

Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study



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Summary

Background The risk of epilepsy shortly after traumatic brain injury is high, but how long this high risk lasts is unknown. We aimed to assess the risk of epilepsy up to 10 years or longer after traumatic brain injury, taking into account sex, age, severity, and family history.

Methods We identified 1 605 216 people born in Denmark (1977–2002) from the Civil Registration System. We obtained information on traumatic brain injury and epilepsy from the National Hospital Register and estimated relative risks (RR) with Poisson analyses.

Findings Risk of epilepsy was increased after a mild brain injury (RR 2·22, 95% CI 2·07–2·38), severe brain injury (7·40, 6·16–8·89), and skull fracture (2·17, 1·73–2·71). The risk was increased more than 10 years after mild brain injury (1·51, 1·24–1·85), severe brain injury (4·29, 2·04–9·00), and skull fracture (2·06, 1·37–3·11). RR increased with age at mild and severe injury and was especially high among people older than 15 years of age with mild (3·51, 2·90–4·26) and severe (12·24, 8·52–17·57) injury. The risk was slightly higher in women (2·49, 2·25–2·76) than in men (2·01, 1·83–2·22). Patients with a family history of epilepsy had a notably high risk of epilepsy after mild (5·75, 4·56–7·27) and severe brain injury (10·09, 4·20–24·26).

Interpretation The longlasting high risk of epilepsy after brain injury might provide a window for prevention of post-traumatic epilepsy.

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Introduction

Traumatic brain injury raises the risk of epilepsy,¹ but little is known about the duration of the increased risk and the factors that modify the risk, especially in children and young adults.² In hospital-based case series, the risk of epilepsy 1–2 years after moderate to severe brain injury is related to some CT or MRI findings and is high in people who had had neurosurgical procedures.^{2–6} In a population-based study, age in people who had traumatic brain injury at age 65 years or older and time since and severity of injury were significant risk factors for epilepsy,¹ but only a few studies have included children and young adults.^{1–4} In some of these studies,^{2,4} acute seizures in the first week after brain injury were associated with a high risk of epilepsy. Studies of epilepsy related to level of consciousness (eg, assessed with the Glasgow coma scale) and duration of post-traumatic amnesia after brain injury have given conflicting results.^{1,3,4}

No effective prophylaxis for epilepsy after traumatic brain injury is available, and trials with preventive drug have been discouraging.⁷ However, better information about prognostic factors might help the development of new prevention strategies and treatment.⁵

We studied the risk of epilepsy in a large population-based cohort of children and young adults and considered time since injury, sex, age, severity, and family history of epilepsy.

Methods

Study population

We used data from the Danish Civil Registration System (CRS)⁸ to identify all people born in Denmark between Jan 1, 1977, and Dec 31, 2002. All liveborn children and new residents in Denmark are assigned a unique personal identification number (CRS number) together with information on vital status, emigration from Denmark, and CRS numbers of mothers, fathers, and siblings. The CRS number links individual information in all national registries and provides identification of family members and links parents with their children.

Identity of individuals in the study was blinded to the investigators, and the study did not involve contact with individual patients. The study therefore did not need approval from the ethics committee according to Danish laws, but the project was approved by the Danish Data Protection Agency.

Data collection

Information about brain injury and epilepsy was obtained from the Danish National Hospital Register,⁹ which contains information on all discharges from Danish hospitals since 1977; outpatients have been included in the register since 1995. All treatment is free of charge for Danish residents. Patients admitted to the only private epilepsy hospital in Denmark are also recorded in the

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	Patients diagnosed with epilepsy	New cases (per 1000 person-years)	Adjusted relative risk (95% CI)	p value
Time (years) since mild brain injury				
0.0–0.5	162	4.67	5.46 (4.67–6.37)	<0.0001
0.5–1.0	78	2.37	2.91 (2.33–3.64)	<0.0001
1.0–2.0	109	1.78	2.26 (1.87–2.73)	<0.0001
2.0–3.0	99	1.79	2.33 (1.91–2.84)	<0.0001
3.0–5.0	138	1.50	1.99 (1.68–2.36)	<0.0001
5.0–10.0	154	1.14	1.56 (1.33–1.83)	<0.0001
≥10.0	97	1.00	1.51 (1.24–1.85)	<0.0001
No mild injury	16 633	0.87	1.00	..
Time (years) since severe brain injury				
0.0–0.5	35	19.62	21.26 (15.25 to 29.62)	<0.0001
0.5–1.0	19	11.52	13.45 (8.57 to 21.09)	<0.0001
1.0–2.0	18	6.06	7.42 (4.68 to 11.79)	<0.0001
2.0–3.0	11	4.26	5.40 (2.99 to 9.76)	<0.0001
3.0–5.0	11	2.69	3.52 (1.95 to 6.35)	<0.0001
5.0–10.0	15	3.22	4.40 (2.65 to 7.30)	<0.0001
≥10.0	7	2.94	4.29 (2.04 to 9.00)	0.0001
No severe injury	17 354	0.89	1.00	..
Time (years) since skull fracture				
0.0–0.5	6	2.90	2.96 (1.33 to 6.60)	0.0078
0.5–1.0	6	2.99	3.51 (1.58 to 7.83)	0.0021
1.0–2.0	13	3.38	4.30 (2.50 to 7.41)	<0.0001
2.0–3.0	5	1.39	1.81 (0.75 to 4.35)	0.1845
3.0–5.0	9	1.36	1.78 (0.93 to 3.42)	0.0838
5.0–10.0	16	1.21	1.55 (0.95 to 2.54)	0.0781
≥10.0	23	1.46	2.06 (1.37 to 3.11)	0.0005
No fracture	17 392	0.89	1.00	..

Each form of injury led to a significant ($p<0.0001$) increase in risk of epilepsy relative to people without brain injury. Relative risk (RR) was adjusted for age and interaction with sex and calendar year. RR of epilepsy in people with brain injury was modified by time since first admission with brain injury for mild ($p<0.0001$) and severe ($p<0.0001$) brain injury but not skull fracture ($p=0.16$).

Table 1: Time since first admission with brain injury and relative risk (RR) of epilepsy

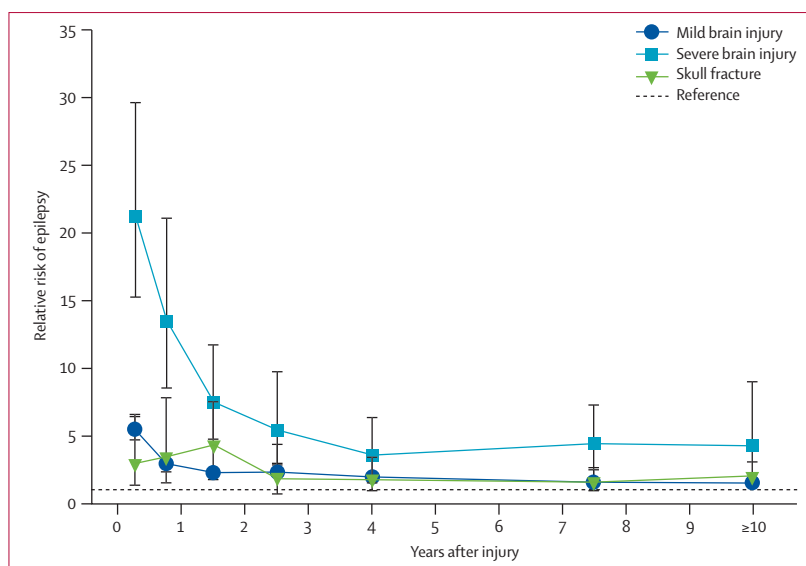


Figure: Relative risk of epilepsy after brain injury in Denmark (1977–2002)

Danish National Hospital Register. Specialists in neurology working in private outpatient clinics also treat patients with epilepsy, but these contacts are not recorded in the Danish National Hospital Register.

Diagnostic information in the National Hospital Register is based on the *International Classification of Diseases*, 8th revision (ICD-8) from 1977–93, and ICD-10 from 1994–2002.

Cohort members, their parents and siblings were classified with epilepsy if they had been hospitalised or in outpatient care with a diagnosis of epilepsy (ICD-8: 345; ICD-10: G40,G41).^{10–13} By use of the CRS numbers, we linked parents and siblings registered with an epilepsy diagnosis in the National Hospital Register. A person was recorded as having a family history of epilepsy if the date of first epilepsy diagnosis in a parent or sibling preceded their epilepsy diagnosis.

Cohort members were classified with mild brain injury (concussion: ICD-8 850.99; ICD-10 S06.0), severe brain injury (structural brain injury: ICD-8 851.29–854.99; ICD-10 S06.1–S06.9), or skull fracture (ICD-8 800.99–801.09, 803.99; ICD-10: S02–S02.1, S02.7, S02.9), respectively, if they had been admitted or been in outpatient care with the relevant diagnosis.^{14,15} Time of onset of epilepsy and brain injury was defined as the first day of the first contact to the hospital with the relevant diagnosis.

The definition of mild brain injury (concussion) in Denmark is based on the definition given by the American Congress of Rehabilitation Medicine.¹⁶ The diagnostic criteria include a relevant direct trauma against the head manifesting with changed brain function (ie, loss of consciousness, amnesia, confusion/disorientation, or focal [temporary] neurological deficit). Severity of mild brain injury should not include loss of consciousness longer than 30 min, a Glasgow coma scale of 13 or less after 30 min, or post-traumatic amnesia longer than 24 h.¹⁷ Severe brain injury (structural brain injury) includes brain contusion or intracranial haemorrhage. Skull fracture liable to be associated with disruption of brain function can occur alone or be associated with other types of brain injury and usually requires verification with a radiograph or CT. Brain injuries recorded in the same patient within 14 days were categorised as the same event according to the hierarchy of brain injury—severe brain injury, skull fracture, and mild brain injury. For each type of brain injury, we calculated the age at first brain injury (0–5, 5–10, 10–15, and ≥15 years), the length of first admission (0, 1–6, 7–13, 14–27, and ≥28 days), and time since first brain injury (0–6 months, 6 months to 1 year, 1–2, 2–3, 3–5, 5–10, and ≥10 years).

Statistical analyses

People were followed from birth until onset of epilepsy, death, emigration from Denmark, or Dec 31, 2002, whichever came first. The incidence rate ratio (for these analyses a good approximation of the relative risk, the term used in this Article) of epilepsy was estimated by

log-linear Poisson regression¹⁸ with the GENMOD procedure in SAS (version 8.1). Because incidence of epilepsy depends on age, sex, and calendar year,¹⁰ all the relative risks were adjusted for these factors. Age, calendar year, age at first brain injury, duration of first admission with brain injury, time since first brain injury, and history of epilepsy in a parent or sibling were time dependent variables;¹⁹ all other variables were treated as time independent. Age was categorised in quarter year age levels from birth to the first birthday, in 1 year age levels from the first birthday to the 20th birthday, and as 20–21 years and ≥ 22 years. Calendar year was categorised in 1 year periods from 1977 to 2002. Likelihood ratio tests were used to calculate p values and 95% CIs were calculated by use of Wald's test.¹⁹ The adjusted-score test²⁰ suggested that the regression models were not subject to overdispersion.

Role of the funding source

The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the Article. All authors had full access to the data and approved the decision to submit the Article for publication in *The Lancet*.

Results

We followed-up 1605216 for a total of 19527337 person-years. During this study period, 78572 people had at least one traumatic brain injury, and in the same period, 17470 people developed epilepsy, of whom 1017 had a preceding brain injury. Follow-up was stopped before the end of the study period for 45677 people (2.9%) because of emigration from Denmark (30362 [1.9%]) or death (15315 [1.0%]).

Relative to no brain injury, the risk of epilepsy was two times higher after mild brain injury (RR 2.22, 95% CI 2.07–2.38); seven times higher after severe brain injury (7.40, 6.16–8.89); and two-times higher after skull fracture (2.17, 1.73–2.71).

Tables 1–3 show the risk of epilepsy after brain injury according to time since first admission with brain injury, age at first brain injury, and duration of first hospital stay with brain injury.

The risk of epilepsy after mild ($p<0.0001$) and severe ($p<0.0001$) brain injury was highest during the first years after injury, but remained high for more than 10 years after the injury as compared with people without such a history (table 1, figure). For patients with skull fractures, risk of epilepsy did not vary significantly with time since injury ($p=0.16$; table 1).

Brain injury was associated with an increased risk of epilepsy in all age groups (table 2). The risk increased with age for mild ($p<0.0001$) and severe ($p=0.02$) brain injury and was highest among people older than 15 years at injury.

Patients who had a long duration of hospital stay with severe brain injury ($p<0.0001$) and skull fracture

	Number of patients with epilepsy*	New cases (per 1000 person-years)	Adjusted relative risk (95% CI)	p value
Age (years) at mild brain injury				
0–5	365	1.64	2.06 (1.86–2.29)	<0.0001
5–10	243	1.56	2.12 (1.87–2.41)	<0.0001
10–15	117	1.54	2.25 (1.88–2.71)	<0.0001
≥ 15	112	2.03	3.51 (2.90–4.26)	<0.0001
No mild injury	16633	0.87	1.00	..
Age (years) at severe brain injury				
0–5	51	6.26	7.20 (5.47–9.48)	<0.0001
5–10	24	4.96	6.18 (4.14–9.23)	<0.0001
10–15	11	3.56	4.91 (2.72–8.87)	<0.0001
≥ 15 years	30	7.47	12.24 (8.52–17.57)	<0.0001
No severe injury	17354	0.89	1.00	..
Age (years) at skull fracture				
0–5	52	1.53	1.95 (1.49–2.56)	<0.0001
5–10	17	2.12	2.86 (1.78–4.60)	<0.0001
10–15	5	1.81	2.55 (1.06–6.12)	0.0368
≥ 15 years	4	1.71	2.75 (1.03–7.34)	0.0433
No skull fracture	17392	0.89	1.00	..

Each form of injury led to a significant ($p<0.0001$) increase in risk of epilepsy relative to people without brain injury. Relative risk (RR) was adjusted for age and interaction with sex and calendar year. RR of epilepsy in people with brain injury was modified by age at first admission with brain injury for mild ($p<0.0001$) and severe ($p=0.02$) brain injury but not skull fracture ($p=0.55$).

Table 2: Age at first admission with brain injury and relative risk of epilepsy

($p=0.02$) had a notably high risk of epilepsy (table 3). For people with mild brain injury there was no association between duration of hospital stay and risk of epilepsy ($p=0.73$; table 3).

Table 4 shows the relative risk of epilepsy after brain injuries subdivided by family history of epilepsy. The relative risk of epilepsy with a family history of the disorder and mild brain injury is between what would have been predicted from a multiplicative model ($3.37 \times 2.24 = 7.54$) and from an additive model ($3.37 + 2.24 - 1 = 4.61$; table 4). The relative risk estimate associated with severe brain injury and family history of epilepsy of is almost the same as would have been predicted from an additive model ($3.35 + 7.81 - 1 = 10.16$; table 4). We had very few people with epilepsy with skull fracture and a family history of epilepsy (table 4).

The relative risk of epilepsy after mild brain injury was higher among women (2.49, 2.25–2.76) than among men (2.01, 1.83–2.22; $p=0.003$). There was no interaction with sex for patients with skull fractures ($p=0.59$) or severe brain injury (0.22). We calculated the risk of epilepsy for patients registered with brain injury according to ICD-8 and ICD-10 (ie, patients diagnosed in the time period 1977 to 1993 and 1994 to 2002, respectively). For patients with mild brain injury, the risk of epilepsy was lower in the ICD-8 period (RR 1.89, 1.71–2.10) than in the ICD-10 period (2.61, 2.37–2.87; $p<0.0001$). For severe brain injury, the risk of epilepsy was almost the same in the ICD-8 period (7.17,

	Number of patients with epilepsy	New cases (per 1000 person-years)	Adjusted relative risk# (95% CI)	p value
Hospital stay (days) for mild brain injury				
0	256	1.73	2.22 (1.96–2.51)	<0.0001
1–6	563	1.60	2.20 (2.02–2.40)	<0.0001
7–13	9	2.08	3.01 (1.56–5.78)	0.0010
14–27	4	2.54	3.68 (1.38–9.82)	0.0091
≥28	5	2.05	2.94 (1.22–7.07)	0.0159
No mild injury	16 633	0.87	1.00	..
Hospital stay (days) for severe brain injury				
0	12	1.73	2.09 (1.19–3.68)	<0.0108
1–6	24	3.71	4.82 (3.23–7.20)	<0.0001
7–13	15	7.04	9.42 (5.68–15.63)	<0.0001
14–27	18	13.11	18.01 (11.34–28.60)	<0.0001
≥28	47	14.86	20.07 (15.06–26.74)	<0.0001
No severe injury	17 354	0.89	1.00	..
Hospital stay (days) for skull fracture				
0	8	2.13	2.72 (1.36–5.45)	0.0046
1–6	48	1.35	1.77 (1.33–2.35)	<0.0001
7–13	10	1.99	2.70 (1.45–5.03)	0.0017
14–27	4	3.08	4.01 (1.51–10.69)	0.0055
≥28	8	5.59	6.69 (3.35–13.38)	<0.0001
No fracture	17 392	0.89	1.00	..

Each form of injury led to a significant ($p<0.0001$) increase in risk of epilepsy relative to people without brain injury. Relative risk (RR) was adjusted for age and interaction with sex and calendar year. RR of epilepsy in people with brain injury was modified by duration of first hospital stay with brain injury for severe brain injury ($p<0.0001$) and skull fracture ($p=0.02$) but not mild brain injury ($p=0.73$).

Table 3: Duration of first hospital stay with brain injury and relative risk of epilepsy

No family history of epilepsy			Family history of epilepsy		
	Number of patients with epilepsy	Adjusted relative risk (95% CI)	p value	Number of patients with epilepsy	Adjusted relative risk (95% CI)
Mild brain injury					
No	15 511	1.00	..	1122	3.37 (3.17–3.58)
Yes	766	2.24 (2.08–2.41)	<0.0001	71	5.75 (4.56–7.27)
Severe brain injury					
No	16 166	1.00	..	1188	3.35 (3.16–3.56)
Yes	11	7.81 (6.48–9.42)	<0.0001	5	10.09 (4.20–24.26)
Skull fracture					
No	16 202	1.00	..	1190	3.35 (3.16–3.55)
Yes	75	2.28 (1.81–2.86)	<0.0001	3	2.71 (0.87–8.41)
Any brain injury					
No	15 338	1.00	..	1115	3.39 (3.19–3.61)
Yes	939	2.47 (2.31–2.65)	<0.0001	78	5.73 (4.58–7.16)

Patients might have been exposed to more than one type of brain injury at separate admissions/outpatient visits. Relative risk adjusted for age and its interaction with sex and calendar year.

Table 4: Family history and relative risk of epilepsy after traumatic brain injury

5.19–9.91) and the ICD-10 period (7.51, 6.02–9.38; $p=0.82$). For skull fracture, the risks of epilepsy were comparable in the ICD-8 period (2.00, 1.54–2.58) and ICD-10 period (2.87, 1.85–4.46; $p=0.17$).

Discussion

As previously shown in studies smaller than ours,^{1,2,6,21} risk of epilepsy increased after brain injury in relation to severity of brain injury. Risk was high for more than 10 years after the brain injuries even for mild brain injury (concussion), a finding in contrast to that of a previous study showing no increased risk of epilepsy 5 years after a mild brain injury.¹ The discrepancy might result from different inclusion criteria for mild brain injury and epilepsy,^{1,11} and an insufficient sample size to identify a moderate increase in risk.¹ Our results suggest that time from brain injury to clinically overt symptoms (seizures) can span several years, leaving room for clinical intervention.⁵ However, animal studies suggest that a specific time window exists shortly after injury in which appropriate drugs might stop the epileptogenic process,²² and antiepileptogenic trials after brain injury in human beings have not shown drug treatment to be effective.⁷ In Denmark, seizure prophylaxis with antiepileptic drugs after brain injury was not used routinely in the study period.²³

We defined the onset of epilepsy as the first day of the first contact, although this is only an approximation. There may be a delay from the first seizure to diagnosis of epilepsy. We have previously validated the epilepsy diagnosis in a sample from the Danish National Hospital Register and found that 64% were registered in the Danish National Hospital Register within 1 year of first seizure, and 90% were registered within 5 years.¹¹ Diagnostic delay might, therefore, explain part of the increased risk of epilepsy after the brain injury. Likewise, a delay between brain injury and diagnosis (eg, in patients with chronic subdural haematoma), could bias the estimates of epilepsy shortly after a brain injury diagnosis, but this effect is likely to be small, especially in children.

Brain injury might be the first presentation of epilepsy, in which the patient has a head trauma during an unwitnessed seizure (reverse causation). In a subanalysis, we excluded patients diagnosed with epilepsy within the first 6 weeks of first brain injury diagnosis and found that the high risk of epilepsy remained for all types of brain injury, albeit in an attenuated form (data not shown). Although patients with infrequent seizures might remain undiagnosed more than 6 weeks, this problem probably affects only a small part of the delayed association between brain injury and epilepsy. The risk of epilepsy increased slightly with age at time of mild brain injury, and was highest for people over 15 years of age, indicating that susceptibility to epilepsy after brain injury increases with age. This finding is in line with results of a previous study identifying people aged 65 or more as being at high risk of epilepsy after brain injury.¹ Alternatively, the severity of brain injuries might increase with age, or doctors might be more likely to hospitalise younger children with less severe brain injuries, resulting in a

low relative risk of post-traumatic epilepsy in young age groups.

Post-traumatic epilepsy is thought to be typical of symptomatic epilepsy (ie, determined by environmental factors). However, twin studies suggest that genetic factors also play a part in localisation-related epilepsies, most of which are thought to be symptomatic or probably symptomatic.²⁴ Family history of epilepsy and mild brain injury independently contribute to the risk of epilepsy.²⁵ Thus, people genetically predisposed to epilepsy (ie, with a family history of epilepsy) have a higher risk of epilepsy than do people without genetic predisposition when exposed to mild brain injury. To our knowledge, no previous studies have studied the risk of epilepsy after brain injury in first degree relatives to patients with epilepsy. In animals, variation in the susceptibility of various rat strains to post-traumatic epilepsy might lend some support to the hypothesis of an underlying genetically determined tendency to develop post-traumatic epilepsy.²⁶

Our registration of family history is not complete because some parents and older siblings might have been diagnosed before the Danish National Hospital Register was established (Jan 1, 1977). This misclassification is likely to cause an underestimation of the effect of family history on the risk of epilepsy.

The relative risk of epilepsy after mild brain injury was slightly higher in female than in male patients perhaps because female patients with epilepsy are more likely registered in the National Hospital Register because of sex-specific factors, such as pregnancy. Alternatively female brains might be more susceptible to epilepsy after mild brain injury than are male brain, as supported by a previous study showing that localisation-related epilepsy with no apparent structural cause is more prevalent in women than in men.²⁷ The sex difference was not present for the other types of brain injury, suggesting that other mechanisms might be involved in post-traumatic epilepsy after skull fracture and more severe brain injuries.

The length of first hospital stay with brain injury was associated with an increased risk of epilepsy for severe brain injury and cranial fractures. The length of admission is probably related to severity of brain injury.

Despite the length and completeness of follow up, the size of the study cohort, and the population-based nature of the study,⁸ we had limited clinical information. In a recent study, we validated the epilepsy diagnosis in the Danish National Hospital Register.¹¹ We found a positive predictive value of an ICD-8 or ICD-10 epilepsy diagnosis according to ILAE criteria²⁸ of 81% for epilepsy and 89% for single seizures, but identified no epilepsy diagnoses based on acute symptomatic seizures.¹¹ Thus, some patients registered with epilepsy in the present study do not fulfil the diagnostic criteria, but the misclassification would only bias the results of the present study away from the null hypothesis if the quality of the epilepsy registration differs between

patients with and without brain injury, which we find unlikely.

The Danish Hospital Register does not capture all patients with epilepsy, because some outpatients might be treated in private practice. However, estimates of incidence (68·8 per 100 000 people per year) and prevalence (0·6%) of epilepsy in Denmark based on data from the Danish National Hospital Register were similar to those found in other developed countries and indicate a high completeness.¹⁰ If cases with epilepsy are missed in the Danish National Hospital Register, the relative risk of epilepsy would be affected only if the incomplete capture of patients differs between those with and without brain injury. Patients with head injury may be followed more closely than the general population, which might increase the completeness and overestimate the relative risk of epilepsy after brain injury. However, the effect of this bias is likely to decrease over time.

Although, most patients with epilepsy are cared for on an outpatient basis, the incidence estimate only increased by 17% after inclusion of outpatients.¹⁰ Hence, most outpatients with epilepsy are also admitted to hospital for that or other reasons and, thereby, included in the National Hospital Register. Some patients with severe brain injury live in care homes in the community after their condition has stabilised, but these patients have the same access to the hospital system as patients without brain injury, and thus we think that they do not have a decreased likelihood of being registered with epilepsy in the Danish National Hospital Register.

People were censored when they died or left Denmark permanently, but less than 3% of the entire cohort did so.⁸ Some people may have had a brain injury or epilepsy during a short stay abroad; but numbers are likely to be very low, and most of these will be treated in Danish hospitals or outpatient clinics when they return to Denmark. Bias due to selection of study participants is therefore an unlikely explanation for our findings. In comparison, 1139 (25%) patients of a total population of 4541 in the Rochester study were lost to follow-up due to migration from Minnesota.¹

A previous study assessed the validity of the hospital codes for brain injury (ICD-8: 851–854) showing that the diagnoses were confirmed in about 88% of cases.²⁹ However, clinical discrimination between different types of brain injury is difficult and the definitions vary between countries.¹⁴ Brain injuries that at first seem mild can turn out to be severe. In a study of 24 patients with post-traumatic amnesia lasting more than 1 week, four had initially been diagnosed with skull fracture and four with concussion.¹⁴ Although, there is debate about the importance of post-traumatic amnesia in the diagnosis of patients with mild brain injury,^{14,30} some patients diagnosed with mild head injury might actually suffer from more severe brain injury, which would likely lead to an overestimated risk of epilepsy associated with mild brain injury.

In the study period (1977–2002), the incidence of mild brain injury decreased,³¹ probably because fewer children were injured or because the need for observation decreased after introduction of new diagnostic methods, most notably CT and MRI.^{14,32} If only the more severe mild head injuries were treated in hospitals in later year, it might explain the increased risk of epilepsy after brain injury in 1994–2002.

However, the diagnostic criteria^{15,29} might have changed when the classification codes were changed from ICD-8 to ICD-10 in 1994,^{10,11} and completeness of epilepsy in the Danish National Hospital Register might have increased when outpatients were included in 1995.¹⁰ In the analyses, we tried to take these factors into account by adjusting for calendar year.

We know, that about 40–50% of all hospitalisations with traumatic brain injuries are related to road-traffic accidents, 20–25% to falls, 8–10% to firearms and assaults, and the remaining related to other causes, such as sporting injuries depending on age and social background.^{14,33} In this study, we did not have information on cause of brain injury, but prevention measures such as the use of bicycle helmets^{34,35} might prevent brain injury and subsequent epilepsy, although the effectiveness of such measures has been questioned.^{36,37}

Traumatic brain injury is a significant risk indicator for epilepsy many years after the injury. Drug treatment after brain injury with the aim of preventing post-traumatic epilepsy has been discouraging, but our data suggest a long time interval for potential, preventive treatment of high risk patients.

Contributors

JC and MV initiated the study and obtained funding. MV, CBP, MGP, JO, PSI, and JC designed the study. MGP and CBP constructed the population. JC, MGP, CBP, and MV analysed the data. JC, MV, and CBP wrote the first draft; JC wrote the revised versions. All authors interpreted the results, revised the paper, and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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