Edinburgh Research Explorer

A nationwide, retrospective, data-linkage, cohort study of epilepsy and incident dementia

Citation for published version:

Digital Object Identifier (DOI):
10.1212/WNL.0000000000010358

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Neurology

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and/or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Title: A nation-wide retrospective, data-linkage, cohort study of epilepsy and incident dementia

Authors:

Christian Schnier\(^1\) (PhD)
Susan Duncan\(^2,3\) (MD)
Tim Wilkinson\(^2,4\) (MRCP)
Gashirai K Mbizvo\(^3\) (MBChB (Hons) MRes (Dis) MRCP)
Richard F. M. Chin\(^3,5\) (PhD)

\(^1\) The University of Edinburgh, Usher Institute of Population Health Sciences and Informatics, Edinburgh, UK

\(^2\) Western General Hospital, Department of Clinical Neurosciences, Edinburgh, UK

\(^3\) Muir Maxwell Epilepsy Centre, Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, UK

\(^4\) Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, UK

\(^5\) Royal Hospital for Sick Children, Edinburgh, UK
Corresponding author:

Christian Schnier, Usher Institute, University of Edinburgh; NINE Edinburgh BioQuarter, 9 Little France Road, Edinburgh EH16 4UX;
christian.schnier@ed.ac.uk

Study funding:

RS McDonald Trust

Search terms/Key words:


Disclosures:

SD has received speaker fees from UCB Pharma. RFMC has provided paid consultation and received speaker fees from Eisai. The remaining authors report no disclosures.

Counts:

Abstract: 246

Main body: 3523

Title: 89 characters with spaces

References: 23

Tables: 3

Figures: 4
Abstract

Objective: To determine the association of epilepsy with incident dementia we conducted a nation-wide retrospective data-linkage, cohort study, to examine whether the association varies according to dementia subtypes and investigate whether risk factors modify the association.

Methods: We used linked health data from hospitalisation, mortality records and primary care consultations to follow-up 563,151 Welsh residents from their 60\textsuperscript{th} birthday to estimate dementia rate and associated risk factors. Dementia, epilepsy and covariates (medication, smoking, comorbidities) were classified using previously validated code lists. We studied rate of dementia and dementia subtypes in people with epilepsy (PWE) and without using (stratified) Kaplan-Meier plots and flexible parametric survival models.

Results: PWE had a 2.5 (95\% CI 2.3 to 2.6) times higher hazard of incident dementia, a 1.6 (95\% CI 1.4 to 1.8) times higher hazard of incident Alzheimers disease (AD), and a 3.1 (95\% CI 2.8 to 3.4) times higher hazard of incident Vascular dementia (VaD). The increased incidence in PWE was modified by a history of stroke. PWE who were first diagnosed at age 25 years or younger had a similar dementia rate compared to those diagnosed later in life. PWE who had ever been prescribed sodium valproate compared those who had not, were at higher risk of dementia (HR: 1.6; 99\% CI: 1.4 to 1.9) and VaD (HR: 1.7; 99\% CI: 1.4 to 2.1), but not AD (HR: 1.2; 99\% CI: 0.9 to 1.5).
**Conclusion:** People with epilepsy, compared to those without epilepsy, have an increased dementia risk.

**INTRODUCTION**

With increasing longevity comes the risk of developing dementia after age sixty years. By 2035, an estimated 10.5 million people will be living with dementia in Europe and 22.7 million in Asia [1]. Dementia may be classified according to presumed aetiology with Alzheimer’s Disease (AD) and Vascular Dementia (VaD) being the most common subtypes. Given lack of successful disease-modifying treatments for dementia, identification of potentially modifiable risk factors is paramount.

The risk of developing dementia increases with increasing age and is associated with genetic variants, several environmental risk factors and other diseases, including epilepsy [2]. However, the relationship between dementia and epilepsy is likely to be complex, because epilepsy is a risk factor for dementia while having dementia is a risk factor for developing epilepsy.

Although there are numerous studies examining the association between established or recently diagnosed dementia and subsequent development of epilepsy, few have investigated risk of dementia in people with epilepsy (PWE)
There is concern that drugs used to treat epilepsy may increase the incidence of dementia, and not the epilepsy \textit{per se} [7].

The aims of the current study were to compare the hazard of dementia overall, of AD and VaD between PWE:

1. and people without epilepsy; adjusting for potential socio-demographic and clinical confounding/effect modifying factors.

2. with an epilepsy diagnosis at age 25 years or younger versus PWE diagnosed older

3. exposed to specific AEDs and PWE not exposed

\textbf{METHODS}

We report this study in accordance with the Standards of Reporting of Neurological Disorders (STROND).

This is a retrospective cohort study using the Secure Anonymised Information Linkage (SAIL) Databank [8]. SAIL provides linked health care-related information for 4-5 million (alive and deceased) residents of Wales. It contains coded information from general practice (GP) consultations (including prescriptions) linked to hospital admissions and death registrations data sets, for approximately 80\% of the Welsh population. Primary care data in SAIL are coded using the Read
version 2 system, with hospital admissions and death registrations data coded using the International Classification of Diseases 10 (ICD-10) system. SAIL has been used for a number of epilepsy studies [9–11]. It holds information on a dementia e-cohort (SAILDeC) recently created by two of the authors (TW and CS) to allow dementia researchers easy access to linked health data in a described cohort [12] and this dementia e-cohort was used in the current study.

Study population, inclusion and exclusion criteria

563,151 residents of Wales, UK, were followed up passively from their 60th birthday to dementia diagnosis, death or the end of follow-up on June 2018. Median year at the start of follow-up (60th birthday) was 2006 (IQR: 2001 to 2011). People were included if, at the time of their 60th birthday, they had been registered with a Welsh GP practice that had signed up to SAIL. Residents were excluded if they have had a dementia related health record prior to their 60th birthday.

To study the effect of age at epilepsy diagnosis and exposure to AEDs on dementia risk we excluded people without epilepsy. Finally, to study the effect of exposure to AEDs on the risk of dementia, we only included PWE with at least one code in the primary care data for a prescription for an AED.

Dementia was classified using dementia-related diagnostic codes in the routinely collected, coded, electronic health records (codes used to identify and classify
dementia subtypes are available from the Edinburgh University Data Share point https://datashare.is.ed.ac.uk/handle/10283/3574). Application of combinations of those codes in a recent UK validation study has shown positive predictive values (PPVs) of 83%, 71% and 44% for dementia, AD and VaD respectively[13].

Where records/codes allowed, dementia was further subclassified into AD and VaD; because of low numbers, dementia with Lewy bodies, mixed dementia and frontotemporal dementia were not analysed as separate subclasses. Because the diagnosis of AD and VaD is often preceded by an unspecific dementia diagnosis we used the date of first dementia related record as the time of diagnosis for all analysis. People diagnosed with AD are at very low risk to be subsequently diagnosed with VaD, so when we compared the risk of AD in those with and without epilepsy, we used the actual diagnosis of AD as outcome and excluded people from the study population who had dementia without subtype information or with a diagnosis of VaD. Similarly, when we compared the risk of VaD we excluded people without dementia sub-type information or with a diagnosis of AD.

**Exposures**

People with at least one diagnostic ICD-10 and Read codes for epilepsy were classified as PWE, with the date of first record taken as the date of diagnosis (codes used to identify epilepsy diagnoses are available from the Edinburgh University Data Share point https://datashare.is.ed.ac.uk/handle/10283/3574).
These validated codes have a sensitivity of 86% (95%CI 8-91%) and a specificity of 97% (95%CI 92–99%) [9]. PWE were defined as “exposed” if they had any epilepsy-related diagnosis at any time before or during follow-up. Because follow-up ended with the first dementia-related diagnosis, people who had an epilepsy-related diagnosis after their first dementia diagnosis were considered as non-exposed (epilepsy-free) in our analyses. To address the issue of potential reverse causality, we took into consideration the uncertainty about the length of pre-clinical phase in dementia and that epilepsy may be an early sign of dementia. We carried out an additional, sensitivity, analysis excluding 120 epilepsy cases that were diagnosed less than 1 year prior to incident coded dementia diagnosis.

Linked EHR were used to classify exposure to cardio-metabolic risk factors (smoking status, hypertension and alcohol misuse), stroke, diabetes, head injuries and bipolar disorder (see https://datashare.is.ed.ac.uk/handle/10283/3268 for a list of codes). Smoking history was classified using Read codes related to tobacco exposure; individuals where no information on smoking status was available were classified as non-smokers. We applied a similar approach for the other potential modifiers; if we found indications for them (e.g. code for stroke) then they were classified positive but if we don’t find them, they were classified as negative. In addition, administrative data were used to classify sex, age and socio-economic status (2012 Welsh Index of multiple deprivation, WIMD). WIMD was classified as
deprivation quintile at the 60th birthday (start of follow up). Finally, records from primary care consultations were used to classify exposure to AEDs (see table 1 for a code list which was obtained from NHS digital (https://isd.digital.nhs.uk/trud3/user/guest/group/0/pack/9)). For statistical reasons, we only analysed the effect of AEDs with more than 100 exposed PWE in the study population. People with at least two records of an AED spaced at least 30 days from each other were defined as exposed, independent of dose or the period of exposure. Exposure to any of the AED was compared to non-exposure to that specific drug (exposure to at least one of the other AEDs).

Statistics
The risk of incident dementia diagnosis was analysed using parametric survival analysis in R (packages survreg and flexsurv). Exposure to epilepsy or any of the covariates, including exposure to AEDs, was analysed as time independent, e.g., exposed people were classified ‘exposed’ independent of year or age at exposure. We tested different parametrizations (Weibull, exponential, Gaussian, logistic, lognormal and loglogistic) and selected the best fitting model (based on Akaike information criterion). While the survival model based on the Weibull distribution had the best fit, visual comparison of the predicted risk with a Kaplan-Meier plot showed decreasing fit with increasing age. Therefore, we used a Royston-Parmar flexible parametric survival model for analysis [14]. All statistical models were adjusting for the effect of sex, while starting follow up for
each person at their 60th birthday controlled for the effect of age. Since some of the variables were highly correlated, and some may be along the causal pathway, to study whether the effect of epilepsy on dementia incidence was associated with exposure to individual cardio-metabolic risk factors (smoking status, hypertension and alcohol misuse), stroke, diabetes, head injuries, bipolar disorder or deprivation on their own, we compared estimated HRs for the effect of epilepsy in survival models that control for exposure to any of the variables singly with estimated HRs from models without control.

The flexible parametric survival model was also used to study the effect of young onset epilepsy and exposure to an AED compared to any other AED on the risk of dementia in PWE. Because initial results from the modelling were suggestive of an association between sodium valproate exposure and stroke and because we expected an association between sodium valproate exposure and bipolar disorder in people with epilepsy, we additionally compared two models of the effect of sodium valproate exposure on the hazard of dementia, AD and VaD with and without controlling for having a diagnosis of stroke and of bipolar disorder.

We provide estimates along with either 95% confidence intervals (95%CIs) or to consider multiple comparisons, 99%CIs.
Ethics
This study has been approved by SAIL’s Information Governance Review Panel (IGRP 0837: Association between medications and risk of dementia).

Data availability
All anonymised linked health records, including the dementia e-cohort used in this study are available through SAIL.

RESULTS
Fifty percent of the study population were male. Information on deprivation was available for 540250 (96%) with 97,853 from the most affluent areas (WIMD 1) and 123,456 from areas with worst deprivation (WIMD 5); 373,125 had indications of ever-smoking, 36,743 of a stroke and 28,153 of a head injury before or during follow-up. Total follow up time was 5,944,283 person-years with median follow-up time of 10 years. 97,622 people died during follow up with median age of death at 69 years.

Sixteen thousand and seven hundred (16,700) of the cohort had dementia, of which 6,916 were classified as having AD and 5005 having VaD. 1060 had codes for both AD and VaD, and 5839 had unspecified dementia and could not be subtyped. Median age at diagnosis of dementia in people without epilepsy was 73 years, and 74 years each for AD and VaD (Figure 1).
There were 19,150 (3.4%) PWE with a bimodal distribution of age at diagnosis (Figure 2). 3274 had an epilepsy diagnosis on or before their 25th birthday, and 12,331 at age 26 years or older but before their 60th birthday. Fifty percent of PWE died within 19 years of their 60th birthday compared to those without epilepsy of whom 50 percent had died within 24 years of their 60th birthday. 12,797 PWE (67%) had exposure to at least one AED, the majority to sodium valproate, carbamazepine and gabapentin (Table 1). A substantial proportion of the cohort had ever had an AED prescription although they did not have a recorded epilepsy diagnosis; most of this was prescription for gabapentin and pregabalin that are often prescribed for other indications such as chronic pain. Others with an AED prescription, such as phenytoin and levetiracetam that are fairly specific drugs for epilepsy, but without concurrent epilepsy diagnosis codes might have been diagnosed prior to the start of EHR data collection and would therefore be misclassified as not having epilepsy. If this were the case, we would not expect substantial bias due to the high sensitivity and specificity of epilepsy diagnostic codes in SAIL.

Compared to people without epilepsy, PWE had a 2.5 (95% CI 2.3 to 2.6) times higher hazard of incident dementia, a 1.6 (95% CI 1.4 to 1.8) times higher incidence of AD, and a 3.1 (95% CI 2.8 to 3.4) times higher hazard of incident VaD (Table 2 and Figure 3). Within 21, 26 and 25 years of follow-up from their 60th birthday, 20% of PWE are predicted to have had a diagnosis of any dementia, AD and VaD. Within 25 and 31 years the hazard increases to 40% for
any dementia and VaD, respectively; for AD, within 31 years the hazard was 31%. When 120 PWE who were diagnosed with epilepsy less than a year prior to dementia diagnosis were excluded from analysis, the HR for dementia, AD and VaD were slightly reduced to 2.3 (95% CI 2.1 to 2.4), 1.5 (95% CI 1.3 to 1.7) and 2.7 (95% CI 2.5 to 3.0). Table 2 shows that the increased HR of incident dementia in PWE (HR: 2.5) did not change substantially when we controlled individually for the effect of smoking, hypertension, social deprivation, alcohol, diabetes, head injury or depression. However, controlling for stroke did reduce the estimated HR for dementia from 2.5 to 2.0 (95% CI 1.9 to 2.1) and for VaD from 3.1 to 2.0 (95% CI 1.8 to 2.3).

The hazard for dementia, AD or VaD was not different in people diagnosed with epilepsy at age 25 years or younger versus those diagnosed with epilepsy at an older age (Figure 3).

Amongst AEDs investigated, only exposure to sodium valproate and lamotrigine showed statistically significant increased hazard ratios for dementia or AD or VaD (Table 3). For PWE having ever been prescribed sodium valproate compared to any other AED was associated with higher hazards for dementia, and VaD but not for AD. Within 17 years of follow-up from their 60th birthday, 20% of PWE ever-exposed to sodium valproate are predicted to have had a diagnosis of any dementia; within 23 years the hazard increases to 40% (Figure
4). Exposure to lamotrigine compared to any other AED was associated with a higher hazard ratio for AD only, but not for dementia or VaD (Table 3).

The addition of an indicator for stroke or bipolar disorder to the flexible parametric survival model predicting the effect of VPA exposure on the hazard of dementia did not substantially change the estimated HR for dementia, AD or VaD (Table 3).

DISCUSSION

The main findings of this study are: (1) PWE had a 2.5 (95%CI 2.3 to 2.6) times higher hazard of incident dementia, a 1.6 (95% CI 1.4 to 1.8) times higher hazard of incident AD and a 3.1 (95%CI 2.8 to 3.4) times higher hazard of incident VaD compared to people without epilepsy - some of this increased risk in incident dementia and VaD can seemingly be explained partly, but not wholly, by PWE having a higher risk of stroke which in turn was associated with an increased risk of VaD; (2) the incidence of dementia in PWE was not associated with age at diagnosis of epilepsy; (3) PWE ever exposed to sodium valproate compared to any other AED had a higher incidence of dementia. However, ultimately, findings from analyses such as these from routine administrative health data that were not collected originally for research, are hypothesis generating and help inform future work. The current study cannot be used to establish a cause–effect relationship
due to the intrinsic study design and source of data. Further, prospective studies are required to establish temporality.

Cognitive impairment, mood and behavioural disturbance, all of which are features of dementia, have long been reported in PWE. There are data that suggest that such disturbances are worse with increased seizure burden which may be due to long duration of epilepsy, higher seizure frequency, higher seizure severity. We were unable to determine details of epilepsy characteristics including aetiology, severity and seizure frequency, so it is possible that there may have been some patients with frequent or even subclinical seizures or an epileptic encephalopathy whose condition mimicked dementia [15] and our results need to be considered in that light. If seizure burden does at least partially contribute to cognitive impairment, improvement in epilepsy management may decrease dementia risk which is supported by recent work showing subclinical epileptic discharges in the hippocampus in people with dementia and improvement in cognition when treated with an AED lamotrigine. The potential adverse cognitive effects of AEDs and their associated usage with dementia has been described [16], and it is possible that our finding is partly attributable to exposure to AEDs. On the other hand, cognitive impairment has also been observed in newly diagnosed patients with epilepsy before the inception of AEDs [17] and has been found in first degree relatives of patients with idiopathic generalised epilepsy. This would suggest the presence of an endophenotype for some epilepsy syndromes and points to an underlying
process independent of AEDs that leads to the parallel development of seizures and cognitive impairment [18].

We investigated potential socio-demographic and clinical confounding/effect modifying factors but aside from a diagnosis of stroke, increased risk of incident dementia in PWE persisted. The fact that risk of VaD but not AD was attenuated with a diagnosis of stroke, may be related to challenges with classification of dementia in a clinical setting. Patients with a history of stroke might be more likely to be diagnosed as having VaD in routine clinical practice, even if some concurrent AD pathology is present in reality.

We were surprised to observe there was no difference of risk for incident dementia according to age of initial epilepsy diagnosis because we hypothesised that longer duration of epilepsy may increase risk. However, we were unable to adjust for other epilepsy characteristics such as seizure frequency and aetiology which may also affect risk and could be correlated with epilepsy duration. In addition, while we did observe the expected bimodal distribution of age at epilepsy diagnosis (Figure 2), an unknown, presumed small proportion of PWE will have been misclassified as late-onset epilepsy because data going back long enough to show they were really diagnosed in early life were not available.
The reasons for taking or not taking antiepileptic treatment and the choice of treatment may be related to variables that influence the risk of dementia such as age, gender and education level. We had no data on indication for choice, duration of length of exposure, nor dosage of any of the AEDs examined in the current study so indication bias cannot be ruled out. It would not be unreasonable to consider the findings of increased risk of dementia associated with antiepileptic treatment as questionable. For many years sodium valproate’s broad spectrum of anti-epileptic effects made it a popular first line AED [19]. It is only in the last decade that serious reservations about its use in certain populations have been expressed. It was, however, used as a drug of choice for the elderly for many years [19]. One often unnoticed side effect is the development of an encephalopathy which in the older age group might be mistaken for dementia [20, 21]. Given the sodium valproate was often used in post-stroke seizures it is conceivable some patients in the current study might have been misdiagnosed as VaD when in fact they had a reversible drug side effect. However, there is some available information that provide some potential biological plausibility to our cautious finding of valproate exposure and increased dementia risk. Sodium valproate has a number of unwanted effects that may predispose to cerebrovascular disease in later life. Changes in lipid profiles, insulin resistance and the development of the metabolic syndrome have been reported in children and adults exposed to the drug [22]. Thus, further studies are needed to examine our observed association.
Strengths and Weaknesses

The strengths of this study lie in the unique large scale, population-based, longitudinal linked data that covers 80% of the Welsh population in SAIL which allowed us to apply a cohort design and to estimate absolute hazards. However, follow-up data from GP practices in SAIL started from 2000 to present; from 1991 to present for hospital admission data and from 1995 to present for death registrations. The extent to which GP data are retrospectively coded from paper records of early years of life into electronic health record varies from GP practice to GP practice. Since our study population is restricted to those followed up from their 60th birthday, and given the above, it is uncertain what percentage of study subjects were covered throughout their life resulting in some possible exposure bias. Misclassification bias may exist from the case definition for epilepsy despite the high sensitivity and specificity of diagnoses in SAIL. This bias is expected to be nondifferential, thus minimising the magnitude of the overall estimate.

Misclassification of dementia and subtypes is also possible, and indeed likely given the challenges of classifying dementia subtypes [13, 23]. Compared to people without a stroke, people with a history of stroke might be more likely to be classified as having VaD. We speculate this may be an explanation why controlling for stroke was having an effect on the association of epilepsy with
incident dementia (especially VaD), while controlling for other cardio-vascular risk factors had less effect. The likelihood of misclassification of dementia and its subtypes along with the moderate effect size of hazard ratios could cast doubt on the observation of valproate and an increased risk of VaD but should be of less concern regarding the association with dementia of any cause.

While the model approach allowed for control of several confounders, there were several that we were unable to account for as described earlier. In addition, we were unable to control for educational level, socioeconomic status, or genetic risk.

CONCLUSION

Our study shows that PWE appear to sustain a parallel but more rapid age-related increase in dementia risk, compared to those without epilepsy. Whether this confirms the cascadic theory of loss of cognitive power in epilepsy and or reflects some other aspect, such as specific treatment exposure, requires further research.
Funding & competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no competing interests. This project received funding from the Muir Maxwell Epilepsy Centre.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination declaration

Results from this study have been presented at the Society for Social Medicine & Population Health and International Epidemiology Association European Congress Joint Annual Scientific Meeting in Cork (Ireland). Upon acceptance of the manuscript, we will liaise with epilepsy and dementia charities through Edinburgh University and NHS press offices to develop and implement support strategies/helplines for people who may require help/are concerned. All projects supported by the Muir Maxwell Epilepsy Centre are presented through the Centre’s website.
**Public involvement**

This study has been funded through a grant from the RS McDonald Trust and is presented through the Centre’s website. A co-author of this study (SD) is currently Vice Chair of Epilepsy Scotland and coordinates dissemination of results to the public through the charity.
**Appendix 1 – Author Contributions:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Role</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christian Schnier, PhD</td>
<td>The University of Edinburgh</td>
<td>Author</td>
<td>Study design, funding, data analysis, data acquisition, drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>Susan Duncan, MD</td>
<td>The University of Edinburgh</td>
<td>Author</td>
<td>Conceptualised study interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Tim Wilkinson, MD</td>
<td>The University of Edinburgh</td>
<td>Author</td>
<td>Interpreted the data; revised the manuscript for intellectual content, data acquisition</td>
</tr>
<tr>
<td>Gashirai Mbizvo, MD</td>
<td>The University of Edinburgh</td>
<td>Author</td>
<td>Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Richard Chin, PhD</td>
<td>The University of Edinburgh</td>
<td>Author</td>
<td>Design and conceptualised study interpreted the data; revised the manuscript for intellectual content, data acquisition.</td>
</tr>
</tbody>
</table>
References


22. Richens A, Davidson DL, Cartlidge NE, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset

Table 1: Number of people exposed to an anti-epileptic drug, total and of those with an epilepsy-related electronic health record.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number exposed</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>PWE</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>9,148</td>
<td>3,660</td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>3,271</td>
<td>590</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>832</td>
<td>792</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>3,112</td>
<td>2,604</td>
<td></td>
</tr>
<tr>
<td>(sodium)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>1042</td>
<td>410</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>6,555</td>
<td>4,162</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2,535</td>
<td>1,866</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>34,925</td>
<td>3,199</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>973</td>
<td>357</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>2,590</td>
<td>1,977</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>16,258</td>
<td>1,604</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>882</td>
<td>694</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Predicted HR of the effect of epilepsy on dementia incidence adjusting for a selection of individual covariates. Each row represents the adjustment for the named covariate alone.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Dementia HR (95% CI)</th>
<th>Alzheimers HR (95% CI)</th>
<th>VaD HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.5 (2.3 to 2.6)</td>
<td>1.6 (1.4 to 1.8)</td>
<td>3.1 (2.8 to 3.4)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.4 (2.3 to 2.6)</td>
<td>1.6 (1.4 to 1.8)</td>
<td>3.0 (2.7 to 3.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.0 (1.9 to 2.1)</td>
<td>1.5 (1.3 to 1.7)</td>
<td>2.0 (1.8 to 2.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.4 (2.3 to 2.6)</td>
<td>1.6 (1.4 to 1.8)</td>
<td>3.0 (2.7 to 3.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.4 (2.3 to 2.6)</td>
<td>1.6 (1.5 to 1.8)</td>
<td>3.0 (2.7 to 3.3)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2.3 (2.2 to 2.5)</td>
<td>1.6 (1.4 to 1.8)</td>
<td>2.9 (2.6 to 3.2)</td>
</tr>
<tr>
<td>Head injuries</td>
<td>2.3 (2.2 to 2.5)</td>
<td>1.5 (1.4 to 1.7)</td>
<td>2.8 (2.6 to 3.1)</td>
</tr>
<tr>
<td>High Deprivation</td>
<td>2.4 (2.3 to 2.6)</td>
<td>1.6 (1.4 to 1.8)</td>
<td>3.0 (2.7 to 3.3)</td>
</tr>
</tbody>
</table>
Table 3: Adjusted hazard ratio of the effect of exposure to anti-epileptic drugs on dementia, Alzheimer’s disease and vascular dementia. Adjusted Hazard ratios compare the dementia hazard in people with epilepsy exposed to a specific drug with the dementia hazard in those not exposed to that specific drug (any other drug).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dementia</th>
<th>Alzheimers</th>
<th>VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (99% CI)$^{1,2}$</td>
<td>HR (99% CI)$^{1,2}$</td>
<td>HR (99% CI)$^{1,2}$</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>1.1 (0.9 to 1.3)</td>
<td>1.2 (0.9 to 1.8)</td>
<td>1.0 (0.8 to 1.4)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1.1 (0.7 to 1.5)</td>
<td>0.9 (0.4 to 2.0)</td>
<td>1.0 (0.6 to 1.9)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.8 (0.6 to 1.2)</td>
<td>0.7 (0.3 to 1.5)</td>
<td>0.7 (0.4 to 1.3)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1.0 (0.9 to 1.3)</td>
<td>1.2 (0.8 to 1.7)</td>
<td>1.0 (0.7 to 1.4)</td>
</tr>
<tr>
<td>Primidone</td>
<td>1.1 (0.7 to 1.7)</td>
<td>1.5 (0.7 to 3.3)</td>
<td>1.5 (0.8 to 2.8)</td>
</tr>
<tr>
<td>Valproate</td>
<td>1.6 (1.4 to 1.9)</td>
<td>1.2 (0.8 to 1.6)</td>
<td>1.7 (1.3 to 2.3)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.1 (0.9 to 1.4)</td>
<td>1.5 (1.0 to 2.3)</td>
<td>1.0 (0.7 to 1.5)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>0.6 (0.5 to 0.8)</td>
<td>0.6 (0.4 to 0.9)</td>
<td>0.7 (0.5 to 1.0)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>1.2 (0.7 to 2.0)</td>
<td>0.4 (0.1 to 2.7)</td>
<td>1.0 (0.4 to 2.6)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1.0 (0.8 to 1.2)</td>
<td>0.7 (0.4 to 1.2)</td>
<td>0.8 (0.6 to 1.2)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>0.7 (0.5 to 0.9)</td>
<td>0.8 (0.5 to 1.4)</td>
<td>0.7 (0.4 to 1.1)</td>
</tr>
<tr>
<td>Valproate$^3$</td>
<td>1.5 (1.3 to 1.8)</td>
<td>1.3 (0.8 to 1.6)</td>
<td>1.4 (1.1 to 1.9)</td>
</tr>
<tr>
<td>Valproate$^4$</td>
<td>1.6 (1.4 to 1.9)</td>
<td>1.1 (0.8 to 1.6)</td>
<td>1.7 (1.3 to 2.3)</td>
</tr>
</tbody>
</table>
1 All estimates adjusted for sex.
2 To compensate for multiple testing, 99%CI's provided
3 Adjusted for sex and stroke.
4 Adjusted for sex and Bipolar Disorder.
Figure 1: Predicted hazard of dementia, Alzheimer’s disease and Vascular dementia for people with and without epilepsy, free of dementia at age 60.

Figure 2: Age at first epilepsy-related electronic health record by sex.

Figure 3: Predicted hazard of dementia, Alzheimer’s disease and Vascular dementia for people free of dementia at age 60, by age at first epilepsy-related EHR.

Figure 4: Predicted hazard of dementia for people free of dementia at age 60, by ever-exposure to different anti-epileptic drugs.