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Association of traumatic brain injury in childhood and attention-deficit/hyperactivity disorder: a population-based study

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BACKGROUND: We evaluated the risk of attention-deficit hyperactivity disorder (ADHD) following childhood traumatic brain injury (TBI).

METHODS: Using Taiwan's National Health Insurance Research Database, we included 10,416 newly diagnosed TBI children (aged ≤12 y) between 2001 and 2002 and 41,664 children without TBI, who were frequency matched by sex, age, and year of the index medical service with each TBI child, as controls. Children who had been diagnosed with ADHD prior to their medical service index were excluded. Each individual was followed for 9 y to identify ADHD diagnosis. We also compared the ADHD risk in children who were treated for fractures but not TBI as sensitivity analysis.

RESULTS: During the 9-y follow-up period, children with TBI had a higher ADHD risk (adjusted hazard ratio (AHR) = 1.32, 95% confidence interval (CI) = 1.19, 1.45) than did those without TBI. Furthermore, children with mild and severe TBI had higher AHRs for ADHD than did those without TBI (AHR = 1.30; 95% CI = 1.10, 1.53; and AHR = 1.37; 95% CI = 1.22, 1.55). However, no significant association was observed between fractures and ADHD.

CONCLUSION: TBI in childhood is associated with a greater likelihood of developing ADHD.

Traumatic brain injury (TBI) is the leading cause of death and disability in children and often results in persistent behavioral disturbances and neurocognitive deficits in attention, learning, and memory (1–3). Children with cognitive impairment following TBI impose a great economic and social burden on their families and communities. In addition, these children are more likely to have slower psychosocial development and exhibit poor academic achievement. Therefore, the relationship between TBI and neuropsychiatric consequences has become a crucial research topic.

Attention-deficit-hyperactivity disorder (ADHD), a neurodevelopmental disorder, is associated with impulsivity, excessive talking, difficulty in sustaining attention, being easily distracted, and injuries (4–6). Studies have reported a relationship between ADHD and childhood TBI (7–10). Unlike other diseases resulting from various pathogenic mechanisms, TBI is caused by a complex interplay among damages occurring in the neuroanatomy, neurochemistry, and neurophysiology because of primary and secondary processes (11). A meta-analytic review showed that neurocognitive outcomes after pediatric TBI have a dose-response relationship with injury severity. Babikian and colleagues found that patients with severe TBI exhibited poorer performance in intelligence quotient tests, executive functioning, processing speed, attention maintenance, verbal immediate memory, and delayed memory, whereas patients with mild TBI exhibited no change (12). In addition, several studies have suggested that children with moderate to severe TBI are significantly more likely to develop ADHD symptoms than are those with mild TBI (8,13–17). A longitudinal birth cohort study reported no association between preschool mild TBI and ADHD after adjusting for potential covariates (18). Nevertheless, a prospective cohort study reported that children with mild TBI have a higher risk of hyperactivity in the first year after injury (19). Nevertheless, a prospective cohort study reported children with mild TBI were associated higher risk for hyperactivity in the first year after injury (20). However, the restricted sample size and relatively brief follow-up period may cause difficulty in generalizing results and reflecting the true incidence. Therefore, the relationship between TBI and ADHD remains controversial in children. Using a nationwide population-based longitudinal study and including an injury severity range from mild to severe would facilitate clarifying the relationship between TBI and ADHD and developing a more satisfactory care procedure for children with TBI.

Earlier studies have shown that children diagnosed or prediagnosed with ADHD are more likely to have suffered from injuries including TBI, fractures, or burns (21,22). In this study, we evaluated the relationship between TBI and ADHD

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through sensitivity analysis to compare the ADHD risk in children receiving index treatment for fractures but not TBI. We conducted a retrospective, population-based cohort study by using a nationwide population-based data set to examine the long-term ADHD risk in children after TBI or fractures. Furthermore, we predicted the cause-specific risk of post-TBI ADHD among different TBI patterns on the basis of clinical characteristics. The findings may facilitate developing an integrated healthcare strategy for children with TBI.

RESULTS

The distribution of sociodemographic characteristics for children with and without TBI is shown in **Table 1**. Of 52,080 children aged ≤12 y enrolled between 2001 and 2002, 10,416 children newly diagnosed with TBI were included as cases and 41,664 children without TBI as controls. The mean age of the 52,080 children was 5 y and 7 mo (SD = 3 y and 4 mo), and 60.9% of them were male. After the cases and controls were matched by age and sex, the children with TBI were significantly more likely to have self-employed (farmer, craftsman, and fisher) parents ($P < 0.001$) and reside in less urbanized areas ($P < 0.001$) compared with the children without TBI. For sensitivity analysis, we included 2,179 children who received treatment for fractures but not TBI between 2001 and 2002 in the fracture group as cases and 8,716 children without fractures or TBI in the nonfracture group as controls (**Supplementary Table S1** online). No differences were observed in urbanization level and parental occupation between the fracture and nonfracture groups.

Table 1. The sociodemographic characteristics of children with traumatic brain injury (TBI) and non-TBI controls in Taiwan, 2001–2002 ($n = 52,080$)

	Children with TBI $N = 10,416$		Non-TBI controls $N = 41,664$		
Variables	No.	%	No.	%	*P* value
Age					—
≤4 y	4,594	44.1	18,376	44.1	—
5–8 y	3,277	31.5	13,108	31.5	—
9–12 y	2,545	24.4	10,180	24.4	—
Sex					—
Male	6,340	60.9	25,360	60.9	—
Female	4,076	39.1	16,304	39.1	—
Urbanization level					<0.001
1 (highest)	2,636	25.3	11,936	28.7	
2	2,801	26.9	12,000	28.8	
3	2,114	20.3	7,926	19.0	
4	1,594	15.3	5,514	13.2	
5 (lowest)	1,271	12.2	4,288	10.3	
Parental occupation					<0.001
Manager, white collar	656	6.3	3,734	9.0	
Employee or manual worker	6,835	65.6	28,512	68.4	
Self-employed (farmer, craftsman, and fisher)	1,699	16.3	4,948	11.9	
Others	1,226	11.8	4,470	10.7	

Table 2 shows crude and covariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for children who developed ADHD during the 9-y follow-up period. Compared with the children without TBI, those with TBI had a significantly higher incidence of ADHD (5.42 vs. 4.01%) during the 9-y period following their medical service index use. HRs were calculated after excluding children who had previous history of preterm births, congenital anomaly, mental illness, epilepsy or cerebral palsy. Conditional Cox proportional hazard regression analysis revealed that TBI was significantly associated with ADHD (adjusted HR (AHR) = 1.24, 95% CI = 1.14, 1.37). After adjustment for children's age, parental occupation, and urbanization level, the results showed that TBI was significantly associated with ADHD (AHR = 1.32, 95% CI = 1.19, 1.45). Furthermore, sensitivity analysis revealed that the ADHD incidence did not differ between the children with fractures and those without fractures (2.89 vs. 2.96%), and no significant association was observed between fracture and ADHD (AHR = 1.03, 95% CI = 0.77, 1.37) (**Supplementary Table S2** online).

The median time for children diagnosed with ADHD during the follow-up period to develop ADHD after their medical service index use was 4 y and 8 mo (4 y and 7 mo; 4 y and 9 mo for children with TBI and those without TBI, respectively). The log-rank test showed that the children with TBI had a significantly higher 9-y cumulative ADHD incidence ($P < 0.001$) than did those without TBI. The 9-y cumulative incidence curve is shown in **Figure 1**.

The AHRs for ADHD for subgroups stratified by age, sex, types of brain injury, and subtypes of severe brain injury are presented in **Table 3**. After adjustment for age, parental occupation, and urbanization level, conditional Cox proportional hazard regression analysis showed that children with TBI onset age, at aged ≤4 and 5–8 y were significantly associated with a higher risk of ADHD compared with those without TBI (AHR = 1.39, 95% CI =1.23, 1.58; AHR = 1.23, 95% CI = 1.03, 1.48, respectively). Boys and girls with TBI showed a significantly increased ADHD risk compared with that in the children without TBI (AHR = 1.32, 95% CI = 1.18, 1.47; AHR = 1.31, 95% CI = 1.03, 1.65, respectively). Children with

Table 2. Crude and covariate-adjusted HRs for ADHD among the sampled patients during the 9-y follow-up period ($n = 52,080$)

	Total sample		Children with TBI		Non-TBI controls	
ADHD occurrence	*N*	%	*N*	%	*N*	%
Yes	2,237	4.30	565	5.42	1,672	4.01
No	49,843	95.70	9,851	94.58	39,992	95.99
Crude HR (95% CI)	—		1.24* (1.14, 1.37)		1.00 (reference)	
Adjusted HR (95% CI)[a]	—		1.32* (1.19, 1.45)		1.00 (reference)	

ADHD, attention-deficit-hyperactivity disorder; CI, confidence interval; HR, hazard ratios; TBI, traumatic brain injury.
[a]Adjustments are made for age, parental occupation and urbanization level. *$P < 0.001$.

mild and severe TBI had 1.30-fold (95% CI = 1.10, 1.53) and 1.37-fold (95% CI = 1.22, 1.55) increased ADHD risks during the 9-y follow-up period compared with that of the children without TBI, respectively. However, children with skull bone fractures showed no significant increase in the ADHD risk compared with that in the children without TBI. Furthermore, according to types of severe brain injury, the ADHD risk was significantly increased in children with brain contusion or subdural haemorrhage (SDH) (AHR = 1.61, 95% CI = 1.22, 2.13; AHR = 1.74, 95% CI = 1.11, 2.72, respectively) after adjustment for age, parental occupation, and urbanization level. However, sensitivity analysis showed no significant difference in the HRs for ADHD between the fracture and nonfracture groups stratified by age, sex, after adjustment for parental occupation, and urbanization level (**Supplementary Table S3** online).

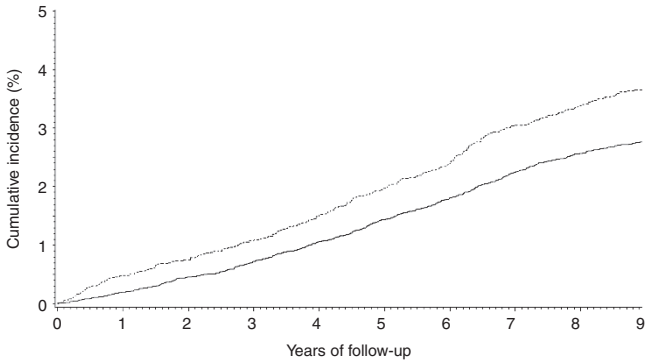

Figure 1 Cumulative incidence of neurocognitive disorders in children with and without traumatic brain injury (TBI). Cumulative incidence of attention-deficit-hyperactivity disorder (ADHD) in 10,416 children with TBI (- - -) and 41,664 without TBI (––).

DISCUSSION

To the best of our knowledge, this is the first study comprehensively describing an association between TBI and ADHD on the basis of large-scale investigation and by considering clinical characteristics of patients in Asia. After adjusting for children's parental occupation and their residential communities' urbanization level, we observed that children with TBI had a higher ADHD risk than did those without TBI during the 9-y follow-up period. In addition, we observed that children with mild TBI and brain contusion on arrival at the hospital were more likely to develop ADHD than those who did not have a brain injury.

Findings from earlier studies are in accordance with those of our study. Allen *et al.* reported that TBI results in unique patterns of neurocognitive impairment, such as deficient in memory and attention abilities (23). Keenan *et al.* observed a significant relative risk of 1.9 compared with healthy controls, but they did not distinguish between mild and severe TBI (24).

Table 3. Adjusted HRs of ADHD for children with TBI vs. children without TBI by age, sex, and types of brain injury during the 9-y follow-up period ($n = 52,080$)

			Crude		Adjusted[a]	
Variables	*N*	ADHD cases	HR	(95% CI)	HR	(95% CI)
Age at first medical care for TBI						
≤4 y	4,594	369	1.28†	(1.14, 1.44)	1.39†	(1.23, 1.58)
5–8 y	3,277	157	1.21*	(1.01, 1.45)	1.23*	(1.03, 1.48)
9–12 y	2,545	39	1.14	(0.78, 1.65)	1.12	(0.76, 1.66)
Sex[b]						
Male	6,340	458	1.25†	(1.13, 1.39)	1.32†	(1.18, 1.47)
Female	4,076	107	1.23	(0.99, 1.54)	1.31*	(1.03, 1.65)
Types of brain injury						
No brain injury	41,664	1,672	1.00	(reference)	1.00	(reference)
Mild brain injury	3,605	150	1.27**	(1.07, 1.50)	1.30**	(1.10, 1.53)
Severe brain injury	5,811	351	1.32†	(1.18, 1.48)	1.37†	(1.22, 1.55)
Skull fracture	1,000	64	0.95	(0.74, 1.23)	1.10	(0.86, 1.42)
Types of severe brain injury[c]						
No brain injury	41,664	1,672	1.00	(reference)	1.00	(reference)
Brain contusion	988	53	1.57**	(1.19, 2.07)	1.61**	(1.22, 2.13)
SAH	313	17	1.20	(0.74, 1.93)	1.30	(0.80, 2.11)
EDH	240	20	1.70	(0.76, 3.80)	1.83	(0.82, 4.11)
SDH	119	6	1.57	(1.00, 2.44)	1.74*	(1.11, 2.72)
ICH	133	11	1.68	(0.93, 3.06)	1.75	(0.96, 3.19)

ADHD, attention-deficit-hyperactivity disorder, CI, confidence interval; TBI, traumatic brain injury.
[a]Adjustments are made for age, parental occupation and urbanization level. [b]The interaction effect between TBI and sex was not statistically significant ($P = 0.88$). [c]Brain contusion, ICD-9-CM 851; SAH, subarachnoid haemorrhage, ICD-9-CM 852.0 and 852.1; SDH, subdural haemorrhage, ICD-9-CM 852.2 and 852.3; EDH, epidural haemorrhage, ICD-9-CM 852.4 and 852.5; ICH, intracerebral haemorrhage, ICD-9-CM 853. *$P < 0.05$; **$P < 0.01$ †$P < 0.001$.

However, two recent longitudinal investigations conducted in New Zealand and Germany, respectively, concluded that TBI is not likely to cause neurocognitive impairment in children and adolescent (18,19). The discrepancy between our study and these two investigations may be explained by differences in study designs and the environmental characteristics of the target populations. The relatively small sample populations in these two studies were obtained from only a few hospitals and study centers. In contrast, our study focused on evaluating the ADHD risk in children with TBI in a large population in Taiwan, thus preventing the selection bias inherent in voluntary registration and hospital referral systems.

The characteristics of ADHD include impairment in attention, hyperactivity, inappropriate motor activity, and disruptive behavior that is inappropriate for the person's age. Our observation that ADHD frequency was higher in the children with TBI in the age group of 0–8 y than that in the age group of 9–12 y suggests a preinjury condition of ADHD, which might have not yet been formally diagnosed. In contrast, children aged 9–12 y were more likely to have been diagnosed with ADHD if they developed the condition. Although a delayed diagnosis of ADHD among children with TBI may confound the relationship between TBI and ADHD, our sensitivity analysis showed no significant ADHD risk in children with fractures. In addition, the cumulative incidence rate of ADHD among the children with TBI was consistently higher than that in the children without TBI during the follow-up period. Our findings strengthen the evidence that TBI is an independent risk factor for ADHD.

Our findings have valuable clinical implications for managing children with mild TBI and brain contusion. Intensive medical monitoring, support, and intervention are mostly required in the first year following a TBI event because the risk of developing neurocognitive disorders increases most rapidly in this period. Early detection of neurocognitive disorders helps children attain their full potential and prevents poor academic performance (25). Awareness of factors that lead to neurocognitive disorders and early signs or symptoms of neurocognitive disorders should be created in families, which have children with TBI through health education and interventions. Inquiry into the history of TBI in children with potential ADHD symptoms seeking medical assistance and consultation can help psychiatrists and clinical psychologists identify the high-risk group. The long-term surveillance of children with mild TBI and brain contusion for potential symptoms of ADHD would be helpful for early detection. These findings could provide clinicians to identify potential risk factors relating to ADHD.

Using a large database has both limitations and strengths. The strengths of our study include the use of a data set that is based on a nationwide population and enabled us to follow up children with and without TBI over a long time period. The comprehensive coverage of the National Health Insurance (NHI) system and the large sample size minimized the selection and nonresponse biases and enabled us to make reasonable estimates of the effects of TBI on neurodevelopmental outcomes. Diagnoses are validated by the National Health Insurance Administration (NHIA) in Taiwan. The NHIA requires that every hospital provide a fixed percentage of claims record from random samples to validate and preserve the quality of diagnoses. In addition, the high validity of TBI and ADHD diagnoses was confirmed by board-certified psychiatrists or physicians; however, some heterogeneity may have occurred in the assessment because of the absence of standardized instruments for diagnosis.

The study is subject to some limitations. First, a limitation imposed by the data set is the lack of details about parental and family factors (family functioning, maternal psychological distress, and social support) as well as biological factors (premature birth, birth weight, and genetic mutations). Therefore, we did not consider these factors in our research. The unavailability of these unmeasured confounders might have biased our results. Additionally, parents might pay more attention to their child who had TBI history than those without TBI exposure and bring their child to a physician when they suspect ADHD symptoms. Also, neurologists may have higher possibility to make a diagnosis when the child has TBI history. Although the diagnosis of ADHD follows the principle of clinical guidelines in Taiwan, the differential surveillance may inflate the ADHD risk and thus would be subject to some information bias. Second, although several TBI studies have reported that the locations of lesions were correlated with neurocognitive impairment (26,27), we were unable to obtain detailed information of neuroimages (lesion characteristics) from Taiwan's National Health Insurance Research Database (NHIRD). Information on some external causes of TBI, such as falls, motor vehicle crashes, and violence, was also unavailable. Third, TBI outpatients who may have very minor TBI or minor symptoms were not considered in this study. We included only children with TBI who were treated at emergency medical care or inpatient care centers, potentially leading to underestimation of the number of children with TBI.

Conclusions

In summary, our results suggest that early TBI in childhood is a potential independent risk factor for ADHD. To facilitate reducing the risk of ADHD among children with TBI, a coordinated and systematic approach including a comprehensive assessment of behavioral outcomes, evolution over time postinjury, cognitive correlates, and therapeutic intervention or rehabilitation should be adopted. Additional studies are required in the future for exploring the mechanisms underlying the relationship between TBI and ADHD and developing specific diagnostic markers for identifying ADHD in children with TBI.

METHODS

Database

Data in this population-based retrospective cohort study were obtained from the NHIRD, which contains the enrollment and claims data of all beneficiaries of Taiwan's NHI program, including data on ambulatory care, records on inpatient expenditures by admissions, and a registry for beneficiaries. The single-payer NHI program was

established in 1995 and provides mandatory universal health insurance to all Taiwanese residents, covering more than 98% of the population of ~23 million people. As one of the largest databases of medical information in the world, the NHIRD provides a unique opportunity for evaluating the risk of neurocognitive disorders following TBI. This study was approved by the Taipei Medical University Institutional Review Board (TMU-JIRB-201408018). To protect patient privacy, the National Health Research Institutes manages claims data and denotes them with random identification numbers in the NHIRD. The requirement for informed consent was waived because we analyzed encrypted anonymous secondary data provided in the NHIRD.

Study Population

This study was designed as a population-based retrospective cohort study. From the NHIRD database, we selected children aged ≤12 y who had visited ambulatory care centers (including the outpatient departments of hospitals or clinics) or had been hospitalized with the principal diagnosis of TBI (ICD-9-CM codes 800–804 or 850–854) between 1 January 2001 and 31 December 2002 (n = 11,453) (**Figure 2**). We assigned these children's first ambulatory care visit or hospitalization for TBI treatments as their medical service index use. We excluded children diagnosed with ADHD (ICD-9-CM code 314) or TBI (ICD-9-CM codes 800–804, 850–854) prior to their medical service index use (n = 586). Because Taiwan's NHI program was initiated in 1995, our study could not account for children diagnosed with neuronal disorders prior to 1996. In addition, we excluded children with a past medical history of preterm birth (28) (ICD-9-CM codes 765.0, 765.1) (n = 62), congenital anomaly (29) (ICD-9-CM codes 758, 759.9) (n = 27), mental illness (30) (ICD-9-CM codes 290–319, except 314) (n = 183), epilepsy (31) (ICD-9-CM code 345) (n = 131), and cerebral palsy (32) (ICD-9-CM code 343) (n = 48) for minimizing potential confounding influence from other known risk factors for ADHD. Finally, we included 10,416 children with TBI. We further categorized TBI children into mild brain injury (ICD-9-CM code 850), severe brain injury (ICD-9-CM codes 851–854), and skull fracture (ICD-9-CM codes 800–804). Mild TBI was defined as brain concussion without structural brain damage. Severe TBI was defined as brain injury including brain contusion, SDH, epidural haemorrhage subarachnoid haemorrhage and intracranial haemorrhage. According to earlier studies (33,34), we categorized the diagnoses of skull fracture combined with intracerebral hemorrhage (children with both skull fracture and intracerebral hemorrhage diagnostic codes (800–804 and 851–854) conditions, or diagnostic codes include skull fracture with intracranial injury (800.1–800.4, 800.6–800.9, etc.)) into the severe brain injury group. We furthermore defined skull fracture group as a fracture of the vault of skull, base of skull, or facial bone as well as multiple skull bone fractures without any intracerebral hemorrhage.

The non-TBI cohort was selected from the Longitudinal Health Insurance Database 2000 (LHID2000). As a subset of the NHIRD, the LHID2000 contains all original claims data for 1 million beneficiaries randomly sampled from the Registry for Beneficiaries of the NHIRD. In addition, we excluded children aged >12 y. Finally, we randomly selected 41,664 children without TBI (four times the number of patients with TBI) who were frequency matched with the children with TBI by sex, age (≤4, 5–8, and 9–12 y), and the year of the medical service use index. We assigned their first ambulatory service use that occurred in the year of the index healthcare use, as the medical service index use. We verified that these children had no history of neuronal disorders, TBI and ADHD prior to their medical index use since 1995. In total, we included 52,080 children (children with and without TBI). Each child was individually followed up for 9 y

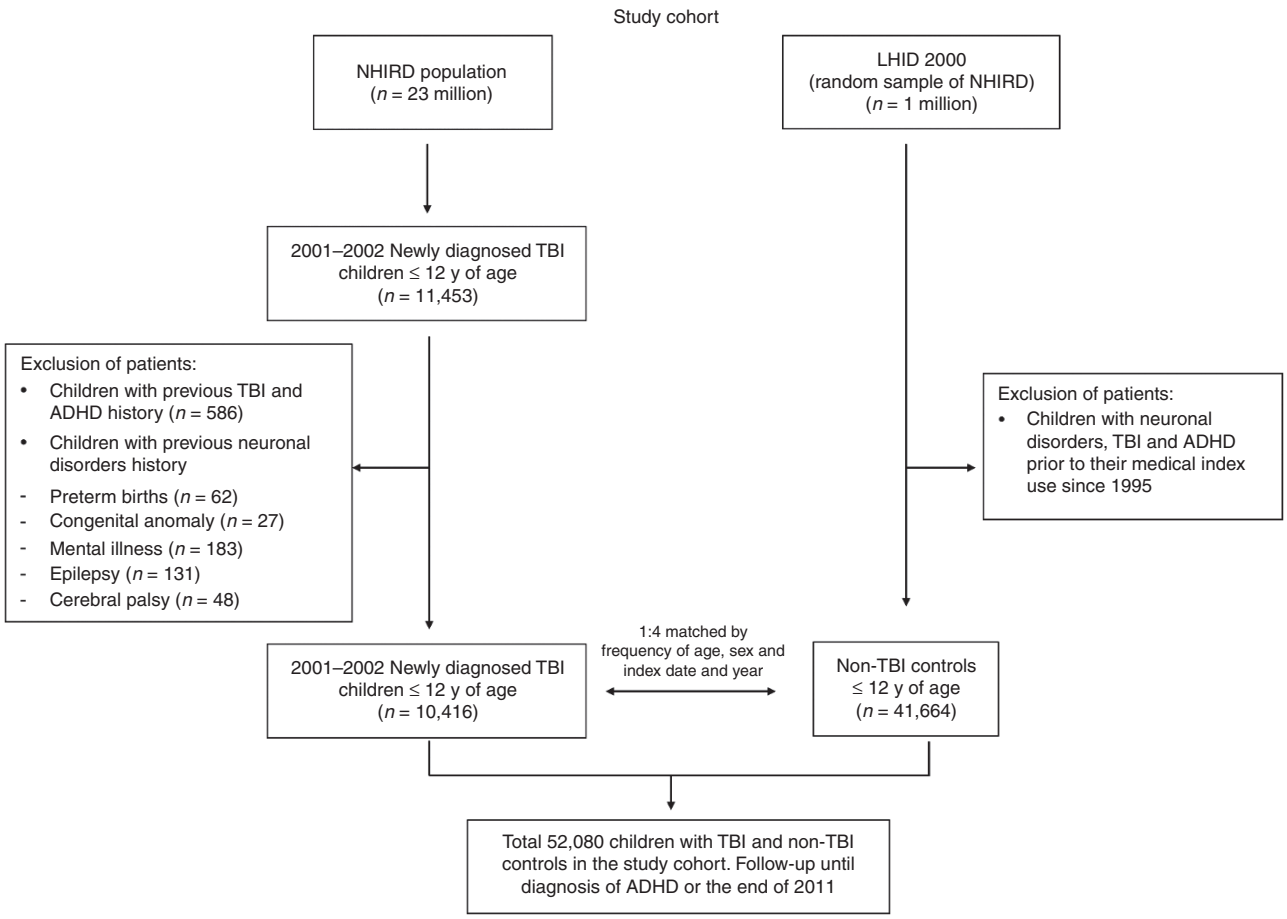

Figure 2 Flowchart of the procedure. Flowchart of case selection for children with and without traumatic brain injury (TBI) from the National Health Insurance Research Database (NHIRD) and Longitudinal Health Insurance Database 2000 (LHID2000).

from the medical service index use to identify patients who subsequently developed ADHD (ICD-9-CM code 314). ADHD diagnosis by pediatric neurologists was based on ICD-9-CM diagnostic criteria. In Taiwan, pediatric neurologists usually provide the first diagnosis of ADHD according to an examination performed on observing ADHD symptoms. However, a second ADHD diagnosis is based on previous test results and clinical examination outcomes and thus provides confirmation. Recent studies reported on participants who were diagnosed at least twice for ADHD by psychiatrists and clinical psychologists to ensure diagnostic validity (35–37). Therefore, we included only patients with TBI who received two or more ADHD diagnoses to increase the diagnostic validity.

Sensitivity Analysis

To consider that ADHD may predispose children to TBI, we performed sensitivity analysis in children who received index treatment for fractures but not TBI. Children aged ≤12 y diagnosed with fracture (ICD-9-CM codes 805–829), including inpatients and outpatients, between 1 January 2001 and 31 December 2002 (n = 2,974) were selected from the LHID2000. We assigned their first ambulatory care visit or hospitalization for fracture treatment as their medical service index use. We excluded children with a history of preterm birth, congenital anomaly, mental illness, and cerebral palsy and those with ADHD or fracture diagnoses prior to their medical service index use (n = 326). In addition, children diagnosed with TBI prior to their medical service index use and 9-y follow-up duration (n = 469) were excluded. In the nonfracture group, children who were not diagnosed with a fracture or TBI were included. Children were randomly selected by frequency matching the fracture cohort patients with the nonfracture controls according to their age (≤4, 5–8, and 9–12 y), sex, and the year of the medical service index use at a ratio of 1:4. Finally, 2,179 children with fractures but not TBI and 8,716 children without fractures were selected as cases and controls, respectively (**Supplementary Figure S1** online).

Statistical Analysis

In this study, used the chi-square test for comparing differences between the cases and controls in socio-demographic characteristics such as parental occupation (white collar, employee or manual worker, self-employed (farmer, craftsman, or fisherman), and others) and the patients' urbanization level (ranging from "most urbanized" (level 1) to "least urbanized" (level 5)) at the baseline. The cumulative incidence rate was calculated using the life table method. The log-rank test was performed for evaluating the difference in the cumulative incidence between cases and controls. In addition, stratified Cox proportional hazard regression, stratified by sex, age, and follow-up year, was conducted for evaluating the association between TBI and subsequent neurocognitive outcomes during the 9-y follow-up period. We presented HRs and their 95% CIs as our results. Two-tailed P values were calculated, and statistical significance was set at $P < 0.05$. All analyses were performed using the Statistics Analysis System (SAS) statistical software, Version 9.3 (SAS Institute, Cary, NC).

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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