Premature mortality of epilepsy in low- and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy

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Running title: Epilepsy Mortality in Lower-income Countries
Word counts: Summary – 305; Main text – 4431

Summary

Objectives: To determine the magnitude, risk factors and causes of premature mortality associated with epilepsy in low and middle income countries (LMIC).

Methods: We conducted a systematic search of the literature reporting mortality and epilepsy in the World Bank-defined LMIC. We assessed the quality of the studies based upon the representativeness, ascertainment of cases, diagnosis, and mortality and extracted data on the standardized mortality ratio (SMR), mortality rate, and incidence of death in epilepsy. We examined the risk factors for death and reviewed the causes of death.

Results: The annual mortality rate was estimated at 19.8 (range 9.7-45.1) deaths per 1000 people with epilepsy with a weighted median SMR of 2.6 (range 1.3-7.2) among higher-quality population-based studies. Clinical cohort studies yielded 7.1 (range 1.6-25.1) deaths per 1000 people. The weighted median SMRs were 5.0 in males and 4.5 in females; relatively higher SMRs within studies were measured among children and adolescents, those with symptomatic epilepsies, and those reporting less adherence to treatment. The main causes of death in people with epilepsy living in LMICs include those directly attributable to epilepsy, which yield a mean proportional mortality ratio (PMR) of 27.3% (range 5%-75.5%) derived from population-based studies. These direct causes comprise status epilepticus, with reported PMRs ranging from 5%-56.6%, and sudden unexpected death in epilepsy, with reported PMRs ranging from 1%-18.9%. Important causes of mortality indirectly related to epilepsy include drowning, head injury, and burns.

Significance: Epilepsy in LMIC has a significantly greater premature mortality, as in high-income countries, but in LMIC the excess mortality is more likely to be associated with causes attributable to lack of access to medical facilities such as

status epilepticus, and preventable causes such as drowning, head injuries and burns. This excess premature mortality could be substantially reduced with education about the risk of death and improved access to treatments, including AEDs.

Keywords: Seizures, convulsions, death, case fatality, developing countries, resource-poor countries, premature mortality

Introduction

Standardized mortality in people with epilepsy in high-income countries (HIC) is estimated to be up to 4 to 15 times higher than the general population in community-based studies and selected high-risk populations, respectively.[1; 2] Comparable estimates of mortality in epilepsy in low- and middle-income countries (LMIC) are scarce, because vital registration of deaths is incomplete or absent in most countries, and many studies examining the risk of premature mortality in people with epilepsy in LMIC have methodological limitations.

Worldwide, approximately 80% of those with epilepsy live in LMIC.[3; 4] The estimated overall incidence of epilepsy is also higher in LMIC than in HIC (incidence rate ratio: 1.8, 95% CI 1.3–2.5).[5] The high prevalence and incidence of epilepsy in LMIC is most likely associated with higher incidence of adverse perinatal events, head injuries, and parasitic infections.[4; 6-10]

Some studies in LMIC[7; 11; 12] have suggested that mortality in epilepsy is higher than in HIC.[2] Higher mortality, whether comparing populations with and without epilepsy or populations of people with epilepsy in LMIC and HIC, can be described by relating age-specific mortality rates, most commonly expressed as standardized mortality ratios (SMR; Supporting Table 1B). In effect, an elevated SMR in a population indicates excess *premature mortality*, i.e., a higher proportion of deaths occurring at earlier ages, relative to the comparison population. Findings of relative excess mortality in LMIC may be attributed to the selection of studies in areas endemic with specific causes, selection of higher-risk cohorts to follow, or lack of access to comprehensive treatment.[6] The epilepsy treatment gap (defined as the proportion of people with epilepsy who either have not accessed biomedical services or are not on

treatment with anti-epileptic drugs [AEDs] or are receiving inadequate treatment[9]) is more than 75% in LMIC, compared with less than 10% in HIC.[10] The large treatment gap may increase mortality from complications such as status epilepticus, accidents including burns and drowning, and sudden unexpected death in epilepsy (SUDEP).

We conducted a systematic review to estimate the magnitude of premature mortality associated with epilepsy in LMIC, and to identify the risk factors and causes of death among people with epilepsy. A companion review focuses on mortality in high-income countries.[13]

Methods

Literature search. We searched the Medline, EMBASE, and LILACS databases with terms in the following three categories:

- epilepsy, seizure, or convulsions
- mortality, death, or SUDEP
- low-income countries, middle-income countries, developing countries, resource-poor countries, Africa, Asia, China, India, "Latin America," "Central America," or "South America"

We included only reports indexed with at least one term in each of the three categories, and restricted our search to reports on human subjects from LMIC as defined by the World Bank.[14,*] The search period was from 1990 to 28th February 2014. We used the criteria for the diagnosis of epilepsy suggested by the

[*] Low-income economies in 2014 were those with annual gross national incomes (GNI) per capita of $1,045 or less, while middle-income economies were those with GNI per capita ranging from $1,046 to $12,735. The country income categories for studies included in this report are indicated in Tables 1 and 2.

International League Against Epilepsy (ILAE) for epidemiological studies, originally in 1993[15] and confirmed in 2010[16] and 2011.[17]

Two reviewers (FL and CRN) evaluated the retrieved citations in a two-stage process. In the first stage they independently reviewed the titles and available abstracts to identify potentially relevant reports meriting full review (Figure 1). The reviewers compared their selections and resolved the list of publications to arrive at a single list for the second stage of analysis. In the second stage they reviewed the full papers and assessed whether the articles met the inclusion criteria below. For those meeting these criteria, they extracted the measures of mortality, risk factors, and causes of death.

Inclusion criteria. Original reports of mortality among people with epilepsy in LMIC, derived from general populations, clinical cohorts (hospital- or treatment program-based), and case-control studies, were included. Studies that did not report quantitative estimates of mortality in epilepsy were excluded.

Data extraction. Data on the epilepsy were extracted according to ILAE guidelines, in particular age at onset, seizure type, and the underlying etiology.[17] Age at onset, i.e., first occurrence of unprovoked seizure, helps identify epilepsy syndromes. Three main categories of *epilepsy/seizure type* as classified by ILAE (generalized, focal, and undetermined) were identified.[16; 17] The ILAE proposed three main categories of etiology: genetic, structural/metabolic, and unknown causes.[16; 17] Epilepsy etiology is classified as genetic when genetic defects are the known or presumed to be prime cause of the disease (including epilepsies formerly known as idiopathic). Structural/metabolic causes (formerly known as symptomatic epilepsies) are considered when a structural lesion or metabolic condition is known to predispose to

epilepsy. It was expected that some studies would still report earlier epilepsy etiology categories as idiopathic, symptomatic, and cryptogenic (now termed unknown).[18]

Estimates of mortality were extracted from the measures reported in the papers which included case fatality ratio (CFR), proportional mortality ratio (PMR), mortality rate (MR), and standardized mortality ratio (SMR) according to standard definitions (Supporting Table 1B).[19] Deaths were categorized occurring: (i) as a direct consequence of epilepsy or seizures (i.e. status epilepticus, or SUDEP); (ii) as indirect causes (i.e., accidents due seizures—such as falls, burns, or drowning—or drug reactions to AEDs); (iii) as unrelated to epilepsy, or (iv) as undetermined (i.e. cause of death not ascertained). The definitions and classification of SUDEP are mainly consistent with the earlier recommendations,[20] which have been updated since publication of most the studies we reviewed.[21]

Quality of studies. The reviewers employed quality assessment criteria for studies of mortality in epilepsy that included the following five elements classified by ILAE's Commission on Epidemiology Task Force on the Burden of Mortality (Supporting Table 1A). These address the most important design features of epidemiologic studies of epilepsy, which we employed in preference to less specific conventional evaluation checklists proposed for observational studies.[22]

- *Representativeness of the study population.* Provides the basis of generalizability of the study findings. Studies conducted in clinical settings or untreated populations may not be representative of entire populations of people with epilepsy.
- *Accuracy of diagnosis of epilepsy.* Evaluates methods employed to diagnose cases of epilepsy; if quantifiable, can be expressed as a positive predictive

value. The use of the case definition provided by ILAE (at least two unprovoked seizures) and diagnosis by trained neurologists is a reference standard that may reduce the number of false positives and negatives.

- *Epilepsy case ascertainment.* Evaluates completeness (sensitivity) of methods employed to screen the population for cases of epilepsy. This is important in population-based studies of epilepsy prevalence or incidence. A door-to-door survey is thought to generate an optimum number of cases in screening of a community.
- *Mortality ascertainment.* Evaluates the completeness of identifying death occurrence in a cohort or population of people with epilepsy. This depends upon the proportion of people with epilepsy followed until death or end of the study. Short follow-up of individuals, high migration patterns and loss to follow-up are critical issues in establishing mortality rates.
- *Accuracy of cause of death.* Evaluates the validity of cause-of-death determinations, especially for causes of interest associated with epilepsy. Accurate determination of the cause of death is essential to determine the proportion of deaths directly or indirectly related to epilepsy. Autopsies are the reference standard, but are rarely performed in LMICs. Verbal autopsies are most commonly used in LMIC[23-25].

A scale with five items was developed to score the quality of studies with respect to each quality measure listed above. The scoring of each item was generated from 4-5 sub-items, each with 5 points, with a total score ranging from 0 to 20 (Supporting Table 1A). The total score of the quality was the sum of scores of each quality item, with 100 representing the highest quality.

Statistical analysis. Total, median, and range were used to generate summary measures of mortality across studies. We disaggregated the estimates by study designs (population-based vs. clinical cohort), sex, type of seizure, etiology, and other risk factors. Summary estimates were also identified as reported, whether SMRs, PMRs, or MRs. If not reported as such, we calculated CFRs and MRs when the reports provided sufficient information to allow this. Standard definition of summary estimates can be found in Supporting Table 1B.

We also examined heterogeneity statistics, which measure the extent to which SMRs vary between studies, including the I^2 statistic, which is the percentage of between-study heterogeneity that is explained by variability in the exposure effect on mortality relative to sampling error[26]. Heterogeneity statistics are crucial in deciding whether summary measure of SMR estimates from studies can be estimated.

Results

Search results. Results of the systematic search are provided in Figure 1. A total of 17 articles met inclusion criteria, among which one article included reports from 4 sites.[27] and two articles reported separate findings from the same cohort.[28; 29] Thus, the articles contained 12 reports of findings from population-based cohorts[7; 8; 27; 29-35] and 8 reports from clinical cohorts.[12; 27; 36-41] South America provided 8 studies,[8; 27; 34; 36-40] Asia 6 studies,[7; 27-29; 33; 41] and Africa 6 studies.[12; 27; 30-32; 35]. Nine studies were conducted in rural populations only,[12; 27; 29-35] 6 in urban only,[7; 8; 27; 38; 41] and 5 in both urban and rural populations.[27; 36; 37; 39; 40]

Quality of studies. Supporting Table 2 provides summary characteristics of population-based studies, all of which included all ages. Population-based studies were mainly of good quality, where 7 out of 12 studies had a quality score of ≥80% (Table 2).[7; 8; 27; 30; 31; 34; 35] Door-to-door surveys were implemented in most studies, where neurologists made diagnoses of epilepsy. Over 85% of deaths were estimated to be captured in these cohorts and verbal autopsy was used to diagnose causes of death. Most studies used an operational definition of epilepsy as defined by ILAE in the diagnosis of epilepsy, although studies of 3 populations were restricted to active convulsive epilepsies.[29; 33; 35]

Clinical cohort studies were of low quality (≤50%), largely due to poor sample representativeness of the general population (Supporting Table 3). There was insufficient information published in most studies to determine the basis of the diagnosis of epilepsy. Individuals in clinical cohorts often had epilepsy described as intractable or refractory.[36; 38; 39] Cohorts of children with severe forms of epilepsy were also enrolled in several studies.[37-40] In health care

settings, causes of death were available from medical records, death certificates, and verbal autopsy for deaths occurring in the communities.

Mortality. From 7 population-based studies with quality scores ≥80% (Table 1)[7; 8; 27; 30; 31; 34; 35], the median annual mortality rate was 19.8 deaths per 1000 people with epilepsy (range 9.7-45.1), with a weighted median SMR of 2.6 (range 1.3-7.2) and an overall CFR of 8.1% (range 3.3-31.6%). The weighted mean follow-up period was 5.8 years (range 1.5-10), with 6,665 person-years observation.

Eight clinical cohorts (Table 2)[12; 27; 36-41] in sum enrolled substantially larger numbers of people with epilepsy compared to higher-quality population-based studies. There were 3,856 people with epilepsy enrolled across these cohorts, of which 88.3% were followed to the end of the studies. The weighted mean follow-up period was 12.4 years (range 3-30), during which 240 deaths were observed, with a pooled annual mortality rate of 7.1 (range 1.6-25.1) deaths per 1000 people with epilepsy. Two out of the 8 studies reported SMRs of 3.2 and 6.3.[27; 37] The overall CFR in these clinical cohort studies was 5.4% (range 1.3-75.3 %).

Mortality risk by age. Figure 2 summarizes 3 population-based studies reporting SMRs among people with epilepsy by age of death.[27; 28; 33] Overall, these showed the highest SMRs in the youngest age groups, declining markedly after young adulthood, with a continuing decline with increasing age. We found insufficient data to characterize the risk of mortality by age of epilepsy onset.

Mortality risk by sex. Figure S1 summarizes mortality estimates for males and females from 6 population-based studies and 6 clinical cohorts. Of five studies[27; 28; 31; 33; 35] comparing SMRs, two reported higher values among males, with a weighted median SMR of 5.0 for males compared to 4.5 for females (Supporting Figure 1, Panel A). Most studies reporting PMRs showed higher mortality in males than in females, with weighted medians of 62% and 38%, respectively (Supporting Figure 1, Panel B).

Cause-specific mortality in epilepsy. Table 3 presents 8 population-based studies that reported cause-specific proportional mortality rates in those with epilepsy.[7; 27; 29; 31-35] Among people with epilepsy, the weighted median PMR for all causes of death directly or indirectly attributable to epilepsy was 47%. Direct causes comprised status epilepticus (median PMR 13%), and possible or probable SUDEP (median PMR 13%; Supporting Table 4). Indirect causes included accidents (falls, road traffic, drowning, and burns; Supporting Table 5). Among accidents, the median PMR was 15% (range 3.3%-45%) for drowning,[7; 28; 31-33] and 7.5% for road traffic accidents[7; 28; 33; 35]; the remaining causes did not have sufficient data for a summary (Supporting Table 5). Among these population studies, the median sum of all listed accident-related PMRs was 36% of all deaths in people with epilepsy. Other important causes of death in these populations that were not attributable to epilepsy included cerebrovascular diseases, tuberculosis, malaria, heart disease, and cancer (Supporting Table 6).

Six clinical cohort studies reported causes of death as PMRs for individuals with epilepsy (Table 3).[12; 27; 36-39] The median PMR for direct and indirect causes of death attributable to epilepsy was 39.3% and 24% respectively. Median PMRs for deaths

due to status epilepticus and SUDEP in clinical cohorts were 14.8% and 11.1% respectively (Supporting Table 4). Data regarding causes of death indirectly attributable to epilepsy and causes not attributable to epilepsy were not sufficiently large to enable generalization.

Mortality risk by seizure type or frequency. Mortality risk by seizure (or epilepsy) type was reported from two population-based[8; 34] and two clinical cohorts[36; 41] in which median PMRs were consistently higher for focal epilepsy (population-based – 55% and clinical cohort – 73%) than for generalized epilepsy (population-based – 39% and clinical cohort – 26%; Supporting Table 7). Two studies reported increased mortality among people with epilepsy with a higher frequency of seizures[31; 40] (Supporting Table 8).

Risk by duration of epilepsy. Two studies reported on mortality by duration of epilepsy[31; 35] (Supporting Table 9). A study in rural Kenya reported the highest mortality rate (45 per 1000 person-years) for people with epilepsy duration of <1 year. In Uganda, SMRs were 8.6 (95% C.I. 4.5-16.5) for people with epilepsy of duration <5 years, 3.6 (1.1-11.4) for those of epilepsy duration 5-9 years, and 23.8 (8.9-65.5) for those of epilepsy duration 10-14 years.

Risk by epilepsy etiology. Symptomatic epilepsies appeared to have higher mortality rates compared to cryptogenic epilepsy,[8; 34; 36; 37] although only two studies provided direct comparisons[34; 36] (Supporting Table 10).

Risk by treatment adherence. Five population-based studies reported mortality risk by treatment adherence,[31-35] treatment allocation,[32] time since last treatment,[34] and dose allocation[33] (Supporting Table 11). In Kenya, mortality rates were three times higher for individuals who did not adhere to AED treatment than for those who

adhered to treatment (mortality rate ratio 3.37,95% CI 1.84–6.16).[35] In Uganda, the SMR was 7.4 (95%CI: 3.9—14.1) for those with self-reported good AED adherence compared to 8.0 (95% CI: 3.8—16.4) for those with poor adherence.[31] In Cameroon, treatment with AEDs alone was associated with 14% of deaths compared to 27% in those using AEDs and traditional medicine.[32] In one Chinese study, people receiving higher daily doses of phenobarbital (201-240 mg) had a lower mortality of 9% compared to those receiving medium doses (90-180 mg) with 44% mortality and low doses (30-90 mg) with mortality of 47%.[33] In a Bolivian study, recent access to AEDs was associated with lower mortality than absence of treatment for an extended period.[34]

Meta-analysis. Meta-analysis revealed high heterogeneity across population-based studies as well as clinical cohort studies, and among high- and low-quality studies as well as short and long follow-up studies (Figures S2 and S3). Accordingly, a formal meta-analytic synthesis was not attempted.

Discussion

Summary findings. This study provides evidence of higher premature mortality in people with epilepsy than in the general populations of LMIC, based on systematic reviews of epidemiologic studies accrued over 25 years. The number of quality studies found is low—especially considering this length of time and the large majority of the world population residing in LMIC—and points to the need for much further research. Nevertheless, these limited studies indicate that the main causes of death in people with epilepsy in LMICs are those directly attributable to epilepsy, i.e. status epilepticus and sudden unexpected death in epilepsy, and indirectly related to

epilepsy, i.e. drowning, head injury, and burns. The burden of premature mortality related to epilepsy appears higher in LMIC than in HIC. Unmet healthcare needs and lack of capacity in managing seizures may be the main reasons for the mortality gap between HIC and LMIC.

Interpretation. Recognizing noteworthy earlier reviews of mortality associated with epilepsy specific to Africa[11] and Latin America,[42] our systematic review now examines a broader range of studies from LMIC across Africa, Asia, and South America. The incidence of epilepsy varies substantially across regions comprising LMICs and is higher in regions with high incidence of encephalitis and meningitis and with endemic parasitic infections such as malaria and neurocysticercosis. The availability of basic public health services as well as specialized health care for epilepsy also varies considerably among LMICs.[43] Both factors may strongly influence epilepsy-related mortality. Thus, any generalizations drawn from the modest number of studies we have reviewed should be applied to other LMIC regions with great caution.

Despite their limitations, these data from LMIC provide clear evidence that the burden of premature mortality, as measured by SMRs, is higher among people with epilepsy than in corresponding general populations. Among the regions represented, the risk of premature mortality in people with epilepsy is particularly high in Africa, where the reported annual mortality rates in population-based studies range from 22.2 to 45.1 per 1000 people with epilepsy,[27; 30-32; 35] among which are reported SMRs of 6.5 and 7.2.[31; 35]

SMRs are especially high in children and young adults with epilepsy. This finding might be explained in part by: (a) the comparatively lower mortality rates in general populations of young age, and (b) the increased mortality of recent-onset epilepsy associated with symptomatic or structural/metabolic etiologies, which occur with a substantial proportion of young cases.[1] In HIC, higher SMRs have likewise been found in studies with age strata including children (range 6.4-8.5).[13] Only one clinical cohort study in Ecuador[27] reported an SMR (9.5) in a stratum similar to those of the HIC studies. Two other studies of lower quality from rural China reported extremely high SMR among children, but with wide confidence intervals.[28; 33]

The burden of premature mortality among people with epilepsy in LMICs appears to be somewhat higher in males, as indicated by the PMRs from several studies. This could possibly reflect a higher incidence among males of symptomatic epilepsies (especially from traumatic brain injury), which have an increased mortality risk. In lower-income regions such as Africa, brain injuries commonly arise from vehicular collisions, occupational accidents, sports, and violence,[44] which may be more frequent among males. The increased risk of premature mortality among males with epilepsy could also reflect mortality during hazardous occupations that carry an increased risk of drowning, falls, or other fatal injuries consequent to seizures.

These data also indicate that among the most important causes of death are those directly related to epilepsy, in particular status epilepticus, previously recognized to have a high case fatality ratio in LMICs.[45] The proportion of deaths from status epilepticus appears substantially higher in LMICs compared to HICs.[13] This difference might be explained in part by better access to AED treatment, better

management of seizures, and better access to prompt treatment for prolonged seizures in HICs compared to LMICs.

SUDEP was identified as another cause directly related to epilepsy in several LMIC studies. The estimated proportions must, however, be viewed with caution as causes of death were seldom diagnosed through post-mortems and diagnoses of SUDEP made by verbal autopsy or clinical history may be inaccurate.[18] Nevertheless, many of the risk factors associated with SUDEP are more common in LMIC than in HIC, e.g., structural causes of the epilepsy and frequent seizures, and thus SUDEP may represent a greater burden in these regions than indicated by some studies. Specific studies to examine SUDEP occurrence in LMIC populations are needed.

In comparison to HIC, a higher proportion of people with epilepsy in many LMIC regions also die due to indirect causes, especially accidents. Many of these causes, e.g. drowning and burns, are potentially preventable through education and safety measures. For other causes, e.g., seizure-caused fatal injuries incurred during work or while driving a vehicle, further studies are needed to understand the frequency and circumstances of these injuries and to identify appropriate prevention measures that are specific for different localities.

Comparing Mortality in LMIC and HIC. Overall, the relative premature mortality risk associated with epilepsy in LMIC appears higher than the risk reported in HICs. In the best quality LMIC studies, the weighted median SMR of 2.6 modestly exceeds the corresponding value of 2.2 in HIC.[13] Such comparisons of SMRs between studies are, however, fraught with potential error, especially given differing age distributions among study populations (with generally larger proportions of young

people in LMIC), problems with case finding (greater in LMIC), and differing overall mortality rates in the study base populations (usually higher in LMIC). Thus, the magnitude of the disparity suggested by SMRs may be deceptive and it appears likely that the actual burden of premature mortality with epilepsy, if this were measured as incidence rates in entire populations, would be much higher in LMIC.

Implications. A limited number of studies demonstrate substantially elevated risks of premature mortality among people with epilepsy in LMIC of three continents. Much of this may be attributed to the restricted distribution of healthcare resources in these countries, resources often far more limited than in HIC.[43] Thus, lack of access and decreased adherence to medical management with AEDs place people with epilepsy at increased risk of fatal medical or injury-related complications of frequent seizures. Lack of access to prompt medical interventions for prolonged seizures places people with epilepsy at increased risk of death from status epilepticus. This mortality could be significantly reduced with improved access to health care including AEDs, and with education about the risks of epilepsy and ways to reduce these risks. In many communities, public education may be important to increase reliance on standard medical treatments of epilepsy as these are available, discourage its sole treatment by unproven folk medicine and traditional healing, and reduce its stigma,[46-48] Also needed are improved public health and safety programs for primary prevention of structural causes of epilepsy—such as malaria, cysticercosis, and other infections of central nervous system—and accidents resulting in traumatic brain injuries.

The limited existing data on epilepsy-related mortality in LMIC are, however, not sufficient for optimum development of prevention programs adapted to local needs. Too many countries and local regions are not described. The circumstances of

fatalities from medical complications, e.g., status epilepticus, are uncertain. What proportion are associated with no AED treatment and in what proportion is AED use interrupted or reduced because of inability to afford its cost? The types and circumstances of fatal injuries arising from seizures are also uncertain. Where do drownings in people with epilepsy occur, how many are occupational, and which occupations are involved? How do fatal burns occur? In how many traffic fatalities are pedestrians, vehicle passengers, or vehicle drivers individuals with epilepsy? How do local laws address motor vehicle driving by people with epilepsy? How many injuries involve falls from heights and how many of these are occupational? How do risks vary according to local resources, customs, and industries (e.g., climbing trees for fruit picking)? While current LMIC data on epilepsy mortality broadly indicate the urgency of prevention programs now, future research can improve such programs by providing answers to questions like those above.

Limitations. There are substantial limitations to these data. The studies that met our inclusion criteria represented only a small number of communities in Sub-Saharan Africa, Asia, and South America, while other major regions of the world, such as North Africa and the Middle East, were entirely unrepresented. Under-representation of major regions may be associated with limitations of economic resources affecting their health care systems' capacity to implement prevention programs, manage seizures in people with epilepsy and conduct epidemiological studies of mortality in epilepsy. Health care systems and practices may also be affected independently by variations in regional culture, thus restricting our ability to generalize the findings from this review to unrepresented regions among LMIC.

The quality of the studies we reviewed varied considerably. The large heterogeneity observed illustrates the high degree of uncertainty in the estimation of the true occurrence of epilepsy-related mortality across LMICs. Incomplete ascertainment of epilepsy cases, a major concern in many of the studies, is likely to yield underestimates of the total burden of epilepsy mortality in general populations of LMIC. However, to the extent that studies over-represent more severe forms of epilepsy that carry higher risk of premature death, comparative measurements of mortality such as SMR could be increased. Some population-based studies included only cases with convulsive epilepsies, while others may have incompletely ascertained cases with non-convulsive epilepsies. Most clinical cohorts over-represented people with severe forms of epilepsy, such as one Brazilian study with 72% of enrollees who reported daily seizures[38] and another that enrolled people with refractory epilepsy awaiting or having undergone epilepsy surgery.[36] The diagnosis of epilepsy in many studies was not made by clinicians with training in the diagnosis of epilepsy; thus the accuracy of the estimates and causes of death in epilepsy in some studies should be viewed with caution. Most of the causes of death were ascertained by review of clinical records or verbal autopsy. The accuracy of verbal autopsies varies depending on the other common causes of death in the population, the tool used, and the experience of the person administering the tool.[23] As for post-mortem examinations, while in HIC the proportion of deaths autopsied in general populations and in people with epilepsy can be low,[49; 50] in comparison, none of the LMIC studies in this review included autopsy data.

More epidemiological studies, involving more LMIC localities, are needed. As with future studies in HIC, studies in LMIC should be performed in conformity with current guidelines for epidemiologic studies.[15; 17] Representative population samples and

incident cohorts should be studied, where acute symptomatic seizures are distinguished from single unprovoked seizures and from epilepsy, and where convulsive and non-convulsive forms of epilepsy are also distinguished. Finally, epileptogenic conditions and all risk factors implicated in the mortality of epilepsy should be clearly described. The collection of such higher quality information will enable us to identify many measures necessary to prevent much of the premature mortality in LMIC.

Disclosures

CN is funded by the Wellcome Trust, UK. DJT is funded by UCB Inc. DCH receives personal fees from UpsherSmith, Cyberonics, the Department of Rehabilitation, Mount Sinai Medical Center, and the NYU Epilepsy Center, as well as grants from the National Institutes of Health, the Centers for Disease Control and Prevention, The Epilepsy Study Consortium, and *Epilepsia*. JWS is based at the UCLH/UCL Bio-Medical Research Centre which received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. His current position is endowed by UK Epilepsy Society and he received research support from the Marvin Weil Epilepsy Research Fund. His department has received research grants from GSK, Eisai, UCB, EU, Dutch Epilepsy Funds, WHO and UK Epilepsy Society. He has received honoraria from UCB, Eisai, GSK, Lundbeck and Teva. GL has no conflict of interest.

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Supporting Information

Additional information can be found in the online version of this article.

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Tables and Figures

Table 1: Mortality estimates from population-based studies

Population- based	Country-Location (Income)	Total Population	Quality	People with epilepsy original cohort	People with epilepsy followed up	Duration of FU (years)*	Estimated Person-years	Deaths	SMR	95% CI	CFR	95% CI	Mortality rate per 1000 person-year	95% CI
Ngugi 2014 [35]	Kenya-Rural (L)	232,164	100	754	606	2.7	2,048	61	6.5	5.00-8.30	8.1	6.1-10	29.8	22.8-38.3
Kochen 2005[8]	Argentina-Urban (M)	70,000	90	106	96	8	768	8	2.45	1.14-4.65*	8.3	2.8-13.9	10.4	4.5-20.5
Kaiser 2007 [31]	Uganda-Rural (L)	4,743	90	61	57	7	399	18	7.2	4.40-11.6	31.6	19.5-43.6	45.1	26.7-71.3
Nicoletti 2009[34]	Bolivia-Rural (M)	55,675	85	118	103	10	1,030	10	1.34	0.68–2.39	9.7	4.0-15.4	9.7	4.7-17.9
Houinato 2013[30]	Benin-Rural (L)	11,688	80	160	150	1.5	225	5			3.3	0.5-6.2	22.2	7.2-51.9
Banerjee 2010[7]	India-Urban (M)	52,377	80	337	337	5	1,685	20	2.58	1.50-4.13	5.9	3.4-8.5	11.9	7.3-18.3
Carpio 2005[27]	India-Rural (Vusai) (M)	16,000	80	51	51	10	510	10	3.9		19.6	8.7-30.5	19.6	9.4-36.1
Summary: Higher quality population studies		**442,647**		**1,587**	**1,400**	**5.8†**	**6,665**	**132**	**2.6‡**		**8.1%‡**		**19.8**	**16.7-23.5**
Carpio 2005[27]	India- Urban (Parsis) (M)	14,010	65	109	104	14	1,456	34	0.76	0.51-1.01	32.7	23.7-41.7%	23.4	16.2-32.6
Kamgno 2003[32]	Cameroon-Rural (L)	NR	60	271	128	10	1,280	37			28.9	21.1-36.8%	28.9	20.4-39.8
Mu 2011 [33]	China-Rural (M)	5,840,000	50	3,568	2,998	4.5	13,491	106	4.9	4.0-6.1	3.5	2.9-4.2%	7.9	6.4-9.5
Ding 2013[29§]	China-Rural (M)	3,185,000	50	2,455	1,986	6.1	12,114	206	2.9	2.6-3.4	10.4	9.0-11.7%	17.0	14.8-19.5
Carpio 2005[27]	Mali-Urban/Rural (L)	7,158	40	36	31	12	372	13			41.9	24.6-59.3%	34.9	18.8-59.8
Summary: Lower quality population studies		**>9,112,561**		**8,894**	**7,233**	**6.0†**	**32,850**	**431**	**2.9‡**		**10.4‡**		**13.1**	**11.9-14.4**

Key: FU: Follow-up, SMR: Standardized mortality ratio, CI: Confidence Interval, CFR: Case fatality ratio, (L): low-income country, (M): middle-income country

*Length of follow-up described variously as median (Ngugi et al., 2014), mean (Ding et al., 2013), or the total interval of cohort assessment (others).

†Mean weighted by study person-years

‡Median weighted by study person-years

§ Follow-up study of cohort described in Ding 2006[24].

Table 2: Mortality estimates from clinical cohort studies

	Country-Location	Quality	People with epilepsy in original cohort	People with epilepsy followed	Duration of follow up (years)	Person-years	Deaths	SMR	95% CI	Case Fatality Ratio (%)	95% CI	Mortality rate per 1000 person-year	95% CI
Carpio 2005[27]	Ecuador- Urban (M)	50	420	379	3	1,137	7	6.3	2.0-10.0	1.8	0.5-3.2%	6.2	2.5-12.7
Almeida 2010[36]	Brazil-Urban/Rural (M)	45	550	550	10	5,500	16			2.9	1.5-4.3%	2.9	1.7-4.7
Terra 2011[38]	Brazil-Urban (M)	35	1012	987	10	9,870	53			5.4	4.0-6.8%	5.4	4.0-7.0
Jilek-Aall 1992[12]	Tanzania, Rural (L)	35	164	146	30	4,380	110			75.3	68.4-82.3%	25.1	20.6-30.3
Thomas 2001[41]	India-Urban (M)	25	447	246	12	2,952	18			7.3	4.1-10.6%	6.1	3.6-9.6
Terra 2010[39]	Brazil-Urban, Rural (M)	25	267	267	13	3,471	9			3.4	1.2-5.5%	2.6	1.2-4.0
Devilat 2004[37]	Chile-Urban/Rural (M)	5	NR	NR	6	NR	16	3.21	1.5-5.0				
Terra 2009[40]	Brazil-Urban/ Rural (M)	5	996	835	8	6,680	11			1.3	0.5-2.1%	1.6	0.8-2.9
Summary: all studies			**3856**	**3410**	12.4†	**33,990**	**240**	**4.8**		**5.4‡**		**7.1**	**6.2-8.0**

Key: FU: Follow-up, SMR: Standardized mortality ratio, CI: Confidence Interval, CFR: Case fatality ratio, (L): low-income country, (M): middle-income country

†Mean weighted by study person-years

‡Median weighted by study person-years

Table 3: Estimates of proportional mortality in epilepsy by cause in population-based and clinical cohort studies

Study	Country-Location	Design	Quality	Number of people with epilepsy followed	Number of deaths	Causes of death (%)			
						Direct	Indirect	Unrelated	Undetermined
Ngugi 2014[35]	Kenya-Rural	Population	100%	606	61	44.3	11.4	34.3	9.8
Kaiser 2007[31]	Uganda-Rural	Population	90%	61	18	33.0	17.0	44.4	5.6
Nicoletti 2009[34]	Bolivia-Rural	Population	85%	103	10	10	20	50	20
Banerjee 2010[7]	India-Urban	Population	80%	337	20	5	30	45	20
Kamgno 2003[32]	Cameroon-Rural	Population	60%	271	37	75.5	10.8	13.7	
Mu 2011[33]	China, Rural	Population	50%	2,998	106	21.6	58.8	19.6	
Ding 2013[29]	China, Rural	Population	50%	1,986	206	14.1	32.5	39.3	14.1
Carpio 2005[27]	Mali-Rural & Urban	Population	40%	36	13	38.0	NR	62.0	NR
Summary: all population-based				**6,546**	**471**	**27.3***	**20.0***	**41.9***	14.1*
Carpio 2005[27]	Ecuador, Urban	Clinical Cohort	50%	379	7	42	30	28	
Almeida 2010[36]	Brazil, Urban-Rural	Clinical Cohort	45%	550	16			62.5	
Terra 2011[38]	Brazil, Urban	Clinical Cohort	35%	987	53	15.1		84.9	
Jilek-Aall 1992[12]	Tanzania, Rural	Clinical Cohort	35%	164	110	17.3	18.2	32.7	31.8
Terra 2010[39]	Brazil-Urban, Rural	Clinical Cohort	25%	267	9	77.8			
Devilat 2004[37]	Chile, Santiago	Clinical Cohort	5%	NR	16	39.3			
Summary: all clinical cohorts				**>2,347**	**211**	**39.3***	**24.1***	**47.6***	

Key: *Median percentage

Figure 1: Summary results of search strategy

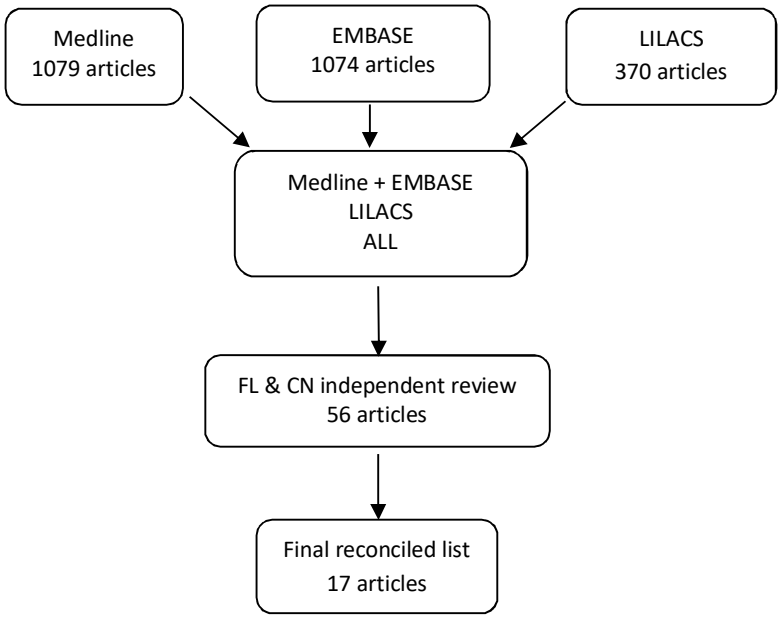
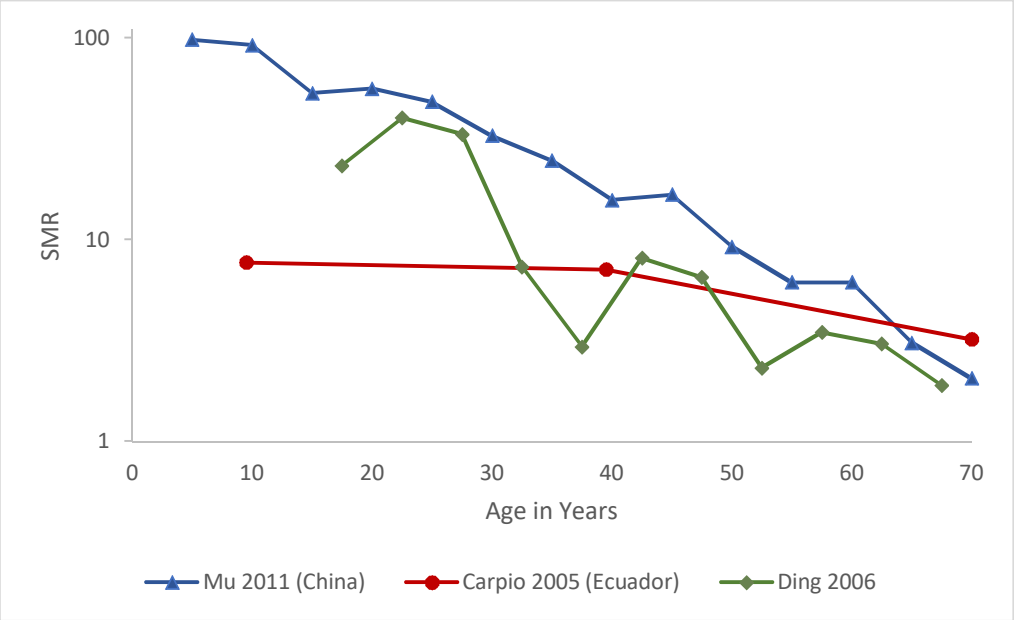


Figure 2: Mortality in epilepsy by age at death



Supporting Information

Supporting Table 1A. Criteria and grading for assessing qualities of mortality studies

Sensitivity of Epilepsy Case Ascertainment (20/20)

- 20/20 = Screening methods appear likely to ascertain nearly all (≥ 85%) cases in population
- 15/20 = Screening methods appear likely to ascertain most (70 - 84%) cases in population
- 10/20 = Screening methods appear likely to ascertain majority (50 - 69%) of cases in population
- 5/20 = Screening methods appear unlikely to ascertain majority of cases in population OR information published is insufficient to assess
- 0/20 N/A = Not applicable: not a population-based study or sensitivity of methods of epilepsy case ascertainment not relevant to quality of study.

Sensitivity of Mortality Case Ascertainment (20/20)

- 20/20 = Fatalities appear likely to be recorded in nearly all (≥ 85%) cases in study population
- 15/20 = Fatalities appear likely to be recorded in most (70 - 84%) cases in study population
- 10/20 = Fatalities appear likely to be recorded in majority (50 - 69%) of cases in study population
- 5/20 = Fatalities appear unlikely to be recorded in majority of cases in study population OR information published is insufficient to assess

Accuracy of Diagnoses of Epilepsy (20/20)

- 20/20 = Cases are diagnosed (or confirmed) by specialist clinician (i.e., with neurologic training), AND ILAE case definition applied
- 15/20 = Cases are often diagnosed by non-specialist clinician, OR minor deviation from ILAE case definition
- 10/20 = All or substantial proportion of cases diagnosed based on self-report or non-clinical sources with specified criteria judged to have fair positive predictive value
- 5/20 = All or substantial proportion of cases diagnosed with poorly defined criteria from non-clinical sources; positive predictive value judged to be poor OR information published is insufficient to assess

Accuracy of Diagnoses of Cause of Death (20/20)

- 20/20 = Determined mainly from either autopsy, ME/coroner investigation, or other clinical investigation (e.g., review of medical records, structured interview of survivors or “verbal autopsy”)
- 15/20 = Determined largely or wholly from death certificate data, when such data are judged to have good positive predictive value for the specific causes of interest
- 10/20 = Determined largely or wholly from death certificate data, when such data are judged to have only fair positive predictive value for the specific causes of interest
- 5/20 = Other sources of data deemed to have poor positive predictive value for the causes of interest OR information published is insufficient to assess
- 0/20 = Cause of death not studied

Representativeness of the study population (20/20)

- 20/20 = Cohort studies of incident epilepsy whose enrolled cases appear highly representative of the population of interest
- 15/20 = Studies of prevalent epilepsy whose enrolled cases appear highly representative of the population of interest
- 10/20 = Studies of epilepsy whose enrolled cases appear somewhat representative of the population of interest
- 5/20 = Studies of epilepsy whose enrolled cases appear poorly representative of the population of interest or where representativeness cannot be assessed.

Supporting Table 1B: Standard definition of epidemiological indicators of mortality in epilepsy

Case fatality Ratio is the proportion of people with epilepsy in a cohort who die, usually expressed as a percentage.
Proportionate mortality Rate (PMR) is the ratio of the number of deaths due to a specific cause in a population to the total number of deaths in the same period.
Mortality rate in epilepsy is the number of deaths (all causes) in a population of individuals diagnosed with epilepsy people with epilepsy, and is calculated from number of deaths per person years of observation.
Age-specific mortality fraction is the number of deaths in a given age group per time, usually expressed per 1,000 or 100,000 persons per year.
Cause specific mortality rate is mortality rate from a specified cause for a population during a specified time period usually expressed per 1,000 or 100,000 persons per year.
Standardized mortality ratio (SMR) is a ratio between the observed number of deaths in people with epilepsy and the number of deaths that would be expected, based on the age- and sex-specific rates in a standard population a. If the ratio of observed/expected deaths >is greater than 1.0, there is said to be "excess deaths" in the study population. With respect to the mortality in epilepsy, this measure is used to compare mortality in epilepsy with mortality in general population.

Supporting Table 2: Summary of characteristics and quality of population-based studies of mortality in epilepsy

Study	Country-Location	Dates	Source	Population (denominator)	Epilepsy cases	Case ascertainment %	Diagnosis	Mortality captured %	Cause of Death	Representativeness	Overall Quality (Max 100)
Kochen 2005[8]	Argentina-Urban	1991-1998	PBS	70,000	106	≥85	ILAE by Neurologist	≥85	DC	Highly	90
Houinato 2013[30]	Benin- Rural	2006-2007	PBS + MR+ KI	11,688	160	≥85	ILAE by Neurologist	≥85	N/A	Highly	80
Nicoletti 2009[34]	Bolivia-Rural	1994-2004	PBS	55,675	118	≥85	ILAE	≥85	NR	Highly	85
Kamgno 2003[32]	Cameroon-Rural	1991-2001	KI	NR	271	50-69	ILAE by Physicians	70-84	NR	Somewhat	60
Ding 2006[28]	China-Rural	2000-2004	PHC	3,185,000	2455†	N/A	NR	70-84	VA	Somewhat	50
Mu 2011[33]	China-Rural		PHC	5,840,000	3568†	N/A	NR	70-84	VA	Somewhat	50
Ding 2013[29]	China-Rural	2000-2008	PHC	3,185,000	2455†	N/A	NR	70-84	VA+DC	Somewhat	50
Carpio 2005[27]	India- Rural	1985-1999	PBS	14,010	109	≥85	Neurologist	≥85	N/A	Poorly	65
Banerjee 2010[7]	India- Urban	2003-2005	PBS	52,377	337	≥85	ILAE by Neurologist	≥85	N/A	Highly	80
Carpio 2005[27]	India- Urban	1989-1994	PBS	16,000	51†	≥85	NR	≥85	VA	Somewhat	80
Ngugi 2014[30]	Kenya- Rural	2007-2010	PBS	232,164	754†	≥85%	ILAE by Neurologist	≥85	VA	Highly	100
Carpio 2005[27]	Mali-Urban, Rural	1988-2000	KI	7,158	36†	50 - 69	NR	70-84	NR	Poorly	40
Kaiser 2007[31]	Uganda- Rural	1994-2001	PBS	4,743	61	≥85	ILAE	≥85	VA	Somewhat	90

Key: DC Clinical Diagnosis; KI: Key informants, MR: Medical records, N/A: Not Available; NR Not Recorded; PBS: Population-based screening, PHC: Primary health care, VA Verbal Autopsy, ILAE: International League Against Epilepsy

*These studies describe the same cohort.

†Convulsive epilepsy only.

Supporting Table 3: Summary of characteristics and quality of clinical cohort studies of mortality in epilepsy

Study	Country-Location	Dates	Source of clinical cohort	Epilepsy cases	Case	Diagnosis	Mortality	Cause of Death	Representativeness	Overall Quality (Max 100)
Carpio 2005[27]	Ecuador-Urban	1997-2000	Tertiary Hospital	420	N/A	ILAE	≥85	N/A	Somewhat	50
Almeilda 2010[36]	Brazil-Both	1992-2002	Tertiary Hospital	550	N/A	Clinical	≥85	N/A	Poor	45
Terra 2011[38]	Brazil-Urban	2000-2010	Tertiary Hospital	1012	N/A	N/R	≥85	SR	Poor	35
Jilek-Aall 1992[12]	Tanzania-Rural	1960-1990	District Hospital	164	N/A	N/R	≥85	N/A	Somewhat	35
Thomas 2001[41]	India-Urban	1985-1997	Tertiary Hospital	447	N/A	N/R	50 - 69	N/A	Somewhat	25
Terra 2010[39]	Brazil-Both	1995-2008	Tertiary Hospital	267	N/A	N/R	> 80	N/I	Poor	25
Terra 2009[40]	Brazil-Both	2000-2008	Tertiary Hospital	996	N/A	N/R	N/R	N/I	Poor	5
Devilat 2004[37]	Chile-Both	1996-2002	Tertiary Hospital		N/A	N/R	N/R	N/I	Poor	5

Key: N/A – Not Available; N/R – Not recorded, ILAE- International League Against Epilepsy

Supporting Table 4: Estimates of proportionate mortality ratio (PRM) from SUDEP and status epilepticus among people with epilepsy

Study	Country-Location	Quality	PMR in % SUDEP	PMR in % SE
Population based studies				
Ngugi 2014[35]	Kenya-Rural	100	6.6[a]	37.7[a]
Kaiser 2007[31]	Uganda-Rural	90	11.1	22.2
Carpio 2005[27]	India-Urban-Vasai	80	20[a]	
Nicoletti 2009[34]	Bolivia-Rural	85		10
Banerjee 2010[7]	India-Urban	80		5
Kamgno 2003[32]	Cameroon-Rural	60	18.9	56.6
Mu 2011[33]	China, Rural	50	14.7[b]	6.9
Ding 2013[29]	China, Rural	50	1[b]	13.1
Median All Population Studies			12.9	13.1
Clinical cohort studies				
Carpio 2005[27]	Ecuador, Urban	50	14.3[c]	23
			28.6[b]	
Almeida 2010[36]	Brazil, Urban-Rural	45	2.9[b]	
Terra 2011[38]	Brazil, Urban	35	13.2	15.1
Jilek-Aall 1992[12]	Tanzania, Rural	35		14.5
Terra 2010[39]	Brazil, Urban-Rural	25	11.1	
Devilat 2004[37]	Chile-Santiago	5	31.25[b]	
	Urban/Rural		6.25[c]	
Terra 2009[40]	Brazil-Urban, Rural	5	1.38	
Median All clinical cohorts			11.1	14.8

Key: PMR: Proportionate mortality ratio, SUDEP: Sudden death in epilepsy, SE: Status epilepticus

[a]Cases described as possible.

[b]Cases described as probable.

[c]Cases described as definite.

Supporting Table 5: Estimates of proportionate mortality ratio (PMR) in epilepsy by type of injury

Study	Country-Location	Quality	PMR by type of injury				
			Falls	Drowning	Traffic injury	Burns	Suicide
Population based studies							
Ngugi 2014[35]	Kenya-Rural	100	3.3	3.3	1.6	1.6	
Kaiser 2007[31]	Uganda-Rural	90		5.6		11.1	
Nicoletti 2009[34]	Bolivia-Rural	85			10		10
Banerjee 2010[7]	India-Urban	80		15	15		
Kamgno 2003[32]	Cameroon-Rural	60		10.8			
Ding 2006[28]	China, Rural	50		37	2.9		
Mu 2011[33]	China, Rural	50	5.9	45.1	4.9		2.9
Clinical cohort studies							
Terra 2011[38]	Brazil, Urban	35	1.9	1.9			
Jilek-Aall 1992[12]	Tanzania, Rural	35		12.7		5.5	

Key: PMR: Proportionate mortality ratio

Supporting Table 6: Estimates of causes of death reported in SMR and MR

Study	Country-Location	Quality	Measure	Causes	Estimate (95% C.I.)
Mu 2011[33]	China, Rural	50	SMR	Cerebrovascular	1.14 (0.36–3.61)
				Cardiac disease	1.60 (0.50–5.22)
				Influenza and pneumonia	1.05 (0.26–4.32)
				Malignant neoplasm	1.94 (0.90–4.18)
				Other diseases	11.41 (4.03–32.43)
Ding 2013[29]	China, Rural	50	SMR	Drowning	39.0 (26.4–55.5)
				Toxic effects	17.0 (6.9–35.7)
				Falls	9.8 (3.6–21.7)
				Suicide	8.2 (4.5–14.0)
				Transport injury	6.0 (2.8–11.4)
				Myocardial infarction	3.6 (1.6–7.2)
				Digestive system diseases	4.4 (2.3–7.7)
				Pneumonia	2.9 (0.7–7.8)
				Cerebrovascular	2.2 (1.5–3.1)
				Neoplasms	1.1 (0.7–1.8)
Terra 2009[40]	Brazil, Urban-Rural	5	MR	Unrelated to epilepsy	22.2

Key: SMR-Standardized mortality ratio, MR-Mortality rate, CI-Confidence interval

Supporting Table 7: Proportionate Mortality Ratio (PMR%) by Type of Seizure

				PMR for epilepsy type		
Study	Location	Source	Quality	Generalized	Focal	Unknown
Kochen 2005[8]	Argentina-Urban	Population	90	37.5	50	12.5
Nicoletti 2009[34]	Bolivia-Rural	Population	85	40	60	
Almeida 2010[36]	Brazil, Urban-Rural	Clinical Cohort	45	14.3	85.7	
Thomas 2001[41]	India, Urban	Clinical Cohort	25	38.9	61.1	

Key: PMR-Proportionate mortality ratio

Supporting Table 8: Estimates of mortality in epilepsy by seizure frequency

Study	Location	Source	Quality	Measure	Frequency	SMR/MR
Kaiser 2007[31]	Uganda-Rural	Population	90	SMR	High (>1 per week)	14.7 (8.5—24.8)
					Low (<1 per week)	1.4 (0.4—5.7)
Terra 2009[40]	Brazil-Urban/Rural	Cohort	5	MR	Daily	0.63
					2-4 per week	0.50
					1 per month	0.13

Key: SMR-Standardized mortality ratio, MR-Mortality rate

Supporting Table 9: Estimates of mortality in epilepsy by duration of epilepsy in population-based studies

Study	Country-Location	Quality	Measure	Duration of epilepsy (years)	MR/SMR
Ngugi 2014[35]	Kenya-Rural	100	MR	<1	45.9(22.9–91.7)
				1–5	30.8(19.1–49.5)
				6–10	35.9(20.4–63.2)
				>10	31.1(20.9–46.4)
Kaiser 2007[31]	Uganda-Rural	90	SMR	0-4	8.6 (4.5-16.5)
				5-9	3.6 (1.1-11.4)
				10-14	23.8 (8.9-65.5)

Key: SMR-Standardized mortality ratio, MR-Mortality rate

Supporting Table 10: Estimates of proportionate mortality ratios (PMR) in epilepsy by etiology

				Etiology			
Study	Country-Location	Quality	Measure	Cryptogenic	Symptomatic	Remote seizure	Undetermined
Almeida 2010[36]	Brazil, Urban-Rural	45	PMR	21.4	78.6		
Devilat 2004[37]	Chile-Urban/Rural	5	PMR		81.3		
Kochen 2005[8]	Argentina-Urban	95	PMR			75	25
Nicoletti 2009[34]	Bolivia-Rural	85	PMR			60	
			SMR	0.74 (0.2–1.8)*		3 (1.2–6.3)	

Key: PMR-Proportionate mortality rate, SMR-Standardized mortality rate

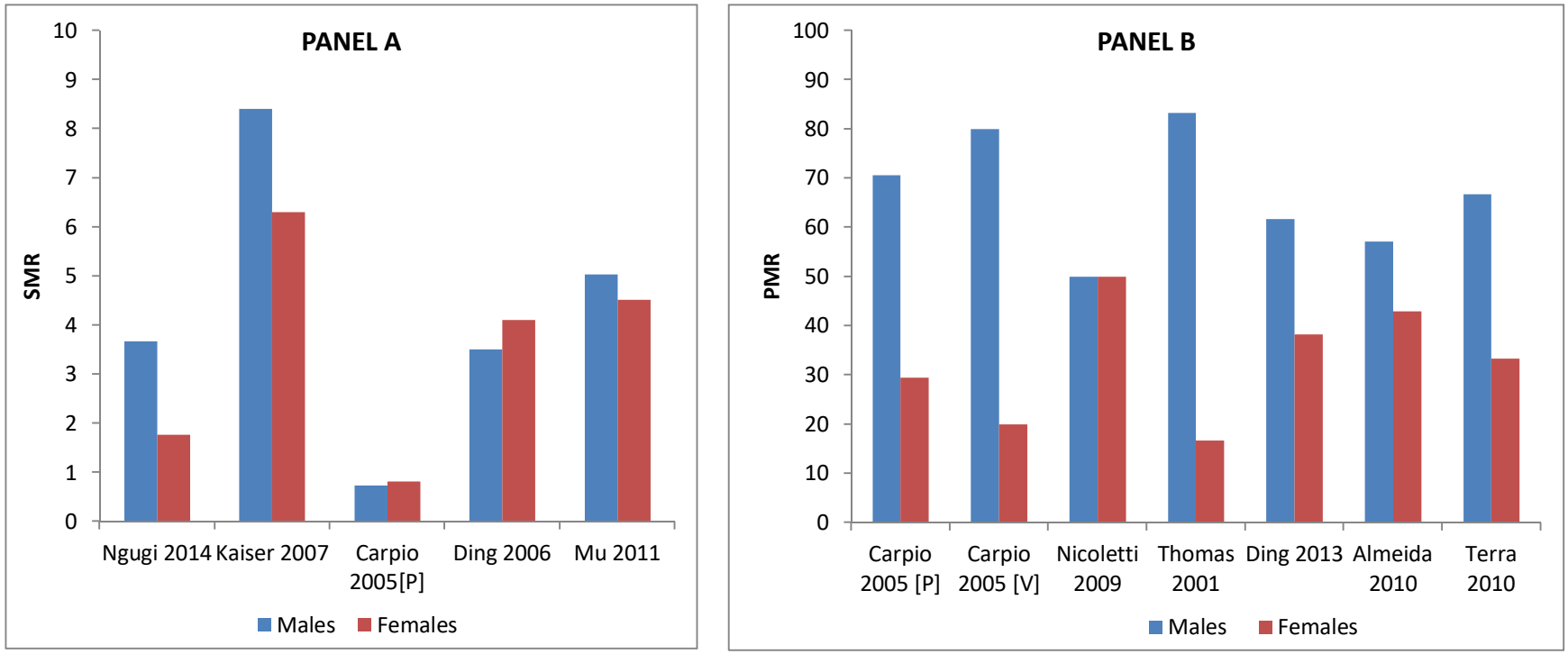
***** Idiopathic

Supporting Table 11: Estimates of mortality in epilepsy by treatment

Study	Country-Location	Quality	Measure	Treatment	Result
Ngugi 2014[35]	Kenya-Rural	100	MR	Adherence	16.1 (9.5–27.2)
				Non adherence	48.8 (36.7–65.0)
Kaiser 2007[31]	Uganda-Rural	90	SMR	Good adherence	7.4
				Poor adherence	8.0
Kamgno 2003[32]	Cameroon-Rural	60	PMR	AED	13.6
				AED + Traditional	27.3
Mu 2011[33]	China, Rural	50	PMR	Phenobarbital Dose: 30–60 mg.	47.2
				Phenobarbital Dose: 90–180 mg.	44.3
				Phenobarbital Dose: 210–240 mg.	8.5
Nicoletti 2009[34]	Bolivia-Rural		PMR	Treatment in past year	20
				No treatment in past year	80
				Treatment in last month	20
				No treatment in last month	80

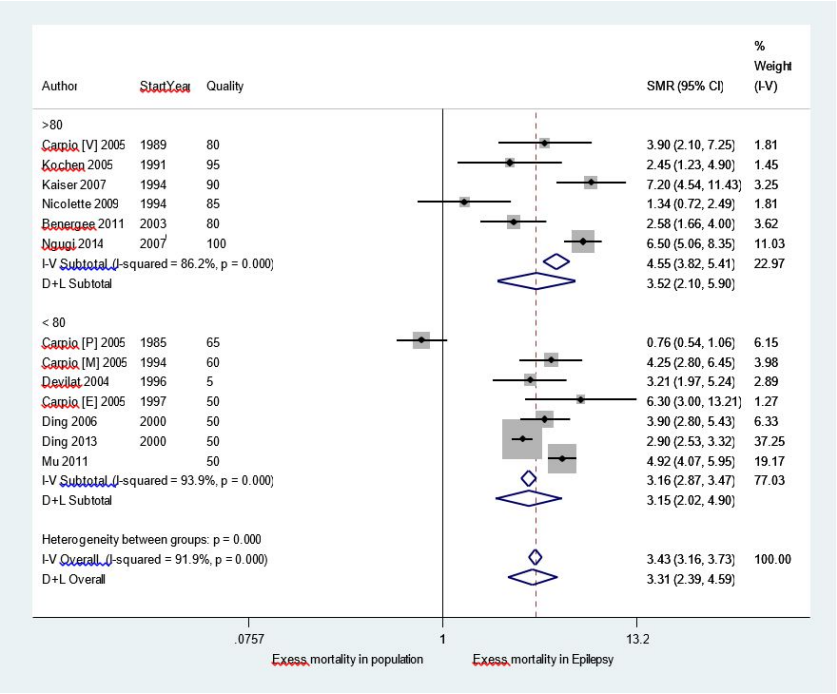
Key: AED-Antiepileptic drug, MR-Mortality rate, SMR-Standardized mortality ratio, PMR-Proportionate mortality ratio

Supporting Figure 1: **SMR and PMR of epilepsy by sex**



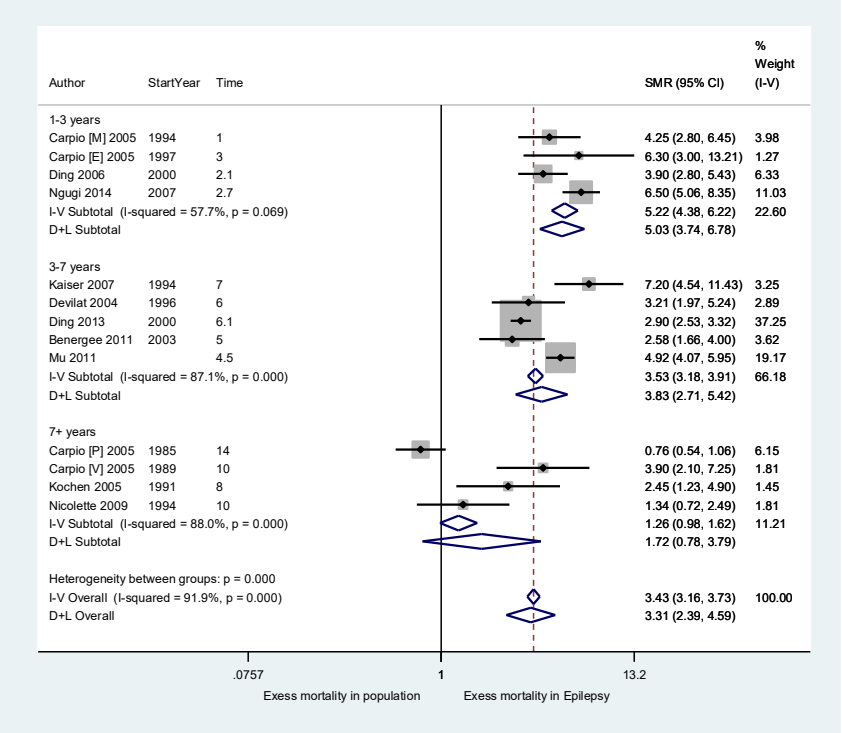
Note: P=Parsis, V=Vusai

Supporting Figure 2: Forest plot of excess mortality in epilepsy by quality of studies



Key: CI-Confidence interval, V-Vusai, P-Parsis, M-Mali, E-Ecuador

Supporting Figure 3: Forest plot of excess mortality in epilepsy by duration of cohort follow-up



Key: CI-Confidence interval, V-Vusai, P-Parsis, M-Mali, E-Ecuador