

Overall and cause-specific premature mortality in epilepsy:

A systematic review

Musa M. Watila^{a,b,c}; Salisu A. Balarabe^d; Olubamiwo Ojo^e; Mark R. Keezer^{b,f,g}; Josemir W.

Sander^{a,b,g}

- a. NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, London WC1N 3BG, UK.
- b. Chalfont Centre for Epilepsy, Chalfont St Peter SL9 0RJ, UK.
- c. Neurology Unit, Department of Medicine, University of Maiduguri Teaching Hospital. PMB 1414, Maiduguri, Borno State. Nigeria.
- d. Neurology Unit, Department of Medicine, Usman Danfodiyo University Teaching Hospital, Sokoto, Sokoto State. Nigeria.
- e. Barking, Havering and Redbridge NHS Trust, London, UK.
- f. Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec, H2X 0C1, Canada.
- g. SEIN — Stichting Epilepsie Instellingen Nederland, Achterweg 5, 2103 SW Heemstede, Netherlands

Corresponding author:

Prof Ley Sander

Box 29, UCL Institute of Neurology, Queen Square, WC1N 3BG London, UK.

E-mail address: l.sander@ucl.ac.uk

Abstract

Background: We conducted a systematic review to ascertain the overall mortality and causes of premature mortality in epilepsy.

Methodology: We searched Pubmed and Embase to retrieve relevant articles reporting mortality in epilepsy. An assessment of the methodological quality and overall quality of evidence of the identified studies was done using appropriate checklists. We extracted data from these studies reporting measures of overall and cause-specific mortality in epilepsy.

Results: Sixty-three articles from fifty-six cohorts met the eligibility criteria, thirty-three population- or community-based and twenty-three hospital- or institutional-based studies. The majority of studies are from high-income countries (HIC). These studies reported overall excess mortality for people with epilepsy, with wide variability reported for population- or community-based studies and from low- and middle-income countries (LMIC). Twenty-seven articles from twenty-three cohorts reported measures of mortality for cause-specific mortality in epilepsy. People with epilepsy from HIC and LMIC have a higher risk of dying from various causes compared to the general population. Those in LMIC, however, have a particularly high chance of dying from external causes such as drowning and suicide. We observed a decrement over time in measures of overall and cause-specific mortality in cohorts.

Conclusions: Despite the heterogeneity in reports, our findings supports the suggestions that people with epilepsy have an increased risk of premature mortality from various causes. Further work is needed to elucidate the mechanisms and to determine biomarkers for predicting those at risk and to understand the implications of counselling and preventive strategies.

Keywords: Epilepsy death; Seizures; Causes; External causes; Neoplasms

1. INTRODUCTION

A diagnosis of epilepsy has the potential to impact negatively on survival, as there is an increased risk of premature mortality compared with the general population [1-4].

Approximately 1,000 epilepsy-related deaths are reported in the UK each year [5], with an estimated 180,000 dying annually worldwide [6]. The reasons for the increased risk of early death are not fully understood but may be accounted for by a complex inter-relationship between epilepsy etiology, age, gender, geographical location and antiepileptic drug (AED) use [7-9].

The cause(s) of death (COD) may be epilepsy-related or non-epilepsy related. Deaths occurring from neoplasms, cardiovascular, gastrointestinal and pulmonary diseases, may be directly-related to the underlying cause of epilepsy or comorbidities [8, 9]. Deaths from sudden unexpected death in epilepsy (SUDEP) and status epilepticus are usually epilepsy-related. Other causes like drowning, accidents, burns, substance abuse and suicide are usually considered as external causes of death, are also common in people with epilepsy [10-13]. People with symptomatic epilepsy and neuro-deficits have an increased risk of early death, compared to those with idiopathic epilepsies or those who are seizure-free [4, 14]. A functional neurological deficit is a major independent determinant of premature mortality in pediatric populations [15], while psychiatric co-morbidity and adverse health behaviors may contribute to deaths from external causes [11].

Uncontrolled seizures are suggested to initiate pathophysiological processes such as inflammation, glycation and oxidative stress, causing detrimental effects that lead to accelerated ageing and premature mortality [16]. This evidence is inconclusive, as those in remission continue to have a higher likelihood of dying than the general population, although the risk of early death is more likely among those with refractory epilepsy [17]. This study aims to review systematically the overall and cause-specific mortality in populations with epilepsy.

2. METHODS

2.1 Search Strategy

We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) standard for the search, extraction, synthesis of results and reporting [18]. Pubmed and Embase were searched using Medline Medical Subject Headings (MeSH) when appropriate, and keyword terms to maximize the sensitivity of the search. The word "epilepsy" was combined with terms such as "mortality", "premature mortality", "death", "fatality", "all-cause" mortality, "cause", "cause-specific" and the various study types. The search was last executed on the 7th of August 2017 with no limit on the year of publication (see [Supplement 1](#) for the details of the search strategy).

2.2 Study Selection

Original articles were initially selected from the titles and abstracts of the search results. The selected articles were then read in full and screened for eligibility. Lists of bibliographies of key articles were cross-checked to identify other relevant studies. MMW and SAB did the search independently and disagreements were resolved by consensus.

2.3 Inclusion and Exclusion Criteria

Original prospective or retrospective (historic) cohort studies were included if they reported measures of overall or cause-specific mortality (standardized mortality ratio (SMR), hazard ratio, relative risk, odds ratio) compared with the general population.

SMR is an indirect method of standardization and the index most often used for mortality studies. It is defined as the ratio of the number of observed deaths in the study population to the expected deaths in that population over a specified time period if it had the same age- and sex-specific death rates as a 'standard' population [19]. Its advantage over direct standardization is that direct methods may be difficult in cases where age- and sex-specific mortality rates are not available. Since SMR uses indirect standardization, comparing SMRs between different populations must be done with great care, paying close attention to any differences in the characteristics of the population [19, 20].

Other measures like odds ratio (OR) and hazard ratio (HR) are less commonly used as

measures of mortality [21, 22, 23]. Another measure is the proportional mortality ratio (PMR), defined as the ratio of the number of deaths within a population due to a specific cause to the total number of deaths in the population during a specified period [24]. A report of PMR was not part of the inclusion criteria in this review, but data on PMR was extracted for the studies meeting the inclusion criteria.

Articles were excluded if they focused on special sub-populations and high risk groups, such as neonates, those with status epilepticus, SUDEP, psychogenic seizures, specific epileptic syndromes, refractory epilepsy, or those who had epilepsy surgeries. Expert opinions, case reports, editorials and reviews were also excluded.

2.4 Data Extraction, Quality Assessment and Synthesis of Results

The data of interest included: the sociodemographic characteristics, author, publication year, country, study design, type of study population, duration of follow-up, and number of deaths. Measures of overall mortality and causes of death were expressed in summary tables along with their 95% confidence intervals (CI). The results were stratified according to source population, while the COD were reported as either seizure-related or not seizure-related [1]. Deaths from external causes were treated together with seizure-related deaths for the ease of reporting.

Information on mortality for these studies were obtained from death certificates, hospital records, departments of health, national death registries and cause of death registers, life tables and necropsy reports, and by record linkages of these sources. The studies from LMIC mainly used verbal autopsies and face-to-face interviews with family members. The CODs were reported according to the ICD-8 or 9 codifications for earlier studies and ICD-10 for later studies. The SMRs were estimated using the mortality rates of the general population of the respective countries as reference.

A quality appraisal was conducted using a quality assessment tool modified from the Newcastle-Ottawa Scale [25] and the ILAE's standards for epidemiology research [26] ([Supplement 2](#)) to evaluate whether studies had a clear statement on selection of the population of interest, the study's quantitative methodology and accuracy of the recruitment

strategy, in addition to the clarity of data collection and analysis of outcome measure. A total potential score of 0 to 9 is awarded, with a score of 0 to 3, 4 to 6, and 7 to 9 considered to represent low, medium, and high quality studies, respectively.

Recognition of the potential diversities in studies was estimated using a funnel plot to visualize publication bias. An I-squared test was also used to test for heterogeneity using the formula: $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the chi-squared statistic, and df is the degrees of freedom. I^2 describes the percentage of the variability in estimates due to true heterogeneity rather than by chance. A value above 50% was considered as having substantial heterogeneity [27]. Analyses were performed with STATA 15.0 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

3. RESULTS

3.1 Study selection

From the 6,179 articles identified, one hundred and sixteen potentially appropriate full-text articles were assessed for eligibility, from which sixty-two were rejected. The commonest reason for exclusion was the lack of report of measures of overall or cause-specific mortality ([Supplement 3](#) for full details). Nine additional relevant articles were identified from the bibliographical search ([Fig. 1](#)). Sixty-three articles from fifty-six cohorts were eventually included [28-90], thirty-three population- or community-based and twenty-three hospital- or institutional-based studies, thirty-five retrospective and thirty-one prospective ([Table 1, 2 and 3](#)). There were thirty-six studies from Europe, eleven from North America, nine from Asia, four each from South America and Africa, and one each from Australia and the Caribbean. Most (~80%) articles come from high-income countries (www.worldbank.org). Eleven studies reported exclusively on children [30, 37, 40, 49-51, 55, 62, 74, 75, 78], while the others were mainly a combination of adults and children.

The quality assessment showed that most of the older studies and those from LMICs were of poorer quality (see [Supplement 4](#)). Cohorts from these LMICs were mainly derived from community-based door-to-door survey [39, 42, 44-46, 48, 59, 60, 63]. We did not eliminate

these studies in our analysis but these surveys had problems with case ascertainment (mainly active convulsive epilepsies) and large loss to follow-up. All studies retrieved reported outcome measures of overall and or cause-specific mortality, with appropriate statistical analyses, clear statements of findings and adequate follow-up period.

3.2 General Characteristics of the selected studies

Population-based studies like the UK National General Practice Study of Epilepsy (NGPSE) [31, 36, 52, 64], the US Rochester project [28, 29], the Icelandic epilepsy study [32, 35] and the Epilepsy Management at Primary Health Level program (EMPHL) in rural China [44, 59] have more than one article with different follow-up periods. Similarly, institutional and hospital-based studies with different follow-up periods have been reported from the UK Chalfont Centre for Epilepsy (CCE) [68, 69, 71], the Austrian study [83, 85, 87] and Dutch Study of Epilepsy in Childhood (DSEC) [74, 78]. These articles are not independent of each other as successive analyses incorporate previous data. The Estonian [53] and the Glasgow [77] studies had two cohorts of newly diagnosed and chronic epilepsy. A single paper reported mortality data from three LMIC countries [41].

A funnel diagram ([Supplement 5](#)) showed a skewed plot with more studies clustering to the left and outside of the funnel plot and may suggest publication bias. It is recommended that all systematic reviews of observational studies should be assumed to have publication bias [91]. The I^2 values for the overall SMRs and causes of death SMR were high (> 50%), suggesting marked heterogeneity of the SMRs. Only hepatobiliary cancer and accidents had an I^2 statistic of less than 50% (detail can be found in Stata output [Supplement 5](#)). Studies not reporting SMR [30, 56-58, 62, 79, 80], and the UK GPRD childhood cohort with severe epilepsy [50] were excluded from the analysis.

3.3 Overall mortality:

There were sixty-nine reports on overall mortality. Apart from the few studies reporting mortality rate ratio (MRR) [30, 62], HR [56, 58, 79, 80], adjusted OR [57] and relative risk [39] ([Table 3](#)), all the other studies reported SMR. The overall SMR for population-based

studies had a wide variability ranging between 0.76 (0.51, 1.01) in the Indian Parsis cohort [41] to 22.40 (18.90, 26.20) in the UK GRPD [50]. Despite the wide variability, the overall SMR in the majority of the studies ranged between 2.0 to 4.0. Differences in SMR occur even among the same cohort with different follow-up periods. This is observed in the NGPSE [31, 64], the Chinese EMPHL [44, 59] and the Austrian cohorts [83, 85], showing a decrease over the follow-up period. The 95% CI of differences overlap and so any apparent difference may not be statistically significant.

The overall SMR for hospital-based studies ranged from 1.40 (1.10, 1.70) in the Georgian cohort [82] to 9.70 (5.70, 15.30) in the Netherland (DSEC) cohort [78]. Forest plots ([Supplement 5](#)) showed an overall pooled SMR for LMIC as 3.71 (3.66, 3.76) which is higher than for HIC at 2.27 (2.24, 2.31). Twenty-six studies reported mortality according to gender [28, 34, 35, 38, 41, 44, 45, 48, 50, 53, 63, 67, 68, 70-74, 76, 80, 81, 87-90] ([Table 1, 2 and 3 for details](#)).

3.4 Cause-specific mortality

Twenty-seven studies, from twenty-three cohort reported measures of cause-specific mortality in epilepsy [28, 29, 31, 34-36, 38, 43, 44, 47, 52, 54, 56, 57, 59, 61, 62, 68, 69, 72, 73, 77, 80, 81, 83, 85, 88]. [Table 4](#) summarizes cause-specific mortality not directly-related to seizures. The SMRs for malignant neoplasm excluding brain tumors were generally lower than for all malignant neoplasms, which is more evident in the Ohio Medicaid cohort where the SMR was 0.95 (0.90, 1.00) for malignant neoplasms excluding brain tumors, but was 7.16 (6.41, 7.91) for all malignant neoplasms [61]. The SMR for pneumonia in the EMPHL Chinese cohort dropped from 21.3 (14.5, 40.0) to 2.9 (0.7, 7.8) four years later [44, 59]. This drop over the years of follow-up was also observed in the NGPSE cohort [31, 36, 52]. The SMR for ischemic heart disease was highest in the Chinese EMPHL cohort 10.70 (5.6, 95.3) and 3.6 (1.6, 7.2) [44, 59], while it ranged from 0.98 to 1.80 (1.20, 3.00) for the other studies. The SMR for cerebrovascular disease was 0.70 (0.0, 2.60) in the Manhattan cohort [47] and 7.00 (6.50, 7.60) in the earlier Chinese study [44], although the original cohort in the Manhattan study excluded those with cerebrovascular disease.

Cause-specific mortality for not seizure-related in hospital-based studies shows an increased mortality for people with malignant neoplasms, but this is more pronounced for neoplasms of the brain, which were in excess of 20 in the Swedish, Taiwanese and Austrian cohorts [72, 81, 83]. Excess mortality was observed for most studies reporting SMRs for neoplasm of lungs, hepatobiliary neoplasms, ischemic heart disease, cerebrovascular disease and pneumonia. The Swedish and Austrian cohorts reported high SMRs for congenital anomaly (17.0 (9.5, 28.1) and 7.1 (2.3, 16.6) respectively) [72, 85].

Results for external causes or seizure-related mortalities and are shown in Table 5, with excess mortality reported for drowning especially higher in the Chinese reports (39.0 (26.4, 55.5) and 82.4 (46.4, 146.4)) and the Californian cohort 12.80 (7.00, 23.20) [43, 54, 59]. SMRs for suicide, transport accidents and accidental falls were particularly higher in Chinese rural areas [44, 54, 59]. An excess mortality was also reported for drowning, suicide, injury and poisoning in the hospital-based studies, this was particularly high in the Taiwanese study [81]. The measures of mortality for other CODs were not estimated due to small number of deaths or for lack of expected population values for these CODs (A more graphical summary can be found in [Supplement 5](#)).

3.5 Mortality according to the etiology of epilepsy

Studies reporting mortality according to etiology, suggest an excess mortality for idiopathic epilepsy, higher for remote symptomatic etiology and much higher for those with a congenital deficit ([Table 6](#)). Comparing SMRs between these studies is difficult as etiologies were classified differently.

3.6 Proportionate mortality ratio (PMR)

Some of the included articles reported PMR for cause-specific mortality. These additional data on PMR are reported in [Supplement 6](#). The PMR for SUDEP appears to be higher in institutional/hospital-based cohorts as compared to population-based incident cohorts.

4. DISCUSSION

This review provides a more comprehensive picture of the overall and cause-specific mortality in epilepsy and supports the evidence that people with epilepsy are at increased risk of premature mortality compared to the general population. In some studies the rates were higher than previously reported [1, 2, 4, 7]. Despite the heterogeneity, the results clearly suggest a premature mortality risk that cannot be explained by chance alone. Our findings are in line with other studies [2, 4, 92, 93]. Interestingly, newer studies have not shown any significant difference in overall mortality compared to the older ones, particularly for HIC. One study looking at temporal trends observed that there is no evidence that the mortality risk of people with epilepsy changes significantly over time following epilepsy onset [2]. Our observations, however, show that mortality may change in the same cohort over the years of follow-up and may even decrease, as observed in the NGPSE, Austrian and the Chinese cohorts [31, 36, 44, 52, 59, 64, 83, 85]. This notable finding of decrease in overall and cause-specific SMRs over the period of follow-up for a cohort may simply reflect a population growing older and a higher expected number of deaths. It may also be due to the influence of treatment on a cohort, or the natural tendency for remission. The varying follow-up time used in different studies makes comparisons of mortality data challenging as it tends to ignore possible consequences of changing factors over the years. It has been suggested that predictors of mortality and health variables are more likely to be unstable during the first years of follow-up and this trend diminishes with longer follow-up periods [94]. These assumptions are inconclusive and require further studies. In contrast, the DSEC cohort had a slightly higher mortality in the latest report compared to the original report (SMR: 9.7 versus 7.0). A possible explanation is that a notable percentage became intractable and those with remote symptomatic epilepsy continued to have significant risk of mortality [74, 78].

The wide variability and discrepancies in measures of mortality between primary studies may be due to differences in the age and sex composition, socioeconomic circumstances, access to treatment and adherence to treatment. The heterogeneity of study design employed,

outcomes measured and the length of follow-up may also contribute [1, 7]. These variations in SMRs have been shown to persist despite data from industrialized western countries with similar medical risks and cultures [95].

The overall SMRs from LMIC appear to be higher than those from HIC, apart from the Indian (Parsi) cohort (SMR: 0.76). The reason for this isolated case is not known, but may be due to the small sample size with less severe epilepsy. It may also be related to the higher baseline mortality rate in India where epilepsy adds little compared to the huge impact of communicable diseases. Few studies reported measures of cause-specific mortality from LMIC but studies from China found higher SMRs for external causes of deaths such as drowning and suicide [44, 54, 59]. These studies from LMIC had high attrition rates and shorter follow-up. They also included mainly people with convulsive epilepsy who are more likely to have severe uncontrolled epilepsy and are less likely to receive standard care, and may therefore have higher mortality rates.

The higher overall SMRs for population-based compared to hospital-based studies we found are in contrast to a previous meta-analysis [4, 95]. These differences may be due to newer population-based studies from LMIC with higher SMRs. The inability to estimate aggregate SMRs makes it difficult to ascertain whether population-based studies report higher SMRs than hospital-based studies, as hospital-based studies may include more people with severe epilepsy and thus have a higher mortality [2].

SMRs for cause-specific mortalities appear to be generally higher for population-based studies than hospital-based cohorts; this is largely due to higher SMR for population-based studies from China. The differences in SMRs of cause-specific mortality may be due to differences in ascertainment of COD.

The SMRs for malignant neoplasm excluding brain tumors were generally lower than for all malignant neoplasms, suggesting an excess mortality caused by brain tumors. Generally, cancer mortality appears to be higher in those with more severe epilepsy as noted in the

residential population from the Chalfont Centre [69]. The relationship between severe epilepsy and the effect of AEDs in developing cancers have been postulated, but this requires further research [96, 97]. Bronchopneumonia is an important cause of mortality in people with epilepsy of all ages, and was associated with high SMRs, especially from the study from rural China [44]; this may be related to aspiration during seizures more likely to occur in people with uncontrolled and generalized epilepsy [98]. In the NGPSE cohort study there was an increase in mortality from ischemic heart disease after 20 years of follow-up. This increase in mortality from ischemic heart disease is congruent with other studies [99, 100], although the Taiwanese study reported a lower SMR for ischemic heart disease [81]. Despite several articles not reporting SMRs for epilepsy-related deaths; the few studies reporting cause-specific SMRs showed an increased risk of death from various causes. SMRs for SUDEP and SE cannot be estimated as these conditions are intrinsically related to epilepsy with no corresponding condition in the general population, and up to half of the cases of SE have no previous history of epilepsy [101]. The precise incidence of SUDEP is not known, but the reported PMR appear higher in institutional/hospital based cohorts [41, 70, 75], while it accounts for the minority of death in incident population-based cohorts [61, 102, 103].

A possible confounder in epilepsy-related deaths is the role of psychiatric co-morbidity which is usually under-diagnosed, and was not considered in the studies retrieved except in the Swedish study [57]. There is evidence showing an increased risk of suicide and accidental death in psychologically vulnerable people [104]. Whilst there is a concern about a possible role of AEDs in promoting suicidal tendencies; studies assessing suicidal risk with AEDs found that the risk of suicide was much higher in those not compliant with AEDs [105]. We have seen a paucity of studies on suicide reporting a wide variability in mortality measures. Despite the conclusive evidence that the risk of suicide is increased in people with epilepsy, it is still difficult to predict those at risk. It is suggested that those with psychiatric disease

should have regular psychiatric evaluation [57]. Further studies are needed to identify susceptibility factors for suicide in people with epilepsy.

People with symptomatic and congenital deficits had the highest mortality rate compared to those with idiopathic and cryptogenic epilepsies. Those with remote symptomatic epilepsy and major neurologic abnormalities are less likely to achieve proper seizure control and the absence of 5-year terminal remission is an important predictor of mortality [49, 98]. The excess mortality risk may also be related to the underlying etiology rather than to the epilepsy itself. Recent findings from a prospective UK cohort observed that the COD is frequently related to the underlying epilepsy etiology and that this relationship changes over time. In people who died within 2 years of epilepsy onset, the etiology of epilepsy was four times as likely to be directly associated with the COD, compared with those who died later [103]. A study comparing two cohorts observed that individuals with a first acute symptomatic seizure were significantly more likely to die in the first 30 days and less likely to experience a subsequent unprovoked seizure over the next 10 years despite the enduring predisposition from brain insults [106]. One of the confounding issues in comparing studies in relation to the etiology of epilepsy is the difference in diagnostic criteria employed over different time periods [107].

The main strength of this review is that we retrieved information from relatively newer articles with longer duration of follow-up years in some cohorts. An additional strength and a challenge is the inclusion of results of 56 cohorts from more than 25 countries.

Several methodological issues are noted. Firstly, the marked heterogeneity of mortality rates and different source populations precluded us from statistical pooling and meta-analysis. SMRs are difficult to compare between cohorts which differ among studies and geographical regions. As age- and sex-specific mortality rates of the population of interest were unknown in some of these studies, indirect standardization was applied. It has been argued that these potential differences hamper the computation of aggregate SMR. The difference in

classifications used for the causes of death in these studies may also hamper direct comparison of SMRs [108, 109]. Comparing data between studies may also be difficult due to methodological differences. Retrospective studies are more likely to introduce information bias than prospective studies. Prevalence studies may recruit people with more severe epilepsy, while incidence studies may recruit those with milder epilepsy and the differing follow-up periods may be misleading because case ascertainment, diagnosis, classification, treatment and even prognosis have changed over the years [1, 109].

Secondly, some studies had less than 5 years follow up. It is difficult to ascertain whether studies with relatively short follow-up are helpful in determining mortality when compared to those with longer follow-up due to the instability of predictors over time [94]. Some studies in the review were useful for observing the trend in mortality over a follow-up period.

Thirdly, records of mortality were obtained from varying sources such as death certificates, hospital records and verbal autopsies. Various methods have their pitfalls; death certificates although useful have been shown to be unreliable compared to autopsy reports [110], while hospital registries have an increased risk of selection bias toward more severe cases and may overestimate mortality rates. Fourthly, this study reported SMRs predominantly from HIC, particularly Europe. It also captured more data from adults and adolescents than from children. It is argued that childhood cohorts have more severe epilepsy [30, 74, 98, 111].

Fifthly, we did not extract information on deaths according to age, seizure type, or the duration of epilepsy. Data extraction on age was difficult, due to the varying age bracket used by the various studies. Lastly, we recognize that SMR can give information on how frequent a COD is compared to the general population, but cannot tell how frequent a COD is in absolute terms, and may not necessarily mean it is an important COD.

5. Conclusions

People with epilepsy have an increased risk of death and this is seen in population-based and hospital-based cohorts. They are at higher risk of dying from various medical conditions, some of which are epilepsy or non-epilepsy related. Deaths in LMIC were higher for external causes whilst in HIC deaths were less often epilepsy-related. A proportion of the excess deaths could have been possibly prevented by educating people with epilepsy and care providers and by optimizing seizure control. Further research is needed to understand the implication of counselling and preventive strategies. Whether or not physicians should discuss mortality issues with individuals is an ongoing debate [112].

Conflict of interest:

MMW, SAB and OO report no conflict of interest. MRK receives research support from UCB and Eisai, and has received unrestricted educational grants from UCB and personal fees from UCB, Sage Therapeutics, and Novartis, outside of the submitted work. He has received research funding from Eisai and UCB, personal fees from Eisai, UCB, Bial and Janssen outside of the submitted work.

Author Contributions:

MMW and JWS developed the concept for the study. MMW, SAB and OO carried out the search, quality assessment and initial data interpretation. MMW and MRK did the statistical analysis. MMW prepared manuscript draft, with revisions and input from MRK and JWS. All authors approved the final version. JWS is the guarantor.

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