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ORIGINAL RESEARCH

Elevated Risk of Stroke in Young Adults After Traumatic Brain Injury: A Nationwide Study of 1 Million Individuals

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BACKGROUND: Although stroke is commonly perceived as occurring in older adults, traumatic brain injury, one of the risk factors for stroke, is a leading cause of death in the younger adults. This study evaluated stroke risk in young-to-middle-aged adults based on traumatic brain injury severity and stroke subtypes.

METHODS AND RESULTS: For this retrospective, population-based, cohort study, data of adults aged 18 to 49 years who were diagnosed with traumatic brain injury were obtained from the Korean National Health Insurance Service between 2010 and 2017. Traumatic brain injury history was measured based on the *International Classification of Diseases*, *Tenth Revision (ICD-10)*, codes. Posttraumatic brain injury stroke risk was analyzed using a time-dependent Cox regression model. At baseline, 518 423 patients with traumatic brain injury and 518 423 age- and sex-matched controls were included. The stroke incidence rate per 1000 person-years was 3.82 in patients with traumatic brain injury and 1.61 in controls. Stroke risk was approximately 1.89 times as high in patients with traumatic brain injury (hazard ratio, 1.89 [95% CI, 1.84–1.95]). After excluding stroke cases that occurred within 12 months following traumatic brain injury, these significant associations remained. In the subgroup analysis, patients with brain injury other than concussion had an approximately 9.34-fold risk of intracerebral hemorrhage than did the controls.

CONCLUSIONS: Stroke prevention should be a priority even in young-to-middle-aged adult patients with traumatic brain injury. Managing stroke risk factors through regular health checkups and modifying health-related behaviors is necessary to prevent stroke.

Key Words: population-based studies ■ retrospective studies ■ stroke ■ traumatic brain injury

See Editorial by Katz and Dwyer.

Traumatic brain injury (TBI) is the leading cause of mortality and morbidity in people aged <45 years worldwide.[1] In the United States, approximately 1.7 million TBIs are reported each year,[2,3] and approximately 69 million new TBIs occur annually worldwide.[4] It is estimated that half of the population globally will experience TBI at least once in their lifetime.[5] In particular, TBI occurs frequently in the young population actively involved in economic activities, which can result in a significant socioeconomic burden.[6]

TBI can cause neurological complications, such as cognitive impairment, dementia, Parkinson's disease, Alzheimer's disease, and epilepsy.[7–10] Stroke is another prevalent neurological disorder associated with TBI. According to a recent meta-analysis, patients with TBI had a 1.8-times greater risk of stroke than did the controls.[11] The previous meta-analysis revealed that TBI

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CLINICAL PERSPECTIVE

What Is New?

- Although traumatic brain injury (TBI) is an important risk factor for stroke, there is a paucity of research on the risk of stroke after TBI in young-to-middle-age groups where TBI is prevalent.
- This retrospective study, based on a large population-based cohort of approximately 1 million people, found that the risk of stroke after TBI was approximately 1.89 times that of controls in adults aged 18 to 49 years, a population with a low prevalence of stroke.
- Notably, the elevated risk of stroke post-TBI persists even after excluding stroke cases that occurred within 1 year of TBI.

What Are the Clinical Implications?

- Stroke prevention should be prioritized in young-to-middle-aged patients with TBI.
- Even young-to-middle-aged patients with TBI should undergo regular health checkups to manage stroke risk factors and prevent stroke occurrence by modifying health-related behaviors.

Nonstandard Abbreviations and Acronyms

ICH	intracerebral hemorrhage
IS	ischemic stroke
NHIS	National Health Insurance Service

was linked to an increased risk of stroke regardless of the stroke subtype.[11]

Strokes are more prevalent in older adults. However, although the overall incidence of stroke is decreasing in developed countries, the incidence of stroke in young adults is increasing.[12] In the United States, the incidence of stroke among young adults aged 20 to 44 years has increased from 17 per 100 000 in 1993 to 28 per 100 000 in 2015.[13] Despite the increasing incidence, stroke in younger patients is often overlooked by clinicians due to its unexpectedness, resulting in missed opportunities for early intervention. Compared with older patients, younger patients with stroke experience stroke sequelae over a longer period, the rest of their lives. Younger patients with stroke are frequently affected by physical disability, depression, cognitive impairment, and loss of productivity, resulting in a significant personal, social, and economic burden.[13] Notably, after 20 years of follow-up, the mortality rate of patients who survived the first 30 days after their stroke was 3.5 times that of the general population.[12]

Therefore, this study aimed to evaluate the risk of stroke following TBI in adults aged ≤49 years using nationwide health insurance data in Korea. Previous studies suggested that the risk of stroke after TBI varied depending on the stroke subtype.[14–16] Therefore, we comprehensively present the risk of stroke subtypes, including ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). We also examined the association between TBI and stroke in the Korean young-to-middle-aged adult population by the combination of the types of TBI and 3 stroke subtypes. Additionally, we investigated whether the association between TBI and stroke is maintained after excluding stroke cases that occurred soon after TBI, consistent with a previous study.[16]

METHODS

Data Source

The Korean National Health Insurance Service (NHIS) provided customized research data for this study (NHIS-2023-1-321). These data do not belong to the authors but to the Korean NHIS, and the authors are not permitted to share it, except in aggregate form. Ja-Ho Leigh had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

The NHIS is a government-mandated social insurance scheme covering approximately 50 million people,[17] 97.2% of all South Koreans.[18] General medical data from inpatient and outpatient procedures are included in the NHIS database. Medical information included in the NHIS were assessed by medical doctors using the *International Classification of Diseases, Tenth Revision* (*ICD-10*). The NHIS database generally contains information regarding primary and secondary diagnoses, surgical history, therapy, medication, and national health checks. Our customized data in this study included information regarding sociodemographic variables, death, primary and additional diagnoses, and health checkups of the study population.

Study Population

Figure S1 shows a flow chart for the study population. Customized data from 2008 to 2017 were reviewed, and the study population was selected. The washout period for previous TBI and previous stroke was set between 2008 and 2009. Participants were included based on their first hospital visit date, regardless of diagnosis between January 1 and December 31, 2010 (baseline), and followed up until December 31, 2017. TBI occurrence was classified using *ICD-10* codes (S06.0, S06.1, S06.2, S06.3, S06.4, S06.5, S06.6, S06.7, S06.8, S06.9, S02.0, S02.1, S02.7, S02.8, and S02.9).[19,20] A total of 1 838 546 patients diagnosed with

TBI between 2010 and 2017 were included, as were 5 511 036 individuals who had never been diagnosed with TBI during the same period (controls without TBI). Overall, 7 349 582 individuals with demographic variables at the baseline were included. After excluding individuals who had a previous diagnosis of TBI (*n*=359 536) or recurrent TBI (*n*=81 839), those who had a previous diagnosis of stroke (*n*=169 134) before baseline or an incidence of stroke within 2 weeks after TBI (*n*=26 123), and adolescents aged <18 years or seniors aged ≥50 years at baseline (*n*=3 519 923), a total of 3 193 027 individuals were selected. Finally, 518 423 patients with TBI and 1:1 age- and sex-matched controls (*n*=518 423) were included in this study. To include matched controls, a pool of eligible cases and a pool of eligible controls was created. By using a lookup table of sample sizes, equal numbers from each subgroup were randomly selected based on the age and sex.[21]

Variables

According to the *ICD-10* codes, the incidence of stroke—including subtypes IS (I63, I64), ICH (I61, I62), and SAH (I60)—was examined.[6] When 2 or more stroke subtypes occurred in 1 patient, the number of total stroke was counted once and that of each stroke subtype was counted individually.

Potential confounders were chosen based on a literature review. All sociodemographic characteristics were included from the baseline. The insurance premium was divided into quartiles based on household income levels. Based on administrative districts, the region of residence was separated into two categories[22]: urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju). To measure comorbidities, we selected diseases associated with stroke from the Charlson Comorbidity Index scores components: myocardial infarction (I21, I22, I25.2), peripheral vascular diseases (I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9), diabetes without complications (E10.0, E10.1, E10.6, E10.8, E10.9, E11.0,E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9) and diabetes with complications (E10.2, E10.3, E10.4, E10.5, E10.7, E11.2, E11.3, E11.4, E11.5, E11.7, E12.2, E12.3, E12.4, E12.5, E12.7, E13.2, E13.3, E13.4, E13.5, E13.7, E14.2, E14.3, E14.4, E14.5, E147).[23] The types of TBI was classified using *ICD-10* codes based on the definition given by the American Congress of Rehabilitation Medicine and other previous population-based studies.[19,20,24] TBIs were classified into concussion (S06.0), brain injury other than concussion (S06.1–S06.9), and skull fracture (S02.0, S02.1, S02.7, S02.8, S02.9). Only skull fracture without a TBI diagnosis was classified as skull fracture.

Of the 1 036 846 study participants, 268 199 received a health examination at baseline (TBI *n*=126 651; without TBI *n*=141 548). All laboratory variable results and information on health-related behaviors were included in the health checkup data at the baseline. Body mass index (BMI) was divided into 4 categories: underweight (BMI<18.5 kg/m^2), normal (18.5 kg/m^2≤BMI<23 kg/m^2), overweight (23 kg/m^2≤BMI<25 kg/m^2), and obese (BMI≥25 kg/m^2).[25] Based on the systolic blood pressure (SBP) or diastolic blood pressure (DBP) measurement results, blood pressure was divided into 4 categories: hypotension (SBP<90 mm Hg or DBP<60 mm Hg),[26] normal (90 mm Hg≤SBP<120 mm Hg or 60≤DBP<80 mm Hg),[26] prehypertension (120 mm Hg≤SBP<140 mm Hg or 80≤DBP<90 mm Hg),[27] and hypertension (SBP≥140 mm Hg or DBP≥90 mm Hg).[26,27] Low-density lipoprotein (LDL) cholesterol level was divided into 5 categories: optimal (LDL cholesterol <100 mg/dL), normal (100 mg/dL≤LDL cholesterol<130 mg/dL), borderline risk (130 mg/dL≤LDL cholesterol<160 mg/dL), high risk (160 mg/dL≤LDL cholesterol<190 mg/dL), and very high risk (LDL cholesterol ≥190 mg/dL).[28] A self-report questionnaire in the health-checkup data was used to obtain information on physical activity, smoking, and alcohol consumption levels.[29]

Statistical Analysis

Summary statistics were used to present the sociodemographic characteristics of the participants. In addition, the chi-square test was used to compare the baseline characteristics and incidence rates[30] between patients with TBI and controls.

Survival curves were estimated using a cumulative incidence plot and compared using the log-rank test. The baseline of this study is the first hospital visit date in 2010, and the end point is the incidence of stroke, death, or the end of the study period (December 31, 2017), whichever occurred first. Participants who died before the onset of stroke were defined as censored. The median follow-up time was 7.44 years and 7.45 years in patients with TBI and controls, respectively.

Although all participants in our retrospective cohort were recruited at baseline in 2010, the date of TBI onset ranged from 2010 to 2017, which may introduce an immortality bias due to the time difference between baseline and TBI onset in the patients with TBI.[31] To avoid this immortal bias, a time-dependent Cox regression model was adapted. Specifically, time-dependent Cox models are frequently employed in scenarios with a waiting period exists between baseline and exposure, as exemplified in organ transplantation.[32] In this

study, TBI was used as a time-varying exposure, as patients with TBI did not have TBI at the baseline but developed it over time (Figure S2). The waiting period of patients with TBI before TBI onset was considered the unexposed survival time.

Subgroup analyses were performed based on the types of TBI and stroke subtype. To exclude patients with strokes that occurred close to the onset of TBI, the washout duration was modified from 2 weeks to 1, 3, 6, and 12 months in the secondary analyses. Subdistribution hazard regression was adopted as the sensitivity analysis to account for competing risks due to mortality. In addition, Bonferroni correction was used for multiple comparisons in the subgroup and secondary analyses.

SAS statistical software, version 9.4 (SAS Institute, Cary, NC), was used for all statistical analyses. The cumulative incidence plot was created using the "survival," "survminer," and "ggplot2" R packages and the Forest plot was drawn with the "forestplot" R package using R, version 4.0.3 (R Development Core Team, Vienna, Austria). All reported *P* values are 2 sided; *P* values <0.05 were considered statistically significant.

Ethics Statement

The Institutional Review Board of Seoul National University Hospital, Seoul, South Korea, waived the need for ethical approval of this study (IRB no. E-2303-005-1408). The requirement for informed consent was also waived because the data were anonymized and deidentified. This article was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Table S1).

RESULTS

In terms of the sociodemographic characteristics of the study population, from 2010 to 2017, 14 518 and 6158 stroke cases occurred in the TBI and control groups, respectively. IS was the most common stroke subtype in both groups. The total follow-up time was 3 799 278 years and 3 829 198 years in patients with TBI and controls, respectively. The stroke incidence rate per 1000 person-years was greater in the TBI group than in the control group (3.82 and 1.61, respectively). The median age was 36 years and the proportion of men was 52.08% in both groups, as age and sex were matched. The proportion of patients with concussion was the highest (82.07%) in the TBI group (Table 1).

Figure S3 depicts the cumulative incidence. The cumulative incidence revealed that patients with TBI have a greater risk of stroke. We calculated hazard ratios (HRs) using time-dependent Cox regression (Table 2). The crude model showed that patients with TBI had a stroke risk 1.97 times that of the controls (HR, 1.97 [95% CI, 1.92–2.03]). After adjusting for sociodemographic factors and comorbidities, the risk of stroke in patients with TBI was 1.89 times that of the controls (HR, 1.89 [95% CI, 1.84–1.95]). Similar results were shown when we considered competing risks due to mortality (HR, 1.74 [95% CI, 1.68–1.80]) (Table S2).

Additionally, we adjusted for traditional stroke risk factors in the subset of this study population that underwent a health checkup at baseline (*n*=268 199). Table S3 summarizes the comprehensive information of the participants who underwent health checkups. Even after additional adjustments for obesity, blood pressure, LDL cholesterol levels, and health-related behaviors, the risk of stroke was 1.84 times as high in the TBI group as that of the control group (HR, 1.84 [95% CI, 1.73–1.95]) (Table S4).

In the subgroup analysis based on the types of TBI, patients with brain injury other than concussion had the highest risk of stroke (HR, 4.85 [95% CI, 4.64–5.08]) (Figure 1). Additionally, even in patients with concussion, the risk of stroke was 1.55 times as high as that of those without TBI (HR, 1.55 [95% CI, 1.49–1.60]). Subgroup analysis based on stroke subtypes shows that patients with TBI had the highest risk of ICH (HR, 2.63 [95% CI, 2.49–2.78]) (Figure 1).

In the subgroup analysis based on the combination of the type of TBI and stroke subtype, the TBI group had a risk of ICH that was higher than their risk of other stroke subtypes. Patients with brain injury other than concussion had a 9.34-fold risk of ICH (HR, 9.34 [95% CI, 8.70–10.02]), patients with skull fractures had a 5.06-fold risk of ICH (HR, 5.06 [95% CI, 4.25–6.04]), and patients with concussion had a 1.93-fold risk of ICH (HR, 1.93 [95% CI, 1.79–2.08]) than did the controls (Figure 2).

In the secondary analysis, stroke cases that occurred within 1, 3, 6, or 12 months following TBI onset were excluded (Figure 3). After excluding stroke cases that occurred within 1 month after TBI, the risk of any stroke following TBI reduced to 1.74 (HR, 1.74 [95% CI, 1.69–1.79]). The risk of any stroke gradually decreased as the washout period became longer but was still significant after Bonferroni correction. Furthermore, even after 12 months of washout, the risk of ICH in patients with TBI was still 20% higher than that in the control group (HR, 1.20 [95% CI, 1.13–1.29]).

DISCUSSION

In this study, we conducted a detailed examination of the risk of stroke in young-to-middle-aged adult patients with TBI according to the combination of the type of TBI and stroke subtype using nationwide data with a long-term follow-up of 7 years. Our results showed that patients with TBI had a 1.89-fold risk of stroke

Table 1. Sociodemographic Characteristics of the Population (*n*=1 036 846)

	TBI (*n*=518 423)	Without TBI (*n*=518 423)	*P* value
Stroke, *n* (%)	14 518 (3.59)	6158 (1.64)	
Stroke subtype, *n* (%)			
Ischemic stroke	8535 (1.65)	4521 (0.87)	
Intracerebral hemorrhage	4761 (0.92)	1208 (0.23)	
Subarachnoid hemorrhage	1578 (0.3)	574 (0.11)	
Person-years, y	3 799 278	3 829 198	
Incidence rate of stroke, per 1000 person-years	3.82	1.61	<0.0001
Median age, y (interquartile range)	36 (27–43)	36 (27–43)	
Age group, *n* (%)			
18–29 y	165 656 (31.95)	165 656 (31.95)	1.0
30–39 y	152 085 (29.34)	152 085 (29.34)	
40–49 y	200 682 (38.71)	200 682 (38.71)	
Sex, *n* (%)			
Male	269 978 (52.08)	269 978 (52.08)	1.0
Female	248 445 (47.92)	248 445 (47.92)	
Region of residence, *n* (%)			
Urban	230 563 (44.47)	244 520 (47.17)	<0.0001
Rural	279 603 (53.93)	268 052 (51.71)	
Missing	8257 (1.59)	5851 (1.13)	
Insurance type, *n* (%)			
Employee insured	294 832 (56.87)	333 078 (64.25)	<0.0001
Self-employed	202 280 (39.02)	173 637 (33.49)	
Medical aid	21 311 (4.11)	11 708 (2.26)	
Insurance premium, *n* (%)			
First quartile (lowest)	126 408 (24.38)	105 159 (20.28)	<0.0001
Second quartile	118 159 (22.79)	108 007 (20.83)	
Third quartile	129 267 (24.93)	133 309 (25.71)	
Fourth quartile (highest)	129 898 (25.06)	156 042 (30.1)	
Missing	14 691 (2.83)	15 906 (3.07)	
Comorbidities, *n* (%)			
Myocardial infarction	899 (0.17)	620 (0.12)	<0.0001
Peripheral vascular diseases	10 170 (1.96)	8196 (1.58)	<0.0001
Diabetes without complications	15 438 (2.98)	12 473 (2.41)	<0.0001
Diabetes with complications	5424 (1.05)	4225 (0.81)	<0.0001
Types of TBI, *n* (%)			
Concussion	425 469 (82.07)	…	
Brain injury other than concussion	72 775 (14.04)	…	
Skull fracture	20 179 (3.89)	…	

TBI indicates traumatic brain injury.

than did the controls in the Korean young-to-middle-aged adult population. These significant associations persisted even when stroke cases that occurred within 12 months after TBI were excluded. In the subgroup analysis, TBI was significantly associated with all stroke subtypes, including IS, ICH, and SAH. Stroke risk was the highest in patients with brain injury other than concussion.

TBI is a common injury in young adults, especially in sports,[33] occupational,[34] and violence-related trauma.[35] According to a previous study in the United States, the direct medical expenses of TBI have been estimated at $13.1 billion, and indirect costs from loss of work or productivity have been estimated at $64.7 billion in 2013. Due to the young age of patients and the potential for severe disability, TBI imposes huge per capita costs.[36] However, young adult patients with TBI generally tend to be considered less critical than pediatric or older patients, and even these patients themselves are often indifferent

Table 2. Time-Dependent Cox Regression for Stroke Occurrence After TBI in Adults Aged ≤49 Years

	Hazard ratio (95% CI)	*P* value
TBI (Model 1)	1.97 (1.92–2.03)	<0.0001
TBI (Model 2)	1.91 (1.85–1.97)	<0.0001
TBI (Model 3, fully adjusted)	1.89 (1.84–1.95)	<0.0001
Age	1.07 (1.07–1.08)	<0.0001
Sex		
Male	1.0	
Female	0.74 (0.72–0.76)	<0.0001
Region of residence		
Urban	1.0	
Rural	1.11 (1.08–1.14)	<0.0001
Missing	0.97 (0.86–1.10)	0.7086
Insurance type		
Employee insured	1.0	
Self-employed	1.27 (1.23–1.31)	<0.0001
Medical aid	2.30 (2.17–2.43)	<0.0001
Insurance premium		
First quartile (lowest)	1.0	
Second quartile	0.90 (0.87–0.94)	<0.0001
Third quartile	0.81 (0.78–0.85)	<0.0001
Fourth quartile (highest)	0.75 (0.72–0.78)	<0.0001
Missing	0.92 (0.84–1.01)	0.0942
Comorbidities		
Myocardial infarction	1.83 (1.51–2.22)	<0.0001
Peripheral vascular diseases	1.46 (1.36–1.56)	<0.0001
Diabetes without complications	1.67 (1.58–1.77)	<0.0001
Diabetes with complications	1.73 (1.60–1.87)	<0.0001

Model 1: crude model. Model 2: adjusted for age, sex, insurance premium, region of residence, and insurance type. Model 3: adjusted for age, sex, insurance premium, region of residence, insurance type, and comorbidities. TBI indicates traumatic brain injury.

to their health conditions. In a previous online survey, 32% of 287 undergraduate students who experienced TBI answered that they had experienced at least 1 untreated mild TBI.[37] Another previous study also reported that younger age groups have reduced awareness of health problems. The discrepancy between self-perceived health status and actual health condition increased with every 5-year decrease in age.[38] According to our present study, the risk of any stroke was 1.55 times as high and the risk of ICH was 1.93 times as high in the patients with concussion as in the controls, even in the young adult population. Furthermore, when we excluded patients with stroke that occurred within 1 year after TBI, the HR for post-TBI stroke decreased from 1.74 (HR, 1.74 [95% CI, 1.69–1.79]) to 1.09 (HR, 1.09 [95% CI, 1.06–1.13]), suggesting that the elevated risk appears predominantly within the first year post-TBI. Therefore, even in young adult patients, active management of stroke risk factors, such as blood pressure, glucose, and lipid control, might be needed for at least 6 months after TBI to prevent hemorrhagic stroke. In addition, it is also important for patients with TBI to manage their risk factors for stroke through regular health checkups and health-related lifestyle modifications.

Previous studies found a significant association between TBI and stroke, which is consistent with our findings. During a 5-year follow-up period, patients with TBI had an increased risk of IS (HR, 1.43 [95% CI, 1.31–1.56]), ICH (HR, 6.33 [95% CI, 5.60–7.83]), and SAH (HR, 4.83 [95% CI, 3.81–7.19]), according to a population-based study using Taiwanese health insurance data.[39] Another Taiwanese population-based study found that TBI was significantly associated with an increased risk of IS (HR, 1.64, [95% CI, 1.49–1.81]) and hemorrhagic stroke (HR, 4.13 [95% CI, 3.57–4.78]).[40] A US statewide study[16] and single-center study among older adults[41] found significant associations between TBI and IS.

Several plausible mechanisms also support our findings. Physical damage to the cerebrovascular system after TBI may disrupt blood flow to the brain, resulting in stroke.[39] TBI also can cause extracranial dissection of the basilar or carotid artery and thrombus formation. Clot formation due to local arterial bleeding at the site of TBI may result in stroke. In a previous cross-sectional study, coated-platelet levels were greatly and constantly increased in patients with mild TBI.[42] Blunt cerebrovascular injury after skull fracture also can lead to ischemic stroke.[16] Among patients with TBI, those with polytrauma, cervical spine injuries, skull fractures, and Le Fort II and III fractures are at high risk for blunt cerebrovascular injury, such as vascular dissection.[43] Indeed, in a prospective cohort study in the Netherlands, the risk of blunt cerebrovascular injury in patients with cervical spine injury and skull fracture was 88 times (odds ratio [OR], 88.7 [95% CI, 45.3–173.9]) and 3.6 times (OR, 3.6 [95% CI, 2.2–6.0]) that of controls, respectively.[43] The possible mechanisms for the occurrence of blunt cerebrovascular injury in those high-risk groups, such as those with cervical spine injury and skull fracture are hyperextension/flexion and rotation of the neck or a direct blow to the vessel. These high-energy mechanisms are in some cases associated with damage to the arterial wall, which can expose the underlying collagen and lead to thrombus formation or occlusion.[43] The use of antipsychotic drugs[39] or a sedentary lifestyle[16] following a TBI may potentially be a risk factor for stroke. Long-term phenotypic alterations in vascular smooth muscle cells after TBI, such as losing contractility,[44,45] may be one of the causes of hemorrhagic stroke. An increase in amyloid-β plaques following TBI[46] may also cause cerebral amyloid angiopathy-related hemorrhagic

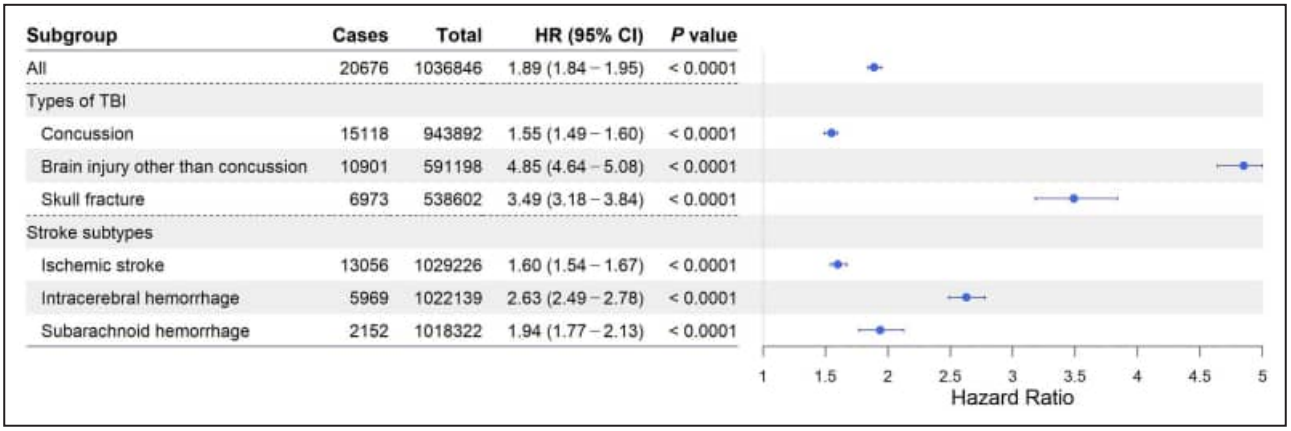

Figure 1. Subgroup analysis based on types of traumatic brain injury or stroke subtype in adults aged ≤49 years.
*Statistical significance threshold after Bonferroni correction=0.05/7=0.007. HR indicates hazard ratio; and TBI, traumatic brain injury.

stroke.[47,48] However, further clinical studies are needed to determine the pathogenetic mechanisms linking TBI and stroke risk.

TBI-related ICH and spontaneous hemorrhage can be separated clinically based on the location and pattern of occurrence. Hemorrhagic parenchymal contusion usually occurs in the anterior and posterior temporal lobes and the inferior frontal lobes. In contrast, spontaneous intraparenchymal hemorrhage is typically localized within the basal ganglia, cerebellum, or occipital lobes. Nevertheless, to prevent confusion between TBI-related ICH and spontaneous hemorrhagic stroke, we excluded all stroke cases that occurred within 2 weeks of TBI. Furthermore, we additionally removed all stroke cases that occurred within 12 months after TBI and performed a secondary analysis. Despite a 12-month washout period, there was still a significant association between TBI and any stroke. In a young-to-middle age group with a lower prevalence of stroke, the 9% increased risk of stroke and 20% increased risk of ICH after TBI, even after 12 months washout, has significant clinical implications. Moreover, the HRs for any stroke, IS, and ICH were sufficiently significant to satisfy multiple correction.

This study had some limitations. First, as we used medical claims data, clinical variables such as the Glasgow Coma Scale score, computed tomography or magnetic resonance imaging findings, or injury severity score were not included. These injury-related clinical variables may improve stroke risk estimation following TBI. Second, data on treatment, medication, TBI mechanisms, and stroke causes are limited in this study. Hence, further studies are required to incorporate this additional information. Third, although professional medical doctors assessed all medical history recorded in the NHIS, the possibility of misclassification remained. Even if stroke diagnosis is made with advanced equipment such as magnetic resonance

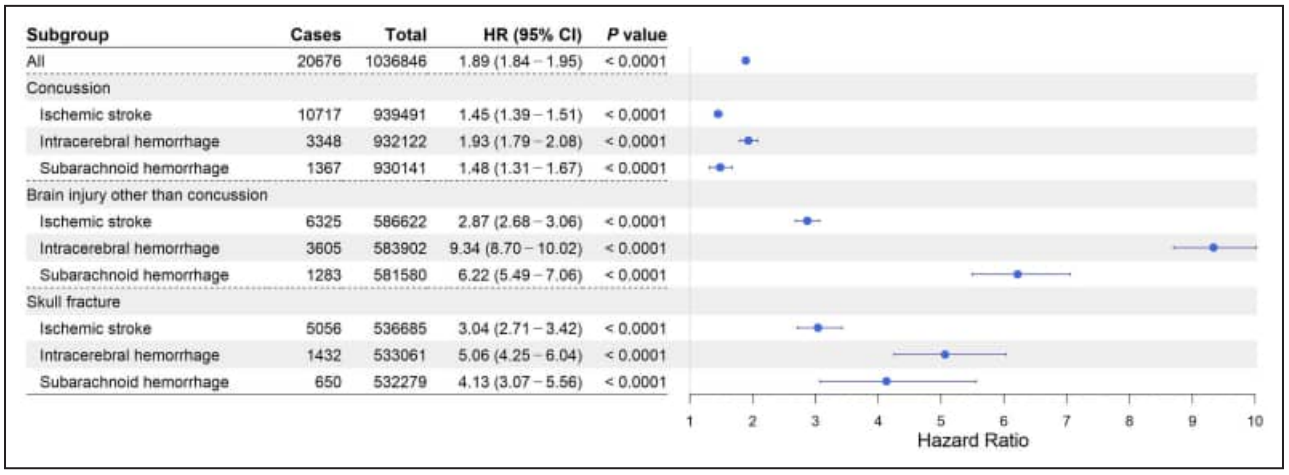

Figure 2. Subgroup analysis based on the combination of types of traumatic brain injury and stroke subtype in adults aged≤49 years.
*Statistical significance threshold after Bonferroni correction=0.05/10=0.005HR indicates hazard ratio; and TBI, traumatic brain injury.

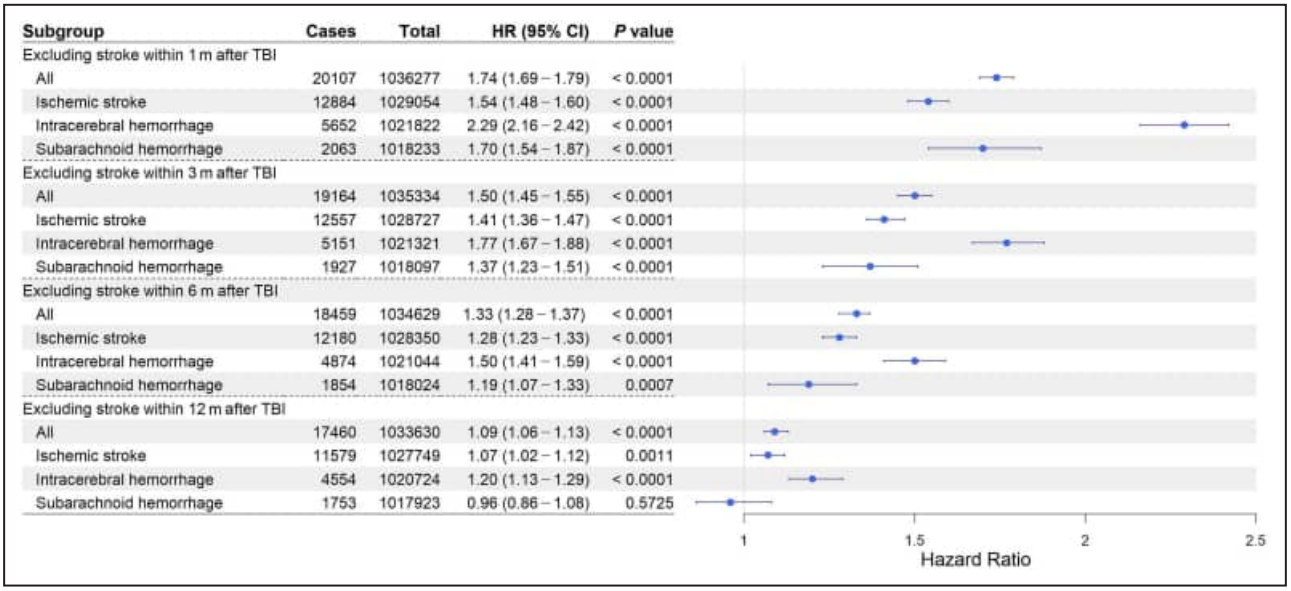

Figure 3. Secondary analysis after excluding early stroke cases following the onset of TBI.
*Statistical significance threshold after Bonferroni correction=0.05/16=0.003. HR indicates hazard ratio; m, month(s); and TBI, traumatic brain injury.

imaging or computed tomography, there remains the possibility that previous lesions, such as past TBI or past strokes, could be misdiagnosed as new strokes. However, we addressed this concern by removing strokes that occurred within 12 months of TBI in secondary analyses. In addition, because this was a large population-based study with more than 1 million participants and more than 20 000 stroke events, we expect that stroke misdiagnosis did not have a significant impact on the overall results. Finally, because this study was conducted in the Korean population, our findings cannot be generalized to other ethnic or socioeconomic groups.

CONCLUSIONS

In this present study, we found that the risk of stroke following TBI increased regardless of TBI severity and stroke subtype in young-to-middle-aged adults aged ≤49 years. After excluding the stroke cases that occurred within 12 months after TBI, these significant associations remained. Our results infer that stroke following TBI will play a significant role in the long-term deterioration of brain aging, brain health, cognitive function decline, and other related factors. Therefore, even in the younger age group, the risk of stroke after TBI should not be underestimated. Young-to-middle-aged patients with TBI should undergo regular health checkups to manage stroke risk factors and prevent stroke occurrence by modifying health-related behaviors.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S2

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