 69.76 % in year 2, and 82.75 % in year 3 (Fig. 2B, Additional file 5).

4. Discussion

Using a large-scale cohort from South Korea, we aimed to investigate whether TBI events occurring after a diagnosis of MCI influence the risk of AD dementia and the incidence of BPSD after a diagnosis of AD dementia. Among patients with MCI, those who experienced at least one TBI had a significantly increased risk of developing AD dementia. This effect varied by age, with a notably higher risk of AD dementia progression in patients under 65 years. Furthermore, the likelihood of BPSD occurrence after an AD dementia diagnosis was significantly higher in the TBI group. TBI severity was classified according to the presence of inpatient treatment. While the risk of AD progression differed by severity, there was no clear difference in the risk of BPSD according to the degree of severity. Additionally, the transition to AD dementia occurred approximately 2.59 years after a TBI event, and the onset of BPSD after an AD dementia diagnosis occurred earlier in the TBI than in the non-TBI group.

Despite variations in TBI definitions, dementia subtype classifications, and study methodologies, large-scale studies have consistently reported associations between TBI and dementia risk. A study of 188,764 U.S. veterans reported a 1.57-fold increased risk of dementia in patients with TBI[8]. Population-based studies from Taiwan (HR 1.68), Finland (HR 1.30), and Wales (HR 2.32) have corroborated these findings[34–36]. Additionally, a systematic meta-analysis focusing on AD-type dementia found a pooled risk ratio of 1.68. Studies implementing a lag period of at least 1 year between TBI events and dementia onset showed a pooled risk ratio of 1.24, indicating a higher dementia risk in patients with TBI [37]. Notably, even mild TBI has been associated with increased AD-type dementia risk in systematic review [27]. These findings suggested relationships TBI and dementia persist across different study designs, populations, and geographic regions. In our study, even after implementing a 1-year washout period post-TBI, the increased AD-type dementia progression risk remained consistent. We extend this knowledge by specifically showing this effect in an MCI cohort and by demonstrating an association with BPSD. This suggests that TBI may not only accelerate cognitive decline but also precipitate earlier emergence of challenging neuropsychiatric symptoms in the course of AD dementia.

Pathological studies have provided evidence that TBI influences the progression of AD pathology. In individuals who died in the acute phase following TBI, a postmortem study showed diffuse Aβ plaques resembling Aβ plaques of early-stage AD, even in very young adults [38,39]. In long-term TBI survivors, the deposition pattern of Aβ plaques appeared to evolve over time, with denser fibrillar plaques becoming more common [13]. Tau pathology has been observed following a single TBI, with widespread accumulation of NFTs with Aβ plaques in approximately two-thirds of long-term survivors [13]. TBI events lead to axonal injury, resulting in demyelination and cytoskeletal damage, which contribute to the accumulation and spreading of p-tau. Additionally, axonal bulb formation promotes the production and dissemination of Aβ, while microglial activation further contributes to the development of AD pathology [40]. It is also unclear to what extent the dementia outcomes in our TBI-affected patients were due to exacerbation of AD pathology versus due to CTE pathology or other trauma-related neurodegenerations. TBI and AD are not mutually exclusive, and they may act in parallel. We lacked biomarkers to differentiate AD from CTE, however, some patients with TBI could develop a tauopathy consistent with CTE that mimics or coincides with AD. We interpret our findings as likely stemming from a combination of these mechanisms.

BPSD occurring after TBI has also been linked to an increase in AD pathology. A longitudinal study following up participants from cognitively unimpaired to dementia found that those with a history of TBI had a higher incidence of apathy and motor disturbances, while anxiety symptoms emerged earlier [41]. In patients with severe TBI, increased white matter ^{11}C-PiB PET uptake was associated with more severe neuropsychiatric symptoms such as psychosis. In autopsy-confirmed CTE patients, higher p-tau aggregation in the frontal cortex was linked to more severe neurobehavioral dysregulation [42]. Animal studies using a repetitive mild TBI model have also demonstrated increased anxiety-like behavior; these mice exhibited persistent microglial activation and astrocytosis, along with progressive white matter atrophy and axonal degeneration[43,44]. Therefore, TBI at the MCI stage may exacerbate frontal lobe-related AD pathology, potentially leading to an earlier onset and increased risk of BPSD.

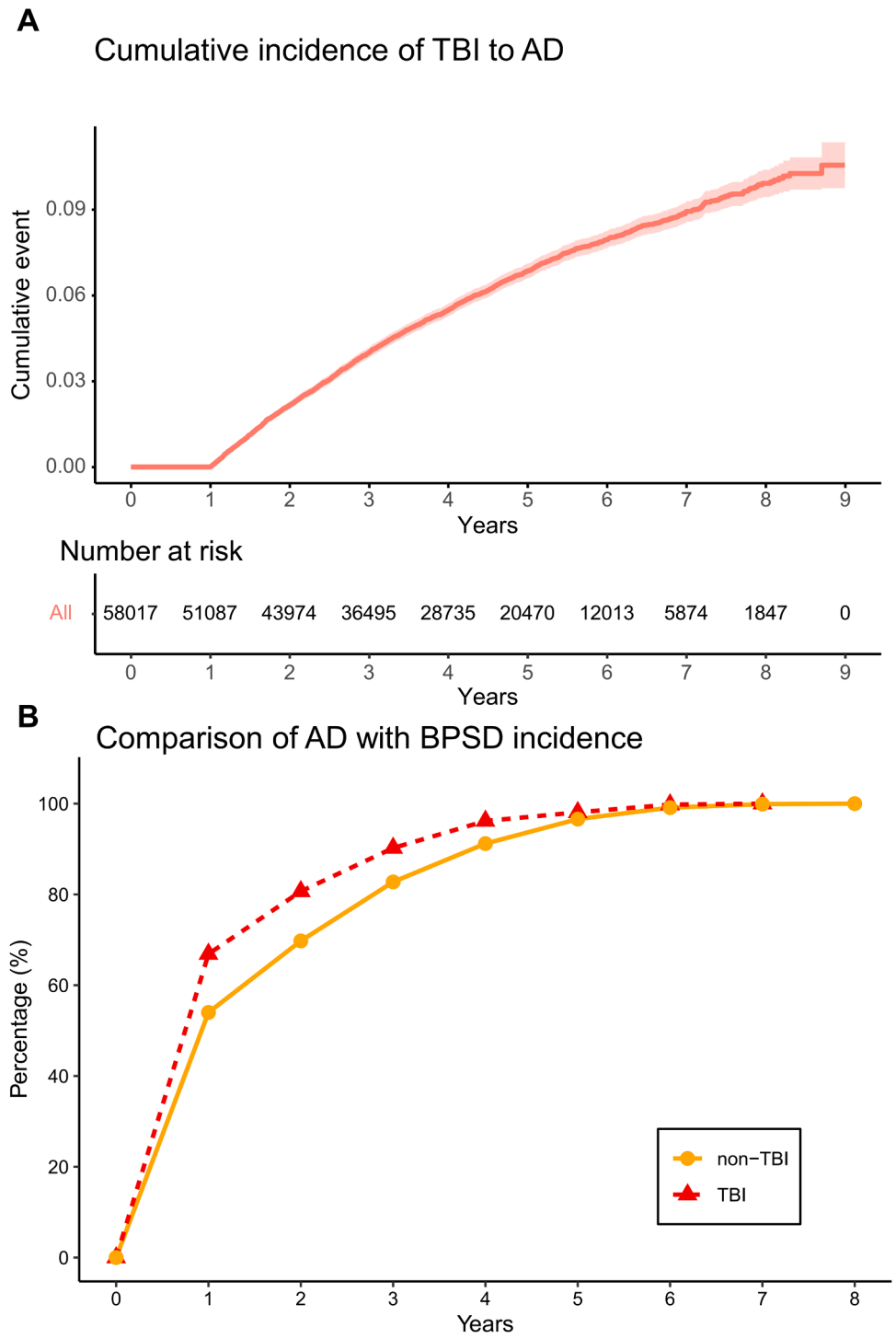

Fig. 2. Cumulative TBI-to-AD dementia incidence and AD with BPSD comparison between TBI and non-TBI groups
Cumulative incidence of Alzheimer's disease (AD) dementia progression following a traumatic brain injury (TBI) event, with a median progression time of 2.59 years (A). Comparison of the time to AD with behavioral and psychological symptoms of dementia (BPSD) onset between the TBI and non-TBI groups, showing a faster occurrence in the TBI group (median 0.27 vs. 0.83 years; B).

In our study, younger patients with MCI exhibited a higher rate of AD dementia progression. Previous large-scale studies have consistently shown that younger patients (<65 years) have a higher risk of developing dementia following TBI. In a large AD registry study, the prevalence of prior TBI was significantly higher in early- than in patients with late-onset AD. Additionally, disinhibition and irritability were more frequent in early-onset cases [45]. A large-scale study in Denmark showed that the younger the age at TBI, the higher the risk of dementia [46]. A study using the Swedish Twin Registry found that in individuals with cardiometabolic diseases, experiencing TBI between the ages of 50–69 years increased the risk of dementia [47]. A meta-analysis demonstrated that the risk of dementia following TBI was significantly higher in individuals under compared to those over 65 years old [48]. Although clear evidence linking TBI at a younger age to an increased risk of AD dementia is limited, hypotheses suggest that axonal shear injury occurring at a younger age may lead to early tau hyperphosphorylation

or facilitate faster spreading of Aβ and tau in younger individuals [49, 50].

4.1. Limitations

This study has several limitations. First, dementia was defined based on diagnostic codes and prescriptions for anti-dementia medications rather than clinical diagnostic criteria. Similarly, the definitions of TBI, BPSD, and other comorbidities were determined solely based on diagnostic codes from claims data, which raises the possibility of misclassification. Given the nature of public data, clinical assessments from memory clinics were not exclusively included. We cannot stratify by setting, but we acknowledge that diagnostic accuracy differs: primary care physicians have modest sensitivity (about 60 %) and high specificity (about 90 %) for dementia [51]. Thus, some misdiagnosis or under-diagnosis of AD and BPSD is possible. Second, we did not collect clinical features of dementia, such as AD biomarker profiles, neuropsychological tests, or scales assessing neuropsychiatric features. Our definition of AD may have misclassified some cases. Some patients labeled 'AD' could have mixed or non-AD dementia. We chose AD, rather than all-cause dementia, to specifically test our hypothesis on AD-related neurodegeneration and to avoid counting direct effects of TBI as outcomes. Third, since TBI was defined based on diagnostic codes, it was challenging to distinguish the severity of TBI. Because the severity of TBI itself was not recorded, we used admission status as a proxy to distinguish severity, however, this may have introduced some bias. Our study's strength lies in the enrollment of patients with MCI—a population at higher risk for AD dementia compared to a healthy cohort—which enabled us to detect the impact of TBI on dementia progression and the earlier emergence of BPSD over a relatively short follow-up period. Moreover, the large sample size provided robust statistical power, highlighting associations that might have otherwise required much longer observation periods in lower-risk populations. Forth, our definition of BPSD was narrow and did not capture mood symptoms, which is a conservative approach that may underestimate total neuropsychiatric symptom burden. Lastly, the performance of the model for BPSD occurrence after an AD dementia was relatively limited, with a C-index of 0.5697. This may reflect the clinical heterogeneity and complexity of BPSD manifestation, which are difficult to fully capture in administrative data. Nevertheless, we believe the descriptive value of our findings remains meaningful, as the study utilized a large, nationally representative population-based cohort to investigate associations between TBI and BPSD among patients with AD.

5. Conclusions

In this large, nationwide cohort of individuals with MCI, we found that TBI at MCI stage modestly increased the future risk of progression to AD and the development of BPSD. When stratified by TBI severity using inpatient admission as a proxy, the risk of AD progression differed according to severity, whereas no clear difference was observed in the risk of BPSD between more severe and less severe TBI groups. These results suggest that while TBI severity may influence AD vulnerability, it does not appear to significantly affect the risk of BPSD. Our findings underscore the clinical relevance of TBI prevention in individuals with MCI, not only to reduce the risk of AD progression but also to mitigate the emergence of BPSD. Clinically, these results highlight that MCI patients with even mild TBIs could be progressed dementia and neuropsychiatric complications. Moreover, those who have a history of TBI merit closer surveillance for dementia conversion and BPSD so that interventions can be implemented early. Future research should clarify the mechanistic links between TBI and neurodegeneration and explore more nuanced measures of TBI severity and timing.

CRediT authorship contribution statement

Han-Kyeol Kim: Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Sojeong Park:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sung-Woo Kim:** Methodology, Investigation, Data curation, Conceptualization. **Yeonju Jin:** Methodology, Investigation, Formal analysis, Data curation. **Hokyung Lee:** Resources, Methodology, Formal analysis, Data curation. **Jin Yong Hong:** Validation, Supervision, Resources. **Ickpyo Hong:** Writing – review & editing, Validation, Supervision, Project administration, Data curation. **Min Seok Baek:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Min Seok Baek reports financial support was provided by Korea Ministry of Science and ICT. Han-Kyeol Kim reports financial support was provided by Korea Ministry of Education. Min Seok Baek reports financial support was provided by Korea Ministry of Trade Industry and Energy. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors have no conflicts of interest to declare.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government Ministry of Science and ICT (grant numbers 2022R1C1C1012535 and RS-2024-00358576), the Ministry of Education (grant number RS-2023-00247986), and the Technology Innovation Program (grant number 20018182) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea). The funders had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100360.

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