Injury Among Children and Young Adults with Epilepsy

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Short title: Epilepsy and Injury

Abbreviations: ADHD – Attention-deficit hyperactivity disorder; AED – anti-epileptic drug; BMD – bone mineral density; CI – confidence interval; CPRD – Clinical Practice Research Datalink; GP – General Practitioner; HR – hazard ratio; IMD – Index of Multiple Deprivation; SHA – Strategic Health Authority; US – United States

Key Words: epilepsy, injury, fractures, burns, poisoning

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What's Known on This Subject

Injuries in children and young adults commonly cause morbidity and mortality. Epilepsy is common among children. There may be an increased risk of injury among those with epilepsy but there are few large, population-based studies making it difficult to estimate risk.

What This Study Adds

Children and young adults with epilepsy are at an increased risk of medicinal poisonings, thermal injuries and fractures compared to those without epilepsy. Young adults with epilepsy are at particularly high risk of medicinal poisonings.

Contributors' Statement:
Vibhore Prasad: Dr Prasad conceived the idea for the study, conducted the data management, drafted the initial manuscript, and approved the final manuscript as submitted.

Denise Kendrick: Professor Kendrick conceived the idea for the study, provided clinical input and interpretation throughout the project, and approved the final manuscript as submitted.

Kapil Sayal: Dr Sayal made contributions to the design of the study, provided clinical input and interpretation throughout the project, and approved the final draft of the manuscript.

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Joe West: Dr West conceived the idea for the study, guided the data management, provided clinical input and interpretation throughout the project, and approved the final draft of the manuscript.

Structured Abstract

Objective To investigate whether children and young adults with epilepsy are at an increased risk of fracture, thermal injury, or poisoning compared to those without.

Patients and Methods A cohort study was conducted using the Clinical Practice Research Datalink (CPRD) (1987-2009), a longitudinal database containing primary care records. 11,934 with epilepsy and 46,598 without, aged between 1-24 years at diagnosis were followed for a median (interquartile range) of 2.6 (0.8 to 5.9) years. The risk of: (i) fractures (including long bone fractures) (ii) thermal injuries, and (iii) poisonings (including medicinal and non-medicinal poisonings) was estimated.

Results Adjusting for age, sex, Strategic Health Authority region, deprivation and calendar year at study entry (and, for medicinal poisonings, behavior disorder): people with epilepsy had an 18% increase in risk of fracture, (HR=1.18 (95% CI 1.09 to 1.27)); a 23% increase in risk of long bone fracture, (HR=1.23 (95% CI 1.10 to 1.38)); a 49% increase in risk of thermal injury (HR=1.49 (95% CI 1.27 to 1.75)) and more than double the risk of poisoning (HR=2.47 (95% CI 2.15 to 2.84), which was limited to poisoning from medicinal products (medicinal HR=2.54 (95% CI 2.16 to 2.99), non-medicinal HR=0.96 (95% CI=0.61 to 1.52)).

Conclusions Children and young adults with epilepsy are at a greater risk of fracture, thermal injury and poisoning compared to those without. The greatest risk is from medicinal poisonings. Doctors and other healthcare professionals should provide injury and poison prevention advice at diagnosis and epilepsy reviews.

Introduction

Epilepsy is a chronic neurological condition causing unprovoked recurrent seizures due to excessive cerebral neurological activity[1 2]. It is common, affecting approximately 2 million adults and 468,000 children in the United States (US)[2]. Worldwide, injuries are a leading cause of morbidity and mortality in children.[3] Unintentional injuries are an important public health problem in the US[4], with an incidence of 2,000 medically attended injuries per 10,000 person years[5] and a total lifetime cost in under 25-year-olds of $130 billion in 2000[5]. The epidemiology of injury varies by age[6-9] and boys are more likely than girls to sustain injuries, especially as teenagers[9-11]. Fractures are common with incidence estimates ranging from 133 to 201 per 10,000 person years in children[12-14] to 254 per 10,000 person years in all ages[5] for medically attended fractures. Thermal injuries are common in children and young adults[15 16], with incidence in the US of 34 medically attended injuries per 10,000 person years in under 25-year-olds, and a total lifetime cost of $440 million in 2000[5]. Unintentional poisonings are a significant cause of deaths worldwide[17] in children and young adults and were the third leading cause of injury hospitalizations in the US in 2000[5], with an incidence of 60 medically attended injuries per 10,000 person years in under 25-year-olds and a total lifetime cost of $583 million[5].

Previous studies, mainly in adults, suggest epilepsy is associated with an increased risk of injuries,[18 19] thought to be due to the seizures themselves, and adverse effects of anti-epileptic drugs (AED's)[20 21]. Earlier studies on epilepsy and injuries may have overestimated injury risk by using populations with more severe epilepsy, such as institutionalised adults[22], or those in epilepsy clinics[18]. Questionnaire-based studies ascertaining injury retrospectively are subject to recall bias, with caregivers or relatives more likely to recall an injury if the participant has epilepsy[19]. Few studies have measured the rate of injuries prospectively in the general population[23-25]. A prospective European study in over 5-year-olds found no increased

injury risk associated with epilepsy[25], whilst a US study concluded the risk of serious injuries in epilepsy is minor[26] and a UK study using the Clinical Practice Research Datalink (CPRD) reported the risk of fracture in people with epilepsy to be double those without epilepsy[27]. None of these studies focused on children and young adults with epilepsy; hence there is a lack of data for informing people with epilepsy about injury risk. We therefore investigated whether children and young adults with epilepsy are at an increased risk of fracture, thermal injury, or poisoning compared to people without epilepsy and estimated the risk of injury up to five years after diagnosis with epilepsy.

Methods

Study population

We conducted a cohort study using medical records of children and young adults from the Clinical Practice Research Datalink (CPRD); a primary care database containing medical records of approximately 12 million people (66 million person years of follow-up) from 625 General Practitioner (GP) (family doctor) practices, and representing 8% of the UK population[28]. The CPRD is subjected to rigorous data quality checks (e.g. ensuring that a minimum of 95% of patient encounter events are recorded, validation checks and audits[29]) and a recent systematic review[30] demonstrated the high validity of a range of diagnoses in the CPRD, with a median of 89% of cases confirmed by GP record request, algorithm and manual review[30]. The CPRD contains information on consultations with the GP, hospital attendances and admissions coded using Read codes[31] as well as information on prescriptions. Read codes use a system similar to the systematized nomenclature of medicine (SNOMED) or International Classification of Disease (ICD) systems for use in UK primary care[31]. Lists of Read and drug codes for epilepsy were drawn up by two researchers. CPRD extracted records of people with a code for epilepsy or anti-epilepsy drug (AED) recorded whilst registered in the database before the age of 25 years from 1st January 1987 up to 31st December 2009. People with epilepsy were frequency-matched by practice and five-year age band to up to five people who did not have epilepsy. The lists of Read code descriptions and drug codes used are available from the authors on request.

We took the date of the first Read code or AED prescription to be the date of diagnosis with epilepsy. We randomly assigned a date of 'pseudodiagnosis' for those without epilepsy that could be on any date starting from three months after they registered with the practice and up to the date they left the practice using a computer algorithm. Age was described in terms of the age of individuals at (pseudo)diagnosis.

Definition of epilepsy

Epilepsy was defined as having at least two Read codes for epilepsy or at least two AED prescriptions. To ensure that people with epilepsy included those with an incident diagnosis, made after they joined the current GP practice, we explored the time between the date of registration with the GP and diagnosis of epilepsy for each age group based on work that showed that, in people of all ages, the time taken for incidence rates of chronic conditions to reach a plateau post-registration can vary from 4-12 months, depending on ages and the condition[32]. Our work suggested that incident diagnoses were those made later than three months from registering with the GP for children 14 years old or less and later than 6 months post registration for people over 15 years old. People with prevalent epilepsy or with only one epilepsy Read code or AED prescription were excluded from the analyses.

Definition of outcome and follow-up

The outcome was the first injury to occur after (pseudo)diagnosis of epilepsy. Each injury type (fractures, thermal injuries and poisonings) was chosen *a priori* and identified using a list of Read codes (descriptions available on request). We included both mechanisms of injury (e.g. accidents caused by fire and flames) and anatomic sites of injury (e.g. burn of lower limbs) to maximise ascertainment of injuries. We followed people from the date of diagnosis of epilepsy (or the pseudodiagnosis date for those without epilepsy) to the earliest of the date of the first injury code, of leaving the CPRD (e.g. transfer to a new practice), or 31st December 2009. People who had a record of the injury before the date of (pseudo)diagnosis were excluded from the analysis of that injury type because people with a previous injury have a higher risk of a subsequent injury[33 34]. We also explored the relationship between epilepsy and long bone fractures (as indicators of severe injury[35 36]), and between epilepsy and medicinal and non-medicinal poisonings separately (as those with epilepsy may have greater access to medicines than those without).

Confounders

Estimates were adjusted for age, sex, Strategic Health Authority (SHA) region of the practice, socioeconomic status and calendar year at study entry. We used the Index of Multiple Deprivation (IMD) of the GP practice as a proxy measure of the person's socioeconomic status. IMD scores were categorised into national (England, Scotland, Wales and Northern Ireland) quintiles. Using Read codes, we identified several comorbid conditions that may confound the relationship between epilepsy and injury. These included attention-deficit hyperactivity disorder (ADHD); behavior disorder (including oppositional defiant disorder, antisocial behavior and behavior disorder), learning disability and cerebral palsy.

Statistical analysis

We described categorical variables using frequencies and proportions. The age bands chosen were: 1;2;3;4;5-9;10-14;15-18; and 19-24 years for analyses on fractures but in the analyses on thermal injuries and poisonings under 5's were grouped together due to small numbers of events. We estimated crude rates for the first type of each injury after diagnosis for people with and without epilepsy, with 95% confidence intervals (95% CI). We estimated hazard ratios (HRs) for people with epilepsy compared to those without, using a Cox regression model. We adjusted hazard ratios for confounders (age, sex, SHA region, practice level deprivation and calendar year at study entry). We then adjusted for each comorbid condition (ADHD, behavior disorder, learning disability, cerebral palsy) in turn. When adjustment for a comorbid condition led to a change of >10% in the adjusted HR the confounder was retained in the model and the remaining comorbid conditions were assessed for inclusion in the model as described.

We explored interactions by age and sex by adding interaction terms to the models with a $p<0.05$ taken as statistically significant. Models were checked by inspection of plots of the

logarithm of cumulative hazard against time, Schoenfeld residuals against time and a statistical test for non-proportional hazards for people with epilepsy compared to those without in the final model. The number of people out of a thousand who had an injury within five years of diagnosis was estimated for each injury type. We undertook sensitivity analyses assessing the robustness of our findings in terms of our definition of epilepsy. Firstly, we used a stricter definition of epilepsy as: people with at least two AED prescriptions and two diagnosis codes, secondly we excluded those with a first AED of either pregabalin or gabapentin because these drugs can be prescribed for other diagnoses, and thirdly, we excluded those with AED prescriptions but no Read code for diagnosis of epilepsy. We also recalculated the risk of injuries in those aged 1-21 years to assess whether the estimates of risk differed when young adults above 21 years were excluded from the population. Lastly, as virtually all those with long-bone fractures would have attended secondary care, we assessed completeness of ascertainment of long-bone fracture risk in the practice records using around half the sample who had linked hospital records from the Hospital Episodes Statistics (HES) database. HES data include diagnosis codes, using the International Classification of Diseases (ICD) version 10[37], and procedure codes, using the Office of Population Censuses and Surveys (OPCS-4) version 4[38] from inpatient admissions to hospital in England. All long bone fracture codes recorded during study follow-up in the hospital records were identified. People who had a long bone fracture recorded in hospital but not by the GP were then reclassified as having a long bone fracture in a separate analysis of the risk of long bone fractures. Statistical analysis was performed using Stata version 12MP (Stata Corp. College Station, TX).

Ethics

Approval was obtained from the CPRD's own independent scientific advisory committee, ISAC. CPRD data are anonymized and further ethics approval was not required.

Results

Table 1 shows participant characteristics. In the analysis of fractures, there were 10,447 eligible people with epilepsy and 42,181 without. In total, there were 231,478 person years of follow-up. The characteristics of those included in the analyses for thermal injuries and poisonings were similar to those included in the analyses for fractures.

Table 2 shows risk of injury in people with epilepsy compared to those without. The highest rate of injuries was for any fractures (16.8 (95% CI 15.8 to 17.9) per 1000 person years in epilepsy vs. 14.4 (95% CI 13.8 to 15.0) per 1000 person years in those without), followed by any poisoning (6.2 (95% CI 5.6 to 6.8) vs. 2.5 (95% CI 2.3 to 2.8) per 1000 person years), and thermal injuries (3.8 (95% CI 3.3 to 4.3) vs. 2.5 (95% CI 2.3 to 2.8) per 1000 person years). After adjusting for age, sex, SHA region, practice-level deprivation and calendar year at study entry, people with epilepsy had a more than doubling of risk of poisoning compared to those without (adjusted HR=2.47 (95% CI 2.15 to 2.84)), a 1.5 fold increase in the risk of thermal injury (adjusted HR=1.49 (95% CI 1.27 to 1.75) and an 18% increase in risk of fracture (adjusted HR=1.18(1.09 to 1.27)). Restricting analyses to long bone fractures had little effect on hazard ratio estimates (adjusted HR=1.23 (95% CI 1.10 to 1.38)). The HR for medicinal poisonings was reduced after further adjusting for behavior disorder (HR=2.54 (95% CI 2.16 to 2.99)) but adjustments for this and for other co-morbidities made little difference to the other HR estimates. Analysing by poisoning agent revealed that the increased risk of poisoning in people with epilepsy reflected medicinal poisonings (HR=2.54 (95% CI 2.16 to 2.99)) rather than poisonings by non-medicinal products (HR=0.96 (95% CI 0.61 to 1.52)).

We explored whether the increased risk of injury in people with epilepsy varied by age and sex. There was some evidence of an interaction with sex for medicinal poisonings (test for

interaction p=0.04), with a greater HR for males compared to females (adjusted HR=3.11 (95% CI 2.41 to 4.01) vs. 2.23 (95% CI 1.81 to 2.74), adjusting for age, SHA region, practice level deprivation, calendar year at study entry and behavior disorder). There was no evidence for an interaction with sex for other injury types. There was strong evidence to suggest the relative risk of poisoning varied by age (test for interaction p<0.001), with the greatest increased risk in the 19 to 24-year-olds (adjusted HR=3.94 (95% CI 2.94 to 5.27)) and least in the 10 to 14-year-olds (adjusted HR=1.52 (95% CI 1.15 to 2.01)), adjusting for age, sex, SHA region, practice level deprivation and calendar year at study entry. After restricting analyses to medicinal poisonings (Figure 1), these age-specific patterns of increased risk persisted (test for interaction p=0.01; adjusted HR for 19-24 year-olds=3.59 (95% CI 2.65 to 4.86); adjusted HR in 10-14-year-olds=1.71 (95% CI 1.23 to 2.37), adjusting for, sex, SHA region, practice level deprivation, calendar year at study entry and behavior disorder). The drug involved in the poisoning incident was only recorded in 5% of medicinal poisonings in people with epilepsy and 5% of those without epilepsy. 2% of all medicinal poisonings in people with epilepsy were due to an AED.

Absolute risks of injury in the five year period following (pseudo)diagnosis in people with and without epilepsy are shown in Table 3. Per thousand people, those with epilepsy experienced an extra 23 poisonings (21 of which were medicinal poisonings), an extra 12 fractures (two of which were long bone fractures) and an extra seven thermal injuries.

Our findings were robust to restricting analyses to people with at least two drug prescriptions and two diagnosis codes for epilepsy, to excluding those prescribed pregabalin or gabapentin as their first anti-epilepsy drug and to excluding 3,554 people with AED prescriptions but no Read code for a diagnosis of epilepsy. Results for people aged 1-21 years were very similar to those for people aged 1-24 years (fractures 1.15 (95% CI 1.06 to 1.25); thermal injuries

1.39 (95% CI 1.18 to 1.65); poisonings 2.26 (95% CI 1.95 to 2.62); long bone fractures 1.20 (95% CI 1.06 to 1.35); medicinal poisonings 2.39 (95% CI 2.01 to 2.84); non-medicinal poisonings 0.89 (95% CI 0.56 to 1.42)). 25,723 people had hospital records linked to their GP record. The risk of long bone fractures for this sub-group was similar to the whole population (adjusted HR=1.25 (95% CI 1.07 to 1.46)).

Discussion

Children and young adults with epilepsy are at greater risk of fractures, thermal injuries and poisonings compared to those without epilepsy. In people with epilepsy fractures are 18% more likely, thermal injuries 50% more likely and poisonings more than twice as likely compared to people without epilepsy, with the increased risk being restricted to medicinal poisonings. Among young adults with epilepsy, aged 19 to 24 years, the risk of medicinal poisoning was four-fold that of the general population of the same age. The absolute risk of injury in the five year period following diagnosis was an additional: 12 fractures (2 long bone); 7 thermal injuries and 23 poisonings (21 medicinal poisonings). Those with epilepsy aged between 19 to 24 years were at the greatest risk of poisonings compared to those without epilepsy.

To our knowledge, this is the first study to explore associations between epilepsy and fractures, thermal injuries and poisonings in children and young adults in the primary care population. As the primary care record contains information on diagnoses made in both secondary and primary care this provides a more complete picture of the risk of fractures, thermal injuries and poisonings than previous studies. Misdiagnosis of epilepsy is unlikely as childhood epilepsy is diagnosed by specialists in secondary care with on-going prescriptions provided in primary care[39 40]. Misclassification of epilepsy could have occurred but our sensitivity analyses using stricter criteria to define epilepsy made little difference to the estimated risks of injuries, suggesting any misclassification is likely to have minimal impact on our findings. Misclassification of the injuries could have occurred if an injury was not coded by the GP or an injury that had not occurred was incorrectly coded as occurring. However, we found similar hazard ratios for all fractures and for long bone fractures, which we expected to have high levels of recording[41]. For a sub-group including long bone fractures recorded in hospital records we found a similar estimated risk. We included both mechanisms

of injury (e.g. accidents caused by fire and flames) and anatomic sites of injury (e.g. burn of lower limbs) to maximise ascertainment of injuries. There is a potential risk of ascertainment bias, whereby people with epilepsy who may have higher GP consultation rates have more opportunities to report injuries than people without epilepsy. Our findings of similar hazard ratios for all fractures and for long bone fractures would suggest this was not occurring to a large degree. We have no reason to suspect that misclassification for poisonings or thermal injuries would be greater than that for fractures and any possible misclassification would tend the hazard ratio towards unity, meaning our estimates were conservative estimates of injury risk. Whilst we adjusted for key confounders, it is possible that some residual confounding remains. We were unable to explore the contribution of anti-epileptic drugs to the increased risk of poisoning because the drug involved was not recorded in most cases of poisoning.

Although any comparison of rates of all injury types in our study with those of previous work are limited, due to the lack of population-based studies in comparable age groups, the rates of fractures in people without epilepsy are broadly comparable to those from previous studies[12-14 42] but lower than those in one CPRD study in all ages which estimated an age- and sex-adjusted incidence rate ratio for fractures among epilepsy patients compared to those without of 1.89 (95% CI 1.81 to 1.98)[27]. The greater fracture risk in that study may be, at least partly, explained by the severity of epilepsy as the study population comprised those with active epilepsy, with drugs or diagnosis codes recorded for more than one year. There are no previous studies reporting the risk of thermal injuries or poisonings in people with epilepsy to those without in the general population, therefore comparison of our findings with previous studies is not possible.

Potential explanations for increased risk of injuries associated with epilepsy include injuries occurring as a result of seizures (e.g. fractures[43 44] and thermal injuries[45-48]). Epilepsy itself

may be associated with pathology of the central nervous system that increases injury risk and in the case of poisonings an increased access to medicines (for unintentional poisoning or for self-harm with any medication[49]) or inadvertent overdosage of AED. We found 19 to 24-year-olds with epilepsy had the highest risk of poisonings, with potential explanations including self-harm or greater risk-taking behavior. Previous work suggests people with epilepsy may have a greater risk of suicide than those without epilepsy[50]. It is therefore possible that some of the observed increased risk of poisoning was intentional as opposed to unintentional poisoning. Although we were unable to explore associations between poisoning with specific drugs and epilepsy, it is possible that easy access to anti-epileptic drugs may be important in this context. Whilst this study does not allow us to explore the reasons why injury risks are increased in people with epilepsy, it allows quantification of risk and highlights that the absolute risk of poisoning is substantially greater than that for fractures or for burns.

Conclusion

All healthcare professionals can use these findings to inform parents, children and young adults diagnosed with epilepsy of their absolute risk of injuries as part of counselling for unintentional injury prevention[51] and to inform existing guidelines on treatment[52]. For fractures and thermal injuries, the increase in absolute risk associated with epilepsy is small. Given the increased risk of poisoning, in particular among young adults, efforts should be made to prevent this injury. For example, information could be provided on the risk of medicinal poisoning and advice about safe storage of all medicines (not just anti-epileptic drugs), not transferring medicines to other containers, supervising children taking medicine and about the dangers of overdosing[53-55]. This information could be provided when prescribing medication and during epilepsy reviews and pharmacists can also provide such

information when dispensing antiepileptic drugs to children and young adults. More research is needed to distinguish intentional from unintentional poisonings, especially in older children and young adults so that the increased risk of poisoning, by intent, can be described in children and young adults with epilepsy. Further research exploring the contribution of anti-epileptic drugs to poisonings in children with epilepsy would also be helpful to enable more specific prevention advice to be provided to parents, children and young adults.

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Table 1 Characteristics of people with epilepsy and those without for analyses of fractures, thermal injuries and poisonings

Study cohort		Fractures		Thermal injuries		Poisonings	
Characteristic		**Non-epilepsy n=42,181**	**Epilepsy n=10,447**	**Non-epilepsy n=46,598**	**Epilepsy n=11,934**	**Non-epilepsy n=46,576**	**Epilepsy n=11,720**
Age group at (pseudo)diagnosis of epilepsy (years) (n, %)	1	1,751 (4.2)	535 (5.1)	1,751 (3.8)	535 (4.5)	1,754 (3.8)	540 (4.6)
	2	1,623 (3.9)	459 (4.4)	1,623 (3.5)	457 (3.8)	1,643 (3.5)	460 (3.9)
	3	1,589 (3.8)	485 (4.6)	1,605 (3.4)	489 (4.1)	1,610 (3.5)	494 (4.2)
	4	1,764 (4.2)	448 (4.3)	1,759 (3.8)	489 (4.1)	1,787 (3.8)	448 (3.8)
	5-9	8,598 (20.4)	2,115 (20.3)	8,950 (19.2)	2,223 (18.6)	9,021 (19.4)	2,247 (19.2)
	10-14	8,983 (21.3)	2,009 (19.2)	10,059 (21.6)	2,284 (19.1)	10,109 (21.7)	2,311 (19.7)
	15-18	6,826 (16.2)	1,792 (17.2)	7,909 (17.0)	2,183 (18.3)	7,889 (16.9)	2,135 (18.2)
	19-24	11,047 (26.2)	2,604 (24.9)	12,942 (27.8)	3,317 (27.8)	12,763 (27.4)	3,085 (26.3)
Sex (n, %)	Males	19,953 (47.3)	5,291 (50.7)	22,598 (48.5)	6,185 (51.8)	22,705 (48.8)	6,152 (52.5)
SHA region (n, %)	East Midlands	2,422 (5.7)	542 (5.2)	2,422 (5.7)	542 (5.2)	5,957 (12.8)	1,523 (13.0)
	East of England	4,457 (10.6)	1,111 (10.6)	4,457 (10.6)	1,111 (10.6)	4,548 (9.8)	1,105 (9.4)
	London	4,288 (10.2)	1,013 (9.7)	4,530 (9.7)	1,119 (9.4)	3,483 (7.5)	976 (8.3)
	North East	1,118 (2.7)	288 (2.8)	1,118 (2.7)	288 (2.8)	3,878 (8.3)	1,005 (8.6)
	North West	5,386 (12.8)	1,341 (12.8)	5,963 (12.8)	1,549 (13.0)	4,190 (9.0)	933 (8.0)
	Northern Ireland	1,219 (2.9)	369 (3.5)	1,219 (2.9)	369 (3.5)	4,569 (9.8)	1,184 (10.1)
	Scotland	3,036 (7.2)	828 (7.9)	3,484 (7.5)	1,003 (8.4)	3,959 (8.5)	994 (8.5)
	South Central	3,586 (8.5)	877 (8.4)	3,586 (8.5)	877 (8.4)	4,893 (10.5)	1,198 (10.2)
	South East Coast	3,542 (8.4)	891 (7.9)	3,875 (8.3)	1,033 (8.7)	3,439 (7.4)	927 (7.9)
	South West	3,792 (9.0)	854 (8.2)	4,196 (9.0)	944 (7.9)	2,371 (5.1)	557 (4.8)
	Wales	3,076 (7.3)	791 (7.6)	3,457 (7.4)	938 (7.9)	2,686 (5.8)	587 (5.0)
	West Midlands	4,138 (9.8)	1,047 (10.0)	4,563 (9.8)	1,198 (10.0)	1,380 (3.0)	417 (3.6)
	Yorkshire & Humber	2,121 (5.0)	495 (4.7)	2,371 (5.1)	556 (4.7)	1,223 (2.6)	314 (2.7)
Deprivation (n, %)	Least deprived	6,674 (15.8)	1,692 (16.2)	7,437 (16.0)	1,945 (16.3)	7,414 (15.9)	1,911 (16.3)
	2nd least deprived	7,443 (17.7)	1,713 (16.4)	8,273 (17.8)	1,966 (16.5)	8,307 (17.8)	1,938 (16.5)
	Medium deprivation	8,160 (19.4)	2,018 (19.3)	8,993 (19.3)	2,290 (19.2)	9,000 (19.3)	2,257 (19.3)
	2nd most deprived	9,307 (22.1)	2,327 (22.3)	10,266 (22.0)	2,632 (22.1)	10,246 (22.0)	2,587 (22.1)
	Most deprived	10,593 (25.1)	2,695 (25.8)	11,624 (25.0)	3,099 (26.0)	11,604 (24.9)	3,025 (25.8)
Calendar year at study entry	1987-1989	230 (0.6)	44 (0.4)	237 (0.5)	47 (0.4)	237 (0.5)	47 (0.4)
	1990-1994	4,804 (11.4)	1,122 (10.7)	5,048 (10.8)	1,217 (10.2)	5,042 (10.8)	1,211 (10.3)
	1995-1999	7,228 (17.1)	1,925 (18.4)	7,786 (16.7)	2,112 (17.7)	7,806 (16.8)	2,097 (17.9)
	2000-2004	12,271 (29.1)	3,382 (32.4)	13,455 (28.9)	3,850 (32.3)	13,487 (29.0)	3,786 (32.3)
	2005 onwards	17,648 (41.8)	3,974 (38.0)	20,072 (43.1)	4,708 (38.5)	20,004 (43.0)	4,579 (39.1)
Behavior disorder		1,550 (3.7)	1,303 (12.5)	1,817 (3.9)	1,507 (12.6)	1,770 (3.8)	1,443 (12.3)
Learning disability		318 (0.8)	961 (9.2)	372 (0.8)	1,038 (8.7)	368 (0.8)	1,029 (8.8)
ADHD		374 (0.9)	363 (3.5)	426 (0.9)	426 (3.6)	428 (0.9)	421 (3.6)
Cerebral palsy		13 (<0.1)	29 (0.3)	14 (<0.1)	31 (0.3)	14 (<0.1)	30 (0.3)

Note: Each study population comprises those without a history of the injury of interest

Note: Deprivation is at practice level

Table 2 Risk of fractures, thermal injuries and poisonings in children & young adults with epilepsy compared to those without

Injury category	Epilepsy or non-epilepsy	Events (n)	pyar	Rate (per 1000)	(95% CI)	HR	(95% CI)	Adjusted HR[a]	(95% CI)
Any fractures	Non-epilepsy	2066	143,336	14.4	(13.8 -15.0)	1		1	
	Epilepsy	948	56,310	16.8	(15.8 -17.9)	1.15	(1.07 -1.24)	1.18	(1.09 -1.27)
Thermal injuries	Non-epilepsy	415	164,247	2.5	(2.3 -2.8)	1		1	
	Epilepsy	253	67,231	3.8	(3.3 -4.3)	1.51	(1.29 -1.77)	1.49	(1.27 -1.75)
Any poisonings	Non-epilepsy	417	165,376	2.5	(2.3 -2.8)	1		1	
	Epilepsy	408	66,021	6.2	(5.6 -6.8)	2.57	(2.24 -2.95)	2.47	(2.15 -2.84)
Injury sub-groups:									
Long bone fractures	Non-epilepsy	931	155,637	6.0	(5.6 -6.4)	1		1	
	Epilepsy	438	63,454	6.9	(6.3 -7.6)	1.17	(1.04 -1.31)	1.23	(1.10 -1.38)
Medicinal poisonings	Non-epilepsy	293	164,946	1.8	(1.6 -2.0)	1		1	
	Epilepsy	341	65,786	5.2	(4.7 -5.8)	3.06	(2.62 -3.59)	2.54 [b]	(2.16 -2.99)
Non-medicinal poisonings	Non-epilepsy	72	164,121	0.4	(1.9 -0.6)	1		1	
	Epilepsy	26	64,760	0.4	(1.9 -0.6)	0.92	(0.59 -1.45)	0.96	(0.61 -1.52)

pyar: Person years at risk (in years)

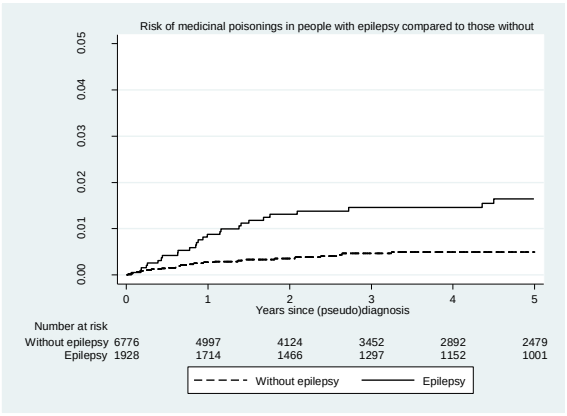
HR: Hazard ratio

[a]All HRs were adjusted for for age, sex, SHA region, deprivation and calendar year at study entry except [b]

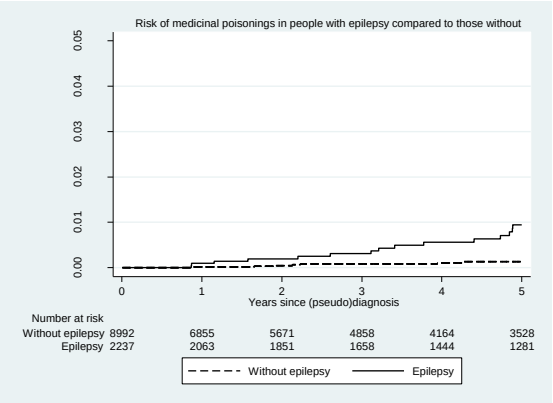
[b]HR additionally djusted for behaviour disorder

Figure 1 Graphs to show risk of medicinal poisonings in people with epilepsy compared to those without by age at (pseudo)diagnosis. Graphs show the proportion who have a medicinal poisoning by time since (pseudo)diagnosis. Frequencies of people in study by year since (pseudo)diagnosis are shown for people with epilepsy and those without.

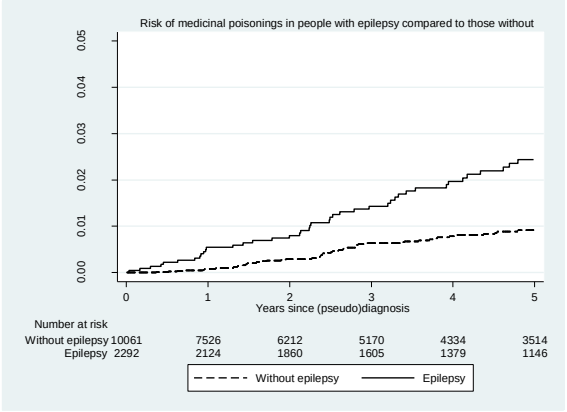
A. Age 1 to 4 years



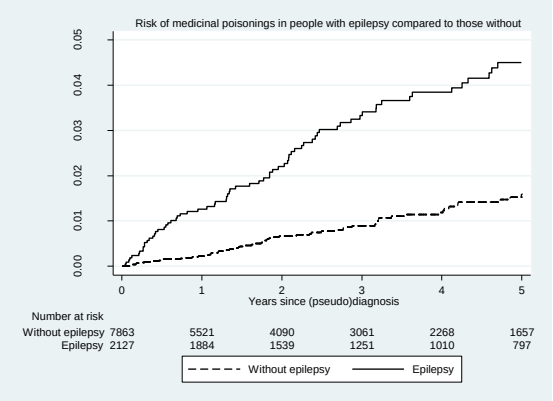
B. Age 5 to 9 years



C. Age 10 to 14 years



D. Age 15 to 18 years



E. Age 19 to 24 years

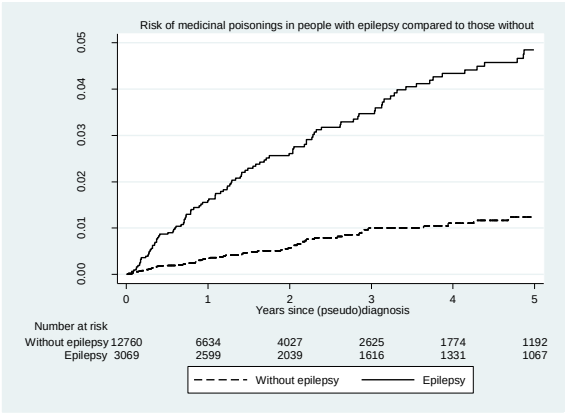


Table 3 Absolute risks of injury in the five year period following (pseudo)diagnosis in people with epilepsy and without epilepsy

	Non-epilepsy			Epilepsy			
Time since diagnosis	**Total at risk (n)**	**Events (n)**	**Injuries per thousand (95% CI)**	**Total at risk (n)**	**Events (n)**	**Injuries per thousand (95% CI)**	**Excess injuries per thousand (95% CI)**
Any fractures							
Up to 5 years	10,605	976	69.5 (65.7 -73.4)	4,520	427	81.1 (74.6 -88.1)	11.6 (8.9 -14.7)
Thermal injuries							
Up to 5 years	12,303	189	12.3 (10.9 -13.9)	5,416	115	19.2 (16.5 -22.4)	6.9 (5.6 -8.5)
Any poisonings							
Up to 5 years	12,411	194	11.9 (10.6 -13.5)	5,310	186	34.7 (30.9 -38.9)	22.8 (20.3 -25.4)
Injury sub-groups:							
Long bone fracture							
Up to 5 years	11,592	479	31.5 (1.3 -34.1)	5,099	200	33.9 (2.1 -38.3)	2.4 (0.8 -4.2)
Medicinal poisonings							
Up to 5 years	12,377	136	8.2 (7.1 -9.5)	5,293	157	29.3 (25.8 -33.2)	21.1 (18.7 -23.7)
Non-medicinal poisonings							
Up to 5 years	12,312	34	2.1 (1.6 -2.9)	5,220	10	2.0 (1.2 -3.2)	-0.1 (-0.4 -0.3)