ARTICLE

Risk for injuries and accidents in epilepsy

A prospective population-based cohort study

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Abstract

Objective

To study the risk for injuries/accidents in people with newly diagnosed epileptic seizures in relation to comorbidities.

Methods

Between September 1, 2001, and August 31, 2008, individuals in northern Stockholm with incident unprovoked seizures (epilepsy; n = 2,130) were included in a registry. For every epilepsy patient, 8 individuals matched for sex and inclusion year (n = 16,992) were randomly selected as references from the population of the catchment area. Occurrence of injuries/accidents was monitored through the national patient and cause of death registers until December 31, 2013. These registers also provided information on comorbidities (e.g., brain tumor, stroke, psychiatric disease, diabetes mellitus).

Results

Injury/accident was demonstrated in 1,033 epilepsy cases and 6,202 references (hazard ratio [HR] 1.71, 95% confidence interval 1.60–1.83). The excess risk was seen mainly during the first 2 years after diagnosis. Sex and educational status had no significant effect on HR. The risk was normal in children but increased in adults. Highest HR was seen for drowning, poisoning, adverse effect of medication, and severe traumatic brain injury. Compared to references without comorbidities, HR was 1.17 (1.07–1.28) in epilepsy without comorbidities, 4.52 (4.18–4.88) in references with comorbidities, and 7.15 (6.49–7.87) in epilepsy with comorbidities.

Conclusion

Presence of comorbidities should be considered when counseling patients with newly diagnosed epilepsy concerning risk for injuries/accidents. Early information is important, as the risk is highest during the first 2 years following seizure onset.

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Glossary

CI = confidence interval; **HR** = hazard ratio; **ICD-10** = *International Classification of Diseases–10*; **RERI** = relative excess risk due to interaction; **SIRE** = Stockholm Incidence Registry of Epilepsy; **TBI** = traumatic brain injury.

Compared to the general population, people with epilepsy have an increased risk for accidental injury.[1,2] Current data are, however, conflicting regarding the level of this increase, as hospital-based studies[3,4] and studies performed on institutionalized patients[5] tend to show high risks, in contrast to population-based studies, which show minor[6–8] or no risk increase.[9] Prospective studies are hampered by short follow-up periods,[10] inclusion of few[11] or prevalent[9] cases, and lack of a suitable reference population.[12,13]

Further examination of types and mechanisms of injuries and accidents as well as of possible risk factors such as sex, age, seizure type, or time since epilepsy onset is important in order to better understand risks associated with epileptic seizures and to facilitate actions that reduce these risks.

The increased risk for injury observed in people with epilepsy may be caused not only by seizures, but also by comorbid conditions affecting cognition, vigilance, or balance, which are frequent in people with epilepsy,[2,14] or might be an effect of interaction between seizures and comorbidities, which also remains to be investigated.

Our aim was to investigate the risk for traumatic injury or accident in persons with epilepsy in relation to a wide range of comorbidities, to explore the nature of the injury, role of seizure type, time from onset, age at onset, and sex. Analyses were based on data from a large population-based study including 2,130 patients newly diagnosed with incident unprovoked seizures and a reference population of 16,992 matched, population-based individuals without seizures.

Methods

Study population

Individuals with epilepsy were identified through the Stockholm Incidence Registry of Epilepsy (SIRE), a population-based incidence register covering cases occurring in the northern parts of Stockholm, an urban region with 998,500 inhabitants, between 2000 and 2008. The SIRE methodology has been described in detail before.[15] In short, from September 1, 2000, all patients older than 15 years, and from September 1, 2001, patients of all ages (>1 month) identified with a first unprovoked seizure or incident epilepsy were included in SIRE. Inclusion finished on August 31, 2008. Potential patients living in the catchment area were identified through reports from neurologists, pediatricians, and geriatricians or nurses in nursing homes in the region. We also screened all medical records of patients referred to the neuro-oncology section of the Karolinska University Hospital and from patients discharged for the first time from the Department of Neurology or Pediatrics at the same hospital with the ICD-10 diagnoses G40, G41, or R56.8. Pediatric emergency room records were evaluated, and all EEG requests to the local EEG laboratory were screened for patients with suspected seizures. Medical records of all potential cases were evaluated by an expert panel and cases were classified based on the available information 6 months after the index seizure according to standards for epidemiologic studies and surveillance of epilepsy by the International League Against Epilepsy.[16] All those with unprovoked seizures confirmed by the medical chart review were included in SIRE and the analysis of this article (n = 2,130, hereafter referred to as epilepsy cases).

For each epilepsy case, 8 persons, matched by sex, catchment area, and year of diagnosis, were randomly selected from the Population Register of Stockholm County (n = 16 992, hereafter referred to as reference population). Members of the reference population with an incident seizure after the date of matching were included in SIRE as epilepsy case from the date of the seizure.

Register linkage

The study population was linked to the Swedish national registers for inpatient and outpatient care and cause of death using the 10-digit personal identification number assigned to all Swedish citizens. The cause of death register is available since 1952, the national inpatient register since 1987, and the outpatient register since 2001 (except for hospital-associated surgery, where data are available since 1997). Loss to follow-up is considered minimal and limited to migration, while diagnoses have been shown to be of high accuracy,[17] and are coded by the Swedish version of the ICD-10 since January 1, 1997. Registration in these health registers is compulsory by law and considered complete nationwide. This provided information on comorbidity and also allowed us to follow-up injuries and accidents.

The Longitudinal Integration Database for Health Insurance and Labour Market Studies rendered information on educational status. Such data were accessible for 90% of the study population, missing primarily in children. Educational status was defined as primary education (1 to 9 years of compulsory education), secondary education (10 to 12 years of education), and tertiary (university) education.

Comorbidity

Information on selected conditions associated with epilepsy[15,18,19] and propensity for injuries and accidents, including stroke (I60–I69, G45),[20] brain tumor (C70-C72, C793, D32, D33, D42, D43),[21] dementia (F00–F03),[22,23] diabetes mellitus (E10-E14),[24] psychiatric disease (F04–F98,[25] including mental retardation, F70–79),[26] disorders of psychological development (F80–F89),[27] behavioral and emotional disorders

with onset usually occurring in childhood and adolescence (F90–F98),[28] and congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99),[29] was collected from the registers from January 1, 1997, until date of injury.

Follow-up of injuries and accidents

Patients were followed in the registers from baseline (which was date of inclusion in SIRE/index date for matched references) until the first of the following events occurred: diagnosis of injury or accident in any of the registers, death, or December 31, 2013. Diagnoses were defined as ICD-10 codes for "injury, poisoning and certain other consequences of external causes" (S00-T98) or "external causes of morbidity and mortality" (V00-Y98) in the registers. Injuries were further subdivided according to their localization or the mechanism causing injury. The examined ICD-10 codes are listed in table e-1 (links.lww.com/WNL/A198).

Statistical analysis

Analyses were conducted using SAS (version 9.3, SAS Institute Inc., Cary, NC).

We used Cox proportional hazard regression to calculate hazard ratios (HR) and 95% confidence intervals (95% CIs) for accidents and injuries in relation to epilepsy. HRs were adjusted for age group (0–14 years, 15–29 years, 30–64 years, or 65 years and older at inclusion), sex, and comorbidity (yes/no). Analyses were stratified by age group, sex, and educational status. Influences of possible effect modifiers, such as seizure classification, etiology, and earlier injury on HR, were examined separately. External causes of accidents and injuries were examined separately. HR of accidents/injuries were calculated in relation to the combination of epilepsy and different comorbidities and additive interaction between epilepsy/comorbidity was calculated by relative excess risk due to interaction (RERI).[30] Sensitivity analysis was performed after exclusion of all individuals with accidents/injuries before baseline. The time course for occurrence of first accident or injury was calculated among epilepsy cases and compared to the reference population by means of a Kaplan-Meier analysis. Information on occurrence of accidents or injuries was evaluated for each register separately as well as for all registers together.

Standard protocol approvals, registration, and patient consents

Approval was granted by the Ethics Review Board at Karolinska Institutet, Stockholm, which deemed that no individual informed consent was required.

Results

Characteristics

Characteristics of the study population are presented in table 1. Median age was 35 years for epilepsy cases and 39 years for reference population. Women represented 45% of cases and controls. Most seizures were of focal onset (66%). Injury before inclusion was seen in 31% of cases and 22% of controls. At least one of the studied comorbidities was diagnosed in 22% of the epilepsy cases and in 5% of the reference population.

Risk for injuries in epilepsy by sex, type of seizure, and age

Epilepsy was associated with an increased risk of injury and accident (HR 1.71), which was attenuated after adjustment for comorbidity (HR 1.30). The excess risk due to epilepsy did not differ by seizure type and was similar in men and women, although women in general had a slightly lower risk than men (HR 0.92, 95% CI 0.87–0.96).

No increased risk was seen in individuals exposed to epilepsy prior to age 15 compared to reference population of the same age, while all other age categories showed a risk increase among epilepsy cases (table 2).

Stratification by education showed a similar increase in HR and 95% CI for all examined groups, ranging from 1.82 (1.53–2.16) for cases with primary education to 1.62 (1.44–1.81) for cases with tertiary education.

Restricting the analysis to individuals without trauma or injury before inclusion yielded similar results.

The HR for accident or injury was 3.99 (95% CI 2.86–5.42) in the cause of death registry, 2.09 (95% CI 1.88–2.32) in the hospital discharge registry, and 1.31 (95% CI 1.22–1.41) in the outpatient registry.

Table 1 Characterization of the study population

	Epilepsy, n (%)	Reference population, n (%)
Total	2,130	16,992
Median age, y (Q1, Q3)	34.8 (10.1, 60.8)	38.6 (21.2, 56.7)
Male	1,166 (54.7)	9,312 (54.8)
Female	964 (45.3)	7,680 (45.2)
Age at baseline, y		
<15	679 (31.9)	3,113 (18.3)
15–30	300 (14.1)	3,042 (17.9)
30–65	721 (33.9)	8,372 (49.3)
>65	430 (20.2)	2,465 (14.5)
Seizure onset		
Focal	1,399 (65.7)	NA
Generalized	201 (9.4)	NA
Unknown	530 (24.9)	NA
Trauma before inclusion[a]	660 (31.0)	3,810 (22.4)
Comorbidity[b]	468 (22.0)	849 (5.0)

Abbreviation: NA = not applicable.
[a] Since introduction of the Swedish version of ICD-10 in 1997.
[b] Registration of any diagnosis of stroke, dementia, CNS neoplasia, psychiatric diseases, chromosomal abnormalities, or diabetes mellitus in the IPR, OPR, or CDR at any time, previous or simultaneously to injury or accident from 1997 onwards.

Table 2 Hazard ratio (HR) and 95% confidence interval (CI) for injuries or accidents among epilepsy cases compared to reference population, stratified by age categories and sex and for different types of seizures, unadjusted and adjusted for comorbidities[a]

	Injuries/total	Reference population, total observation time, y (median)	Injuries/total	Epilepsy, total observation time, y (median)	Adjusted for comorbidity	
					Not adjusted HR (95% CI)	Adjusted HR (95% CI)
Total population	6,202	126,983 (8.16)	1,033	11,663 (5.53)	1.71 (1.60–1.83)	1.30 (1.21–1.39)
Age at inclusion, y						
<15	1,291	22,737 (8.02)	308	4,572 (7.66)	1.17 (1.04–1.33)	1.05 (0.92–1.19)
15<30	1,060	23,453 (8.44)	142	2,038 (7.55)	1.54 (1.30–1.84)	1.23 (1.02–1.47)
30<65	2,702	66,488 (8.61)	384	3,763 (4.77)	2.47 (2.22–2.75)	1.47 (1.31–1.65)
≥65	1,149	14,304 (5.95)	199	1,296 (1.60)	1.94 (1.67–2.25)	1.55 (1.33–1.80)
Sex						
Female	2,719	57,959 (8.27)	462	5,237 (5.36)	1.84 (1.66–2.03)	1.35 (1.26–1.50)
Male	3,483	69,024 (8.07)	571	6,433 (5.66)	1.64 (1.49–1.79)	1.27 (1.16–1.40)
Seizure onset						
Focal	—	—	1,399	7,062 (4.53)	1.78 (1.64–1.93)	1.31 (1.20–1.42)
Generalized	—	—	201	1,219 (6.58)	1.77 (1.46–2.14)	1.28 (1.06–1.56)
Unknown	—	—	530	3,390 (7.38)	1.54 (1.36–1.75)	1.29 (1.14–1.47)
No earlier trauma[b]	4,524/13,182	102,991 (8.52)	689/1,470	8,731 (6.34)	1.69 (1.55–1.83)	1.34 (1.23–1.46)

[a] Including stroke, brain tumor, dementia, diabetes mellitus, psychiatric disease (including mental retardation, disorders of psychological development, behavioral and emotional disorders with onset usually occurring in childhood and adolescence), and congenital malformations, deformations, and chromosomal abnormalities.
[b] Epilepsy cases and reference population without trauma or accident from introduction of the Swedish version of ICD-10 in January 1, 1997, until inclusion in the study.

Locations and types of injuries

Injuries were most frequently localized to the upper extremity, followed by the lower extremity and the head (table 3). The most frequent types were fractures, superficial injuries, and open wounds. The highest HR was seen for drowning and nonlethal submersion accidents, followed by poisoning by medication, unspecified adverse effect of drug or medication, and severe traumatic brain injury (TBI).

When adjusting for comorbidity, epilepsy cases had an increased risk only for injuries to head, neck, and torso. The risk for fractures was still increased, as well as the risk for complications of surgical and medical care (not elsewhere classified) and other and unspecified effects of external causes. There was still an increased risk for drowning, poisoning by drugs, adverse effect of medicaments, severe TBI, infections following a procedure, luxation of shoulder, and mild TBI.

The most frequent external causes of accidents were falls, exposure to unspecified factors, and medical and surgical complications, while the highest HR was observed for medical or surgical complications, followed by self-harm of intentional or of undetermined intent and falls.

When adjusting for comorbidity, the only causes remaining with increased risk among epilepsy cases were falls and complications of medical and surgical care.

Risk for injury or accident in relation to the combination of epilepsy and comorbidities

The effect of comorbidities on the risk of injuries or accidents is presented in table 4. The HR for trauma in epilepsy without any of the analyzed comorbidities was estimated at 1.17, whereas the HR in individuals with any of the comorbidities among the reference population was 4.79.

The risk for trauma was elevated more than 7-fold in individuals with a combination of epilepsy and comorbidity and interaction was confirmed with a RERI of 2.27. Out of the different comorbidities investigated, significant interaction with epilepsy was seen for malignant brain tumor, stroke, diabetes mellitus, and psychiatric disease, and this interaction was most pronounced for malignant brain tumor.

Time course of injury risk

The risk for injuries was highest among epilepsy cases during the first 2 years after inclusion. Within this time span, 23% of epilepsy cases and 11% of the reference

Table 3 Hazard ratio (HR) and 95% confidence interval (CI) for different locations and types of injuries and accidents in relation to epilepsy[a]

	Epilepsy		Reference population		Adjusted for comorbidity	
Diagnosis (ICD-10 code)	Injury, n	Person-years (median)	Injury, n	Person-years (median)	Not adjusted HR (95% CI)	Adjusted HR (95% CI)
Localization of injury						
Head	323	15,558 (8.26)	1,419	152,821 (9.39)	2.00 (1.77–2.27)	1.43 (1.26–1.63)
Neck-thorax-abdomen-lower back-spine-pelvis	160	16,444 (8.68)	893	155,296 (9.50)	1.75 (1.47–2.07)	1.23 (1.03–1.46)
Upper extremity	357	15,401 (8.18)	2,408	147,348 (9.19)	1.30 (1.16–1.45)	0.95 (0.84–1.07)
Lower extremity	348	15,665 (8.33)	2,241	148,514 (9.24)	1.45 (1.33–1.62)	1.01 (0.89–1.13)
Injuries involving multiple body regions	14	17,133 (8.98)	34	159,228 (9.62)	4.13 (2.20–7.74)	1.82 (0.89–3.72)
Injuries to unspecified part of trunk, limb, or body region	63	16,914 (8.90)	278	157,968 (9.59)	2.08 (1.58–2.74)	1.30 (0.98–1.73)
Effects of foreign body entering through natural orifice	41	17,005 (8.93)	262	158,229 (9.59)	1.41 (1.01–1.97)	0.95 (0.67–1.34)
Type of injury						
Superficial	288	15,808 (8.39)	1,628	151,834 (9.36)	1.52 (1.34–1.73)	1.11 (0.98–1.27)
Open wound	235	16,068 (8.51)	1,352	152,845 (9.39)	1.55 (1.35–1.78)	1.15 (0.99–1.32)
Fracture	438	15,187 (8.06)	2,300	148,304 (9.25)	1.80 (1.62–1.99)	1.26 (1.14–1.41)
Dislocation, sprain/strain joint	192	16,258 (8.62)	1,270	152,698 (9.39)	1.35 (1.16–1.58)	0.89 (0.76–1.05)
Burns and corrosions	16	17,116 (8.96)	79	158,904 (9.60)	1.65 (0.86–2.85)	1.53 (0.89–2.66)
Frostbite	0	17,000 (9.00)	3	159,391 (9.62)	—	—
Poisoning by drugs, medicaments, and biological substances	55	16,938 (8.90)	186	158,632 (9.61)	2.98 (2.19–4.04)	1.29 (0.93–1.79)
Toxic effects of substances chiefly nonmedicinal	31	17,046 (8.93)	143	158,933 (9.61)	2.25 (1.52–3.33)	1.48 (0.99–2.21)
Other and unspecified effects of external causes	61	16,888 (8.88)	307	157,874 (9.59)	1.70 (1.29–2.25)	1.44 (1.09–1.91)
Certain early complications of trauma	11	17,148 (8.96)	39	159,241 (9.61)	2.82 (1.43–5.57)	1.57 (0.77–3.21)
Complications of surgical and medical care, not elsewhere classified	189	16,248 (8.65)	714	156,646 (9.55)	2.93 (2.49–3.45)	1.59 (1.34–1.88)
External causes of morbidity and mortality						
Transport accidents	46	16,793 (8.84)	285	157,009 (9.54)	1.42 (1.11–1.81)	1.15 (0.90–1.48)
Falls	448	15,267 (8.10)	2,256	150,525 (9.30)	2.02 (1.82–2.24)	1.41 (1.27–1.57)
Exposure to external forces	136	16,637 (8.74)	1,007	155,127 (9.47)	1.15 (0.96–1.39)	0.90 (0.75–1.09)
Accidental drowning and submersion	1	17,181 (8.99)	2	159,298 (9.62)	6.09 (0.54–68.56)	6.09 (0.54–64.55)
Other accidental threats to breathing	10	17,186 (8.99)	18	159,267 (9.62)	6.37 (2.86–14.20)	2.60 (0.99–6.81)
Exposure to smoke, fire, and flames	5	17,175 (8.99)	19	159,227 (9.62)	2.79 (1.03–7.56)	1.10 (0.38–3.14)
Smoke or contact with heat and substances	5	17,161 (8.98)	41	159,138 (9.61)	0.97 (0.38–2.47)	0.97 (0.37–2.54)

Continued

Table 3 Hazard ratio (HR) and 95% confidence interval (CI) for different locations and types of injuries and accidents in relation to epilepsy[a] *(continued)*

	Epilepsy		Reference population		Adjusted for comorbidity	
Diagnosis (ICD-10 code)	Injury, n	Person-years (median)	Injury, n	Person-years (median)	Not adjusted HR (95% CI)	Adjusted HR (95% CI)
Contact with venomous animals and plants or exposure to forces of nature	6	17,157 (8.97)	49	159,079 (9.61)	1.16 (0.49–2.73)	0.87 (0.36–2.13)
Accidental poisoning by and exposure to noxious substances	20	17,113 (8.96)	50	159,119 (9.61)	3.92 (2.31–6.63)	1.57 (0.87–2.82)
Overexertion, travel, and privation	16	17,124 (8.97)	85	158,985 (9.61)	1.72 (1.00–2.95)	0.86 (0.47–156)
Accidental exposure to noxious substances	239	16,380 (8.62)	1,469	154,408 (9.42)	1.52 (1.32–1.74)	1.08 (0.93–1.24)
Intentional self-harm/event of undetermined intent	65	16,901 (8.88)	259	158,282 (9.59)	2.44 (1.85–3.22)	1.25 (0.94–1.66)
Assault	28	17,070 (8.95)	198	158,518 (9.60)	1.25 (0.84–1.86)	1.17 (0.78–1.75)
Legal intervention and operations of war	0	17,189 (8.99)	0	159,302 (9.62)	—	—
Complication of medical and surgical care	171	16,469 (8.74)	700	157,054 (9.55)	2.72 (2.30–3.22)	1.67 (1.41–1.99)
Selected types of injuries associated with high HR						
Mild TBI	96	16,740 (8.84)	374	157,742 (9.59)	2.22 (1.76–2.78)	1.42 (1.12–1.80)
Severe TBI	53	16,965 (8.93)	121	158,978 (9.61)	4.45 (3.20–6.17)	2.07 (1.46–2.93)
Luxation of shoulder	27	17,043 (8.95)	87	159,026 (9.61)	3.19 (2.06–4.93)	1.61 (1.00–2.59)
Drowning[b] and nonfatal submersion	3	17,193 (8.99)	3	159,399 (9.62)	11.39 (2.28–56.98)	39.27 (3.47–444.04)
Suffocation[c]	8	17,176 (8.99)	40	159,203 (9.61)	1.98 (0.92–4.27)	1.12 (0.49–2.53)
Poisoning by antiepileptic, sedative-hypnotic, and antiparkinonism drugs	15	17,116 (8.97)	32	159,290 (9.62)	5.08 (2.74–9.44)	2.71 (1.30–5.62)
Other and unspecified drugs, medicaments, and biological substances	35	1,7033 (8.92)	119	158,918 (9.61)	2.92 (1.99–4.28)	0.95 (0.62–1.44)
Infection following a procedure, not elsewhere classified	73	16,829 (8.89)	198	158,650 (9.61)	4.12 (3.14–5.40)	1.79 (1.34–2.40)
Unspecified adverse effect of drug or medicament	26	17,038 (8.95)	57	159,210 (9.61)	4.87 (3.04–7.80)	2.70 (1.63–4.48)

Abbreviation: TBI = traumatic brain injury.
[a] Adjusted for age and sex.
[b] Excluding causes of drowning (accident to watercraft causing drowning and submersion and water transport–related drowning and submersion without accident to watercraft [V90 and V92], and W65–W74).
[c] Excluding W75–W84 (other accidental threats to breathing).

population without any comorbidity had an injury or accident. Thereafter, the excess risk among epilepsy cases gradually declined and eventually approached the risk in the reference population (figure). Epilepsy greatly increased the risk for having an accident or injury among persons with comorbidity and markedly shortened the time until this occurred. While it took 4.12 years until 50% of the reference population with comorbidity had an accident or injury, half of epilepsy cases with comorbidity had an accident or injury within 1.89 years.

Discussion

In this population-based study, we confirmed that epilepsy was associated with an increased risk of injuries and accidents; that sex and education had no significant influence;

Table 4 Hazard ratio (HR) and 95% confidence interval (CI) for injury or accident in relation to epilepsy and different comorbidities[a]

	Epilepsy	No. of injuries/accidents	No. of person-years (median)	HR (95% CI)	RERI (95% CI)
Any comorbidity					
No	No	5,352	123,015 (8.34)	1.0	
Yes	No	850	3,884 (4.12)	4.52 (4.18–4.88)	
No	Yes	563	10,276 (7.09)	1.16 (1.07–1.27)	
Yes	Yes	470	1,387 (1.89)	7.16 (6.51–7.89)	2.48 (1.76 to 3.21)
Malignant brain tumor					
No	No	6,193	126,840 (8.16)	1.0	
Yes	No	9	60 (8.07)	3.07 (1.60–5.90)	
No	Yes	964	11,519 (5.74)	1.61 (1.50–1.73)	
Yes	Yes	69	144 (1.25)	9.65 (7.60–12.25)	5.54 (2.37 to 8.70)
Benign tumor of brain					
No	No	6,188	126,849 (8.16)	1.0	
Yes	No	14	50 (2.23)	5.00 (2.96–8.46)	
No	Yes	996	11,562 (5.63)	1.66 (1.56–1.78)	
Yes	Yes	37	101 (1.74)	6.82 (4.93–9.42)	1.15 (−2.23 to 4.57)
Stroke/TIA					
No	No	5,965	125,714 (8.21)	1.0	
Yes	No	237	1,186 (4.74)	3.19 (2.78–3.65)	
No	Yes	860	11,164 (6.01)	1.53 (1.42–1.64)	
Yes	yes	173	499 (1.85)	5.98 (5.12–6.97)	2.26 (1.28 to 3.25)
Diabetes mellitus					
No	No	5,970	125,736 (8.20)	1.0	
Yes	No	232	1,164 (4.90)	3.42 (2.99–3.92)	
No	Yes	976	11,498 (5.70)	1.68 (1.57–1.80)	
Yes	Yes	57	164 (1.65)	6.30 (4.85–8.19)	2.20 (0.50 to 3.90)
Dementia					
No	No	6138	126,634 (8.17)	1.0	
Yes	No	64	80 (1.47)	2.94 (2.28–3.79)	
No	Yes	999	11,583 (5.64)	1.68 (1.57–1.80)	
Yes	Yes	34	266 (3.40)	5.25 (3.73–7.37)	1.62 (−0.29 to 3.54)
Congenital malformation[b]					
No	No	6,149	126,664 (8.17)	1.0	
Yes	No	53	236 (3.82)	4.42 (3.37–5.80)	
No	Yes	979	11,404 (5.56)	1.68 (1.56–1.79)	
Yes	Yes	54	258 (4.70)	4.14 (3.17–5.42)	−0.96 (−2.59 to 0.67)
Psychiatric disease[c]					
No	No	5,809	125,257 (8.25)	1.0	

Continued

Table 4 Hazard ratio (HR) and 95% confidence interval (CI) for injury or accident in relation to epilepsy and different comorbidities[a] *(continued)*

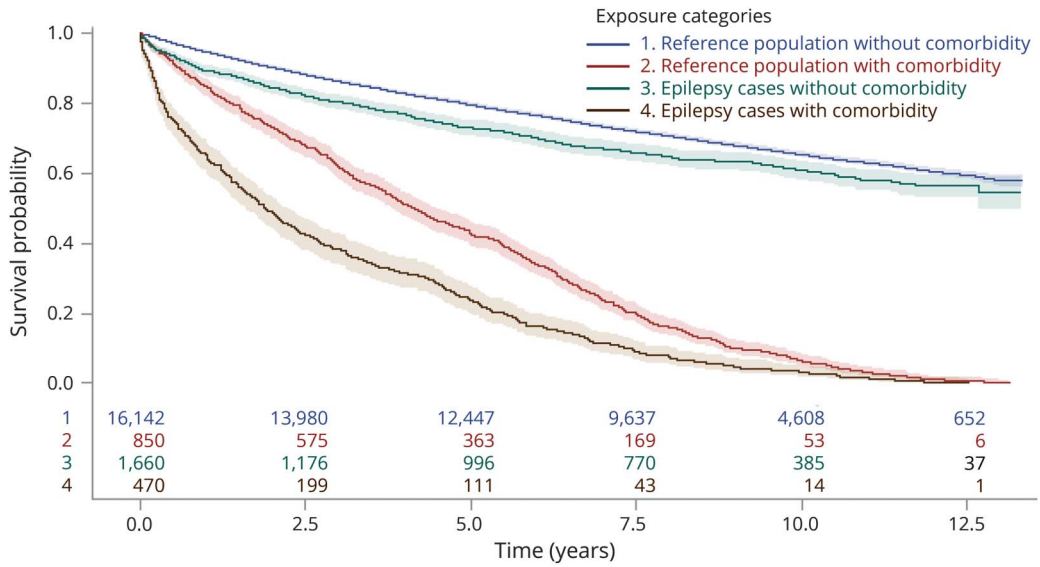
	Epilepsy	No. of injuries/accidents	No. of person-years (median)	HR (95% CI)	RERI (95% CI)
Yes	No	393	1,643 (3.72)	4.52 (4.08–5.02)	
No	Yes	846	11,084 (6.02)	1.55 (1.44–1.66)	
Yes	Yes	187	579 (1.93)	6.35 (5.49–7.35)	1.28 (0.26 to 2.30)
Psychoactive substance use[d]					
No	No	6,005	126,168 (8.21)	1.0	
Yes	No	197	732 (2.87)	5.08 (4.40–5.86)	
No	Yes	942	11,421 (5.82)	1.62 (1.51–1.74)	
Yes	Yes	91	242 (1.12)	7.74 (6.29–9.53)	2.04 (0.29 to 3.79)
Psychosis					
No	No	6,163	126,712 (8.17)	1.0	
Yes	No	39	187 (5.01)	3.84 (2.79–5.28)	
No	Yes	1,019	11,624 (5.58)	1.70 (1.59–1.82)	
Yes	Yes	14	39 (1.93)	6.23 (3.69–10.52)	1.69 (−1.79 to 5.17)
Affective disorders					
No	No	6,063	126,271 (8.18)	1.0	
Yes	No	139	628 (4.20)	4.05 (3.41–4.80)	
No	Yes	991	11,553 (5.63)	1.68 (1.57–1.80)	
Yes	Yes	42	110 (0.99)	7.12 (5.25–9.65)	2.39 (0.13 to 4.65)
Neurotic disorders[e]					
No	No	6,108	126,515 (8.17)	1.0	
Yes	No	94	384 (3.69)	4.66 (3.80–5.72)	
No	Yes	1,000	11,586 (5.62)	1.68 (1.58–1.81)	
Yes	Yes	33	77 (1.17)	8.16 (5.79–11.50)	2.81 (−0.13 to 5.75)
Other psychiatric diseases					
No	No	6,123	126,582 (8,17)	1.0	
Yes	No	79	318 (3.86)	4.04 (3.23–5.05)	
No	Yes	962	11,387 (5.63)	1.65 (1.54–1.77)	
Yes	Yes	71	276 (3.14)	4.71 (3.72–5.95)	0.13 (−1.41 to 1.43)

Abbreviation: RERI = relative excess risk due to interaction.
Analysis of the RERI for epilepsy and comorbidity.
[a] Adjusted by age and sex.
[b] Congenital malformations, deformations, and chromosomal abnormalities.
[c] Psychiatric disease includes all diagnoses below.
[d] Mental and behavioral disorders due to psychoactive substance use.
[e] Neurotic, stress-related, and somatoform disorders.

that the risk was normal in children but increased in adults; that comorbidities had a major influence on the risk and that there was an excess risk due to interaction between epilepsy and many comorbidities; that the excess risk for a first injury or accident was seen mainly during the first 2 years after diagnosis; and that the highest HR was seen for drowning, poisoning, adverse effect of medication, and severe TBI.

The main strengths in this study are in the population-based design with a large cohort of validated incident cases of unprovoked seizures followed for a long time with minimal loss

Figure Product-limit survival estimate with number of patients at risk and 95% confidence limits



Probability of injuries and accidents in epilepsy cases and reference population in relation to comorbidity over time since inclusion.

to follow-up and with a matched reference population. The use of multiple health care registries permits us to evaluate the risk for various types of injuries and assess the influence of comorbidities with high accuracy, while recall bias is avoided.

Among limitations, the seizure diagnosis was based on review of data available in medical records 6 months after the index seizure, which in some cases is too short for a detailed classification. In addition, we do not have access to information on seizure control after the first 6 months since the index seizure. Being based on ICD codes and register data, we did not have information on if accidents or injuries were seizure-related. Our study setup did not allow reliable estimates on occurrence of sudden unexpected death in epilepsy. Milder injuries will not be identified, but are less of a burden for the patient. Our results regarding outcome also rely on the validity of the diagnoses in the registries. Traumatic injuries and accidents are expected to be diagnosed with high accuracy in the utilized registers.[17,31] In the current analysis, we examined the risk of having a first event of trauma/injury. No information on further traumatic accidents of the same kind was considered, as this risk is expected to increase after a first injury.

Several earlier studies have demonstrated that people with epilepsy are at higher risk for traumatic injuries than healthy controls. As in other population-based studies,[4,9] we found a less than doubled risk increase in our epilepsy cases compared to the reference population, and the increased risk for fractures[3,7] and for head injuries[32,33] is in line with earlier studies. Vestergaard[34] in a meta-analysis reported a HR of 2.2 (95% CI 1.9–2.5) for fractures in persons with epilepsy, which is in line with our results (HR 1.80; 95% CI 1.62–1.99).

While some earlier studies adjust their results for comorbidities,[6,35] we are not aware of any other study analyzing interactions between epilepsy and different diseases known to increase the risk for accidents due to cognitive impairment or by affection of vigilance or balance. As such diseases are common among people with epilepsy, this approach is important, as the interaction of diagnoses could result in an overestimation of the risk attributed to epilepsy. In our study, the influence of epilepsy alone on the risk for persons having injuries or accidents is modest in comparison to the effect of the examined comorbidities, while persons with a combination of epilepsy and comorbidity appear to have a supra-additive effect on the risk of accidents and injuries. This effect seems to be especially high in patients with malignant brain tumor and epilepsy.

The risk of having an injury or accident was not elevated among epilepsy cases younger than 15 years at inclusion (when adjusting for comorbidity[28]). A possible explanation is supervision of children with epilepsy by family and other caregivers.

The increased risk during the first 2 years after diagnosis was gradually normalized later in the observation period. This is in line with previous studies on fractures and epilepsy[3,36] and is probably a consequence of a combination of remission of the epilepsy, effective patient counseling, and that some persons with comorbidities die.

Compared to others, people with epilepsy are admitted to the hospital more often after an accident or injury. This may be a consequence of the severity of the injury, a comorbidity, seizure-related hospitalization, or a more cautious attitude

among health professionals towards people with epilepsy.[8] In our study, the HR was higher for severe TBI than for mild TBI. We also found a higher HR in the cause of death registry and the hospital discharge registry compared with the outpatient registry, suggesting that more severe injuries occurred in epilepsy cases compared to the reference population.

As expected, the risk for traffic accidents,[37] burns and scalds,[38] as well as drowning[39] were increased among epilepsy cases. While traffic accidents were more frequent among epilepsy cases, the risk for car accidents was not increased, in contrast to a doubled risk for bicycle accidents. All bicycle accidents affect the driver of the vehicle, while car accidents may also include passengers. HR therefore is expected to be lower for car than for bicycle accidents among epilepsy cases. Motor vehicle driving for persons with active epilepsy is also restricted by law, and our data indicate that current restrictions are effective. When adjusting for comorbidity, the risk was normalized for both burns and scalds as well as for traffic accidents.

Drowning in epilepsy has been assessed in a meta-analysis,[40] reporting a standardized mortality ratio of 18.7 (95% CI 15–23.1) for persons with epilepsy from 51 cohorts with 88 drowning deaths among people with epilepsy. Our estimated HR of 11.39 (95% CI 2.28–56.98) for drowning and nonfatal submersion is comparable to these results. Two of 3 epilepsy cases with fatal drowning were considered intentional self-harm and 1 case was due to alcohol intoxication. One fatal drowning in the reference population was classified as being of undetermined intent, while the other 2 references had nonfatal accidental drowning. The low number of incidents of fatal drowning accidents among controls in our study (1/126,983 person-years) is in line with the average number of drowning deaths in Sweden in general (1.13/100,000 person-years according to official statistics from Svenska Livräddningssällskapet), which is low compared to the international figure (7.4/100,000 person-years[40]).

Being population-based, our results are generalizable for people with newly diagnosed epilepsy regarding injuries or accidents requiring hospital-associated health care, as long as it is applied to persons living in urban societies of the western world with similar access to hospital and outpatient care as Sweden. As all hospital-associated patient contacts and deaths are registered in these registers, catchment of injury diagnoses severe enough to need the health care resources of hospitals or hospital-associated outpatient clinics should be complete for all patients within the borders of Sweden and the number lost to follow-up is minimal.

Our data highlight the importance of considering comorbidities in counseling patients with newly diagnosed epilepsy for risk for injuries and accidents. Early information is important, as the risk for initial injury is highest during the first 2 years following seizure onset.

Author contributions

Benno Mahler: acquisition of data, statistical analyses, interpretation of data, drafting first manuscript, takes full responsibility for the conduct of the research, has full access to all of the data and the right to publish any and all data separate and apart from any sponsor. Sofia Carlsson: study concept and design, interpretation of data, critical revision of manuscript for intellectual content. Tomas Andersson: study concept and design, statistical analysis, interpretation of data. Torbjörn Tomson: study concept and design, interpretation of data, critical revision of manuscript for intellectual content.

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Disclosure

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FULL-LENGTH ARTICLE NPub.org/hvh7l8

Risk for injuries and accidents in epilepsy

A prospective population-based cohort study

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Study question

Does the presence of comorbidities influence the risk of accidents and injuries among individuals with epilepsy?

Summary answer

Epilepsy was associated with an increased risk of injuries and accidents—particularly drowning, poisoning, adverse effects of medication, and severe traumatic brain injury—in adults only, which was higher for patients with various comorbidities.

What is known and what this paper adds

Previous studies have demonstrated that patients with epilepsy are at higher risk for traumatic injuries than healthy controls. This study demonstrates that the risk for accidents/injuries is higher in patients with epilepsy and comorbid conditions (e.g., brain tumor, stroke, and psychiatric disease) than in those with epilepsy alone.

Participants and setting

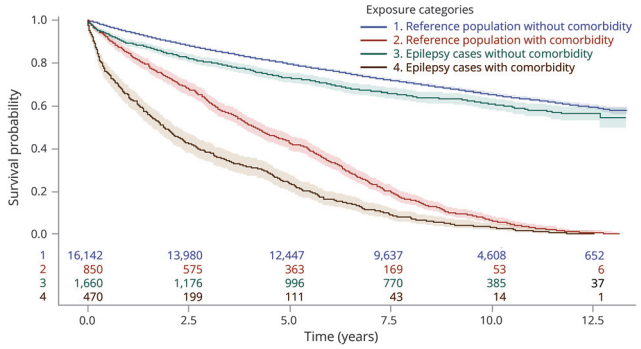
This population-based cohort study included 2,130 patients with epilepsy from northern Stockholm who had experienced unprovoked, incident seizures between 2001 and 2008, and 16,992 controls matched for sex and year of inclusion.

Design

Individuals with epilepsy were identified through the Stockholm Incidence Registry of Epilepsy (SIRE). Information on selected conditions associated with epilepsy and the propensity for injuries and accidents was collected, and patients were followed until the diagnosis of injury or accident, death, or until December 31, 2013. Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for accidents and injuries in relation to epilepsy.

Main results and the role of chance

Epilepsy was associated with an increased risk of injury and accident (HR = 1.71), which was attenuated after adjustment for comorbidity (HR = 1.30). No increased risk was observed in individuals diagnosed with epilepsy prior to age 15. The highest HRs were observed for drowning and non-lethal submersion accidents, followed by medication poisoning, unspecified adverse effects of medication, and severe traumatic brain injury. The risk for trauma was elevated more than seven-fold in individuals with a combination of epilepsy and comorbidity. The risk for injury among patients with epilepsy was highest during the first 2 years after inclusion.



Bias, confounding factors, and other reasons for caution

Seizure diagnosis was based on data available 6 months after the index seizure, which may have inhibited detailed classification.

Generalizability to other populations

The study findings may be generalizable to patients with newly diagnosed epilepsy living in urban areas of the Western world.

Study funding/potential competing interests

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A draft of the short-form article was written by D. Drobish, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.