PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Epilepsy and mortality: a retrospective cohort analysis with a nested case-control study identifying causes and risk factors from primary care and linkage-derived data
AUTHORS	Wojewodka, Gabriella; Gulliford, Martin; Ashworth, Mark; Richardson, Mark; Ridsdale, Leone

VERSION 1 – REVIEW

REVIEWER	La Vecchia, Carlo IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”
REVIEW RETURNED	05-May-2021

GENERAL COMMENTS	The manuscript considers mortality and causes of death in a cohort of people with epilepsy. it is unclear to me why a case-control rather than a simple cohort design was used, apart from possibly some software simplification. More important, data are available at least to age 64, while the focus is now on 35 or less. A standard presentation with SMRs (or ORs) at all ages, and then at age under 35 would be informative.

REVIEWER	Cursio, John The University of Chicago, Public Health Sciences
REVIEW RETURNED	10-May-2021

GENERAL COMMENTS	Thank you for this important research that looks at an important clinical population. My main comments are as follows: 1) Setting missing values to "no" can be problematic and can cause biased estimates. I suggest a multiple imputation approach outlined in the following document:http://bstt513.class.uic.edu/Addict2007.pdf. Please consider this approach. 2) The authors mention that age has different impacts on the risk of death for people with epilepsy. Did they consider using categories for age instead of a continuous measure? One approach may classify adults as less than 65, versus 65 or more another can use bins of 10 year widths as appropriate. 3) Were any interactions tested in the final models? Some disease factors may have different impacts depending on age.

REVIEWER	Chin, Richard University of Edinburgh Centre for Clinical Brain Sciences, Muir Maxwell Epilepsy Centre,
REVIEW RETURNED	28-May-2021

GENERAL COMMENTS	This study by Wojewodka is a welcome addition to the field. I have a few comments that I would ask the authors to consider. - The ILAE guidelines for epidemiological studies on epilepsy highlights the importance of validation of epilepsy diagnoses. Epilepsy was defined in the paper as “having a documented epilepsy diagnostic code and at least two prescriptions of antiepileptic drugs (AEDs)”. Further detail on these are needed – what codes were used and the bases for their usage? How the definition related to validation of epilepsy diagnosis would strengthen the paper. Someone who had a symptomatic seizure and had two prescriptions for an emergency medication only eg diazepam/midazolam – would that person be included as having had epilepsy? - PWE is defined as a foot note under Table 1 but would be better placed earlier under the description of the cohort study participants - Any patient with a diagnostic code of “epilepsy resolved” was removed from the study (Medcodes 8385 and 12848). This raises a few questions. First, CPRD tends to use Read codes for diagnostic codes but Medcodes are also used and there are of course medication codes. A brief overview of what types of Codes are available from CPRD, and which ones were used with some description of how valid and accurate those codes are for the condition/drug etc is needed. What are “Therapy data?” In addition, why were these patients excluded? It would be reasonable given the authors argument that with QOF that may be improved care during the study period, so it is conceivable that some patients may have had resolution of their epilepsy and may explain the reduced number of PWE recorded over the later years. Reduction in the PWE population will reduce the size of denominators in analyses and with enhanced outcome recording during QOF may result in increase in the size of the numerator. Would these be potential contributors to the observed increase in death proportion? What would be trend if the epilepsy resolved patients were included in the analyses? - Amongst the variables investigated, it is unclear how they were defined. Were they based on Read code diagnostic codes/Medical codes and or medication codes? Recommend that a table (could be offered as supplemental material) with a description of the definitions. If a definition has not been validated before – then this needs to be at least discussed as a limitation. If there has been validation, then it(they) should be referenced. - There is discrepancy between the numbers provided in the first paragraph of the results with those in Fig 1 – please clarify. - Amongst the 11,241 recorded deaths only 7405 (66%) had linked ONS cause of death data. Why was this so low? Were some deaths outside of England and Wales? Did the ONS death linkage dates match completely with the study dates? What steps have the authors taken to reduce the chance of bias in the sample? - How were missing data dealt with? It is noted that for some, the authors assumed that absence of data was ascribed as “no” which is limitation for some factors. Did the authors consider any other approaches to dealing with any missing data and if not, why? - Adherence is defined according to repeat prescriptions but there was a lack of detail on this. Did the prescriptions need to be consecutive and cover a specified period? Further,

	monitoring/assessing adherence is very challenging and the pros and cons of using repeat prescriptions need to be discussed. - Did the authors look at correlations and or interaction amongst risk factors and if there were any, how were they addressed in the modelling? It would not be surprising that someone who had an episode of status epilepticus to have also had an emergency department visit but they were both included in the model? - P8, “However, they differ in middle-age. At age 40, epilepsy-contributing deaths were 2fold higher in male compared to female PWE.” The table does show that within the age groups covering 40-54, the point estimates in males are indeed higher than females. Given the sample size, the CI’s are likely to be narrow but it would be helpful if the authors were able to confirm that the CI’s did not overlap. The age 40 statement is quite specific did the authors mean to provide a range? Pease clarify. - Depression was a factor considered as a risk factor, but in the discussion the authors spoke more widely about mental health problems in PWE. With this in mind, is it possible that the authors have underestimated the burden/contribution of mental health problems? Would there have been an advantage to include psychoses/anxiety/schizophrenia which have already had validated Read codes/drug codes in CPRD?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Prof. Carlo La Vecchia, IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, University of Milan Comments to the Author:
The manuscript considers mortality and causes of death in a cohort of people with epilepsy.

it is unclear to me why a case-control rather than a simple cohort design was used, apart from possibly some software simplification.

As we were looking at a specific time period, 12 months prior to the date of death, we opted for a nested retrospective case-control study. We have added a sentence in the methods section to address this: “As we looked at the specific 12-month period prior to date of death to establish preventable risk factors, we opted to use a nested case-control study design.” (Marked copy, last paragraph “Case-control study participants”, page 5).

More important, data are available at least to age 64, while the focus is now on 35 or less.
A standard presentation with SMRs (or ORs) at all ages, and then at age under 35 would be informative.

We agree with the reviewer that this would be beneficial for the paper. We have included the analysis for PWE under 35 in Table 4, and have added a reference to this new analysis in the methods. “The analysis was conducted for the whole dataset and subsequently for the subset of PWE aged under 35.” (Marked copy,, “Statistics” paragraph, Page 6).

Reviewer: 2
Dr. John Cursio, The University of Chicago Comments to the Author:
Thank you for this important research that looks at an important clinical population.
My main comments are as follows:
1) Setting missing values to "no" can be problematic and can cause biased estimates. I suggest a multiple imputation approach outlined in the following document:https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fbstt513.class.uic.edu%2FAddict2007.pdf&data=04%7C01%7Cgabriella.wojewodka%40kcl.ac.uk%7C286755de815e4ffb280e08d927650a3c%7C8370cf1416f34c16b83c724071654356%7C0%7C1%7C63758413718383

9257%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=d68hTIjGUMreNX4CqeCOddGeD5FqD7wytEwl0705Mec%3D&reserved=0. Please consider this approach.

We recognise the limitations with assuming missing data means “no”. The article suggested by the reviewer presents an approach to missing smoking status, which is a similar approach we took for smoking status in our study (using the last known status). However, this approach may not be applicable to all variables. There have been studies exploring the best method for dealing with missing data. The conclusions showed that multiple imputation may not be the best approach for primary care databases as data is “missing not at random”(Marston, L., Carpenter, J.R., Walters, K.R., Morris, R.W., Nazareth, I. and Petersen, I. (2010), Issues in multiple imputation of missing data for large general practice clinical databases. Pharmacoepidem. Drug Safe., 19: 618-626; Steele AJ, Denaxas SC, Shah AD, Hemingway H, Luscombe NM (2018) Machine learning models in electronic health records can outperform conventional survival models for predicting patient mortality in coronary artery disease. PLoS ONE 13(8): e0202344).
Conducting multiple imputation while not knowing the reasons why data is missing can introduce bias. As GPs record information needed for the care of the patient, data, such as a diagnosis, may be missing because it would not be relevant to the issue at hand.
To explore this limitation further, we have added a sentence about other statistical methods in dealing with missing data. “Missing data in routine primary care databases are not missing at random and thus statistical methods of dealing with missing data, such as multiple imputation, may not be appropriate.” (Marked copy, paragraph 1, page 13)

2) The authors mention that age has different impacts on the risk of death for people with epilepsy. Did they consider using categories for age instead of a continuous measure? One approach may classify adults as less than 65, versus 65 or more another can use bins of 10 year widths as appropriate.

We opted to show the impact of age as a continuous variable to consider its overall impact on mortality. As our controls are matched by year of birth +/- 1 year, we are not able to separate into bins for the analysis.

3) Were any interactions tested in the final models? Some disease factors may have different impacts depending on age.

We thank the reviewer for this comment. We have tested for the following interactions: Age and emergency admissions, age and injury, age and dementia, age and stroke. In addition, due to Reviewer 3 also commenting on testing interactions, we tested for: status epilepticus and emergency admissions, number of AEDs and seizure freedom, prescription issue and number of AEDs. These were not significant.
A significant interaction was included (injury and emergency admission) for the full data set but not for the subset of under 35 years. This interaction is included in Table 4. And we have added the testing of interactions in the Methods section (Marked copy, “Statistics”, page 6)

Reviewer: 3
Dr. Richard Chin, University of Edinburgh Centre for Clinical Brain Sciences Comments to the Author:
This study by Wojewodka is a welcome addition to the field. I have a few comments that I would ask the authors to consider.
- The ILAE guidelines for epidemiological studies on epilepsy highlights the importance of validation of epilepsy diagnoses. Epilepsy was defined in the paper as “having a documented epilepsy diagnostic code and at least two prescriptions of antiepileptic drugs (AEDs)”. Further detail on these are needed – what codes were used and the bases for their usage?

We have added the list of codes used to identify epilepsy in Supplemental File 1, Table S1 and have added a reference to this list to the methods. “Codes used to identify epilepsy and seizures are presented in Table S1 (Supplemental File 1).” (Marked copy, “Cohort study participants” paragraph, page 5).

How the definition related to validation of epilepsy diagnosis would strengthen the paper. Someone who had a symptomatic seizure and had two prescriptions for an emergency medication only eg diazepam/midazolam – would that person be included as having had epilepsy?

Previous research has shown using a GP epilepsy diagnostic code along with AED prescriptions is a robust way to identify PWE in datasets collected routinely.(Fonferko-Shadrach et al. Validating epilepsy diagnoses in routinely collected data. Seizure. 2017;52:195-198; Tan M et al. Development and validation of an epidemiologic case definition of epilepsy for use with routinely collected Australian health data. Epilepsy Behav. 2015 Oct;51:65-72.) Due to the nature of the CPRD database, which includes only prescriptions issued by GPs, any medication used in emergency hospital settings would not be recorded.
There will be some missed cases of true epilepsy diagnosis, and inclusion of patients who may not have epilepsy, such as having dissociative seizures. However, this number is unlikely to significantly impact the sample as GPs were incentivised to conduct annual reviews of their patients with epilepsy, thus had the opportunity to revisit patients' diagnoses.
We have added a sentence and a reference to strengthen the out definition of PWE in the methods section. "Using a diagnostic or seizure code with prescription data has been validated to identify cases of epilepsy in routinely collected data."(Reference 19 – study by Fonferko-Shadrach, 2015) (Marked copy, "Cohort study participants" paragraph, page 5).

We have also added to the limitations that our dataset and definition may misclassify cases of epilepsy. "However, we relied on clinical data which has some limitations as compared to epidemiological studies. It is possible that a small number of cases might have been misclassified as having epilepsy but our case definitions of an epilepsy diagnostic code and AED prescription have been validated and used in previous studies. Conversely, patients who presented to emergency departments or were managed only by hospital specialists might not have been included." (Marked copy, last paragraph, page 12)

- PWE is defined as a foot note under Table 1 but would be better placed earlier under the description of the cohort study participants

The definition of PWE can be found in the "Cohort study participants" section in the methods (Marked copy, page 5). "For the mortality and cause of death cohort study, adults with epilepsy were included who were least 18 years old at time of death. Epilepsy was defined as having a documented epilepsy diagnostic code or seizure code and at least two prescriptions of antiepileptic drugs (AEDs)."

- Any patient with a diagnostic code of "epilepsy resolved" was removed from the study (Medcodes 8385 and 12848). This raises a few questions. First, CPRD tends to use Read codes for diagnostic codes but Medcodes are also used and there are of course medication codes. A brief overview of what types of Codes are available from CPRD, and which ones were used with some description of how valid and accurate those codes are for the condition/drug etc is needed. What are "Therapy data?" In addition, why were these patients excluded? It would be reasonable given the authors argument that with QOF that may be improved care during the study period, so it is conceivable that some patients may have had resolution of their epilepsy and may explain the reduced number of PWE recorded over the later years. Reduction in the PWE population will reduce the size of denominators in analyses and with enhanced outcome recording during QOF may result in increase in the size of the numerator. Would these be potential contributors to the observed increase in death proportion? What would be trend if the epilepsy resolved patients were included in the analyses?

We have added a paragraph to explain the different types of codes used within patient records and the CPRD, and the different categories of data available. This is in the Methods section under "Types of data" on page 5 (Marked copy).
"The CPRD includes "patient data" which include demographic information, "clinical data" include information on clinical events such as diagnosis or symptoms, and "additional clinical details" that include lifestyle factors. It also includes "therapy data" which contains information on prescriptions, product codes, doses and treatment schedules. Clinical data are entered initially as alpha numeric

Read codes by the GP into electronic medical records. These are converted into numeric Medcodes within the CPRD for easier analysis by researchers. Medication types are recorded in "therapy data" as numeric Prodcodes."
The patients with epilepsy resolved codes were removed as they no longer met the inclusion criteria of having an epilepsy diagnosis. Only 181 were excluded based on epilepsy resolved code which would not explain the reduction of PWE in the database over time.

We thank the reviewer for highlighting this gap in the paper and Figure 1 now shows this information.

- Amongst the variables investigated, it is unclear how they were defined. Were they based on Read code diagnostic codes/Medical codes and or medication codes? Recommend that a table (could be offered as supplemental material) with a description of the definitions. If a definition has not been validated before – then this needs to be at least discussed as a limitation. If there has been validation, then it(they) should be referenced.

We have expanded information on the definition of the variables in Supplemental File 1:
"Lists of Medcodes and corresponding Read codes used for each variable can be found in Supplemental file 2. An initial list of Read codes was created for each variable, either based on previous research or by searching specific words in a Read code browser. Medcodes were matched to the Read code list using the CPRD Medical Dictionary. An additional search of the Medcodes was conducted to ensure all appropriate codes were used. Medcodes were used during the analysis in STATA as these are numeric codes. For variables using medication data, lists of prodcodes were generated by searching the CPRD product code list, which lists prodcodes against British National Formulary (BNF) information." (Supplemental File 1, page 2)
Supplemental File 1 also includes more specific descriptions of each variable with references.
Supplemental File 2 includes the complete lists of the codes used for each variable, which include Medcodes used and corresponding Read codes.
We have also added a paragraph in strengths and limitations about the definitions of our variables.
"We defined the exposure variables based on previous studies, if available. The CPRD information has been validated for long term-conditions, such as dementia and Alzheimer's disease, and for diagnoses made by hospital consultants. As GPs issue prescriptions via electronic systems, the CPRD "therapy data" has been found to be highly accurate for medication variables. However, we included variables which may not have been previously validated such as injury and emergency department visit or emergency admission which is a limitation of this study." (Marked copy, second paragraph, page 13).

- There is discrepancy between the numbers provided in the first paragraph of the results with those in Fig 1 – please clarify.
We thank the reviewer for this comment. The correct figure 1 has been uploaded.

- Amongst the 11,241 recorded deaths only 7405 (66%) had linked ONS cause of death data. Why was this so low? Were some deaths outside of England and Wales? Did the ONS death linkage dates match completely with the study dates? What steps have the authors taken to reduce the chance of bias in the sample?
The CPRD includes data for the whole of the UK (England, Scotland, Wales and Northern Ireland). ONS data only includes mortality information for England and Wales, when available. We have added this limitation to page 13, specifying that the cause of death analysis is not generalisable to Scotland and Northern Ireland. "A limitation of our cohort study is the use of linked ONS data, which is only available for consenting individuals from England and Wales. Thus, data was not available for our whole cohort, and findings are not generalisable to Scotland and Northern Ireland." (Marked copy, paragraph 4, page 13)
The date of death did match between the two databases for the most part, however we do not have the data available at this stage to determine exact numbers. If there was a discrepancy between the dates, the earliest date of death was used. A sentence to clarify this has been added to the methods on page 5. "Date of death was available both from the CPRD and ONS data and the earliest date of the two was used if there were discrepancies." (Marked copy, paragraph 3, page 5)

- How were missing data dealt with? It is noted that for some, the authors assumed that absence of

data was ascribed as “no” which is limitation for some factors. Did the authors consider any other approaches to dealing with any missing data and if not, why?

We describe how we dealt with missing data on Page 13 and have added a sentence about how other ways to deal with missing data (such as multiple imputation) are not appropriate for this type of data. “Missing data in routine primary care databases are not missing at random and thus statistical methods of dealing with missing data, such as multiple imputation, may not be appropriate.” (Marked copy, paragraph 1, page 13).

We recognise the limitations with assuming missing data means “no”. There have been studies exploring the best method for dealing with missing data, including using “last known status” which we have done for smoking status. The conclusions showed that multiple imputation may not be the best approach for primary care databases as data is “missing not at random”.(Marston, L., Carpenter, J.R., Walters, K.R., Morris, R.W., Nazareth, I. and Petersen, I. (2010), Issues in multiple imputation of missing data for large general practice clinical databases. Pharmacoepidem. Drug Safe., 19: 618-626; Steele AJ, Denaxas SC, Shah AD, Hemingway H, Luscombe NM (2018) Machine learning models in electronic health records can outperform conventional survival models for predicting patient mortality in coronary artery disease. PLoS ONE 13(8): e0202344)
Conducting multiple imputation while not knowing the reasons why data is missing can introduce bias. As GPs record information needed for the care of the patient, data, such as a diagnosis, may be missing because it would not be relevant to the issue at hand.

- Adherence is defined according to repeat prescriptions but there was a lack of detail on this. Did the prescriptions need to be consecutive and cover a specified period? Further, monitoring/assessing adherence is very challenging and the pros and cons of using repeat prescriptions need to be discussed.
We thank the reviewer for these comments. We have removed this variable altogether from the model as it did not accurately represent adherence and it may lead to misinterpretation of the data. We have also removed the corresponding paragraph in the discussion section.

- Did the authors look at correlations and or interaction amongst risk factors and if there were any, how were they addressed in the modelling? It would not be surprising that someone who had an episode of status epilepticus to have also had an emergency department visit but they were both included in the model?
We thank the reviewer for this comment. We have explored interactions and have included this in our model (Table 4). There was no interaction between status epilepticus and emergency department visit in our data. We have tested for the following interactions: Age and emergency admissions, age and injury, age and dementia, age and stroke. In addition, due to Reviewer 3 also commenting on testing interactions, we tested for: status epilepticus and emergency admissions, number of AEDs and seizure freedom, prescription issue and number of AEDs. These were not significant. A significant interaction was included (injury and emergency admission) for the full data set but not for the subset of under 35 years. This interaction is included in Table 4. And we have added the testing of interactions in the Methods section (Marked copy, “Statistics”, page 6)

- P8, “However, they differ in middle-age. At age 40, epilepsy-contributing deaths were 2fold higher in male compared to female PWE.” The table does show that within the age groups covering 40-54, the point estimates in males are indeed higher than females. Given the sample size, the CI’s are likely to be narrow but it would be helpful if the authors were able to confirm that the CI’s did not overlap. The age 40 statement is quite specific did the authors mean to provide a range? Pease clarify.
We thank the reviewer for highlighting this oversight. We have now included CIs in Table 3 and have clarified the text to refer only to the specific 40-44 age range. (Marked copy, page 8)

- Depression was a factor considered as a risk factor, but in the discussion the authors spoke more widely about mental health problems in PWE. With this in mind, is it possible that the authors have underestimated the burden/contribution of mental health problems? Would there have been an advantage to include psychoses/anxiety/schizophrenia which have already had validated Read

codes/drug codes in CPRD?
We had explored severe mental illness as a risk factor but was not statistically significant and thus not included in out model. We have now included a list of factors we explored but are not part of the final model.
“We explored other factors such as severe mental illness, self-injury, patient-level index of multiple deprivation, alcohol use, substance use, pregnancy and learning disability. These were found statistically not significant and not included in the final overall model or the under-35 model.”
(Marked copy, 2nd paragraph, page 13)

VERSION 2 – REVIEW

REVIEWER	Chin, Richard University of Edinburgh Centre for Clinical Brain Sciences, Muir Maxwell Epilepsy Centre,
REVIEW RETURNED	06-Sep-2021

GENERAL COMMENTS	My concerns have been addressed in the main. The authors should be congratulated for a well-written manuscript with clear clinical messages. I have only one remaining comment. Given that status epilepticus is often considered an emergency, do the authors find it surprising that there was no significant interaction/correlation between a diagnosis of SE and emergency attendance/admission? Would welcome the authors's thoughts on this and potential implications (if any) on study findings. Do they think the lack of interaction/correlation is related to lack of validation of emergency department visits or emergency admissions or miscoding of status epilepticus as something else eg seizure or epilepsy?

VERSION 2 – AUTHOR RESPONSE

My concerns have been addressed in the main. The authors should be congratulated for a well-written manuscript with clear clinical messages. I have only one remaining comment. Given that status epilepticus is often considered an emergency, do the authors find it surprising that there was no significant interaction/correlation between a diagnosis of SE and emergency attendance/admission? Would welcome the authors's thoughts on this and potential implications (if any) on study findings. Do they think the lack of interaction/correlation is related to lack of validation of emergency department visits or emergency admissions or miscoding of status epilepticus as something else eg seizure or epilepsy?

We thank the reviewer for the positive feedback. The reviewer raises an interesting question. Based on the statistically significant interaction between emergency department visits and injury, we presume that the under reporting of status epilepticus rather than the emergency visits variable has led to a lack of interaction. As GPs record emergency attendance after receiving a discharge letter, we hypothesise that status epilepticus may be recorded as “epilepsy” as the cause for the emergency visit due to this being part of QOF reporting while status was not. We have added this limitation and the implication on study findings to the manuscript (tracked version page 13, 1st paragraph).