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The primary prevention of epilepsy: A report of the Prevention Task Force of the International League Against Epilepsy

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Summary

Among the causes of epilepsy are several that are currently preventable. In this review, we summarize the public health burden of epilepsy arising from such causes and suggest priorities for primary epilepsy prevention. We conducted a systematic review of published epidemiologic studies of epilepsy of 4 preventable etiologic categories—perinatal insults, traumatic brain injury (TBI), central nervous system (CNS) infection, and stroke. Applying consistent criteria, we assessed the quality of each study and extracted data on measures of risk from those with adequate quality ratings, summarizing findings across studies as medians and interquartile ranges. Among

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Disclosures

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higher-quality population-based studies, the median prevalence of active epilepsy across all ages was 11.1 per 1000 population in lower- and middle-income countries (LMIC) and 7.0 per 1000 in high-income countries (HIC). Perinatal brain insults were the largest attributable fraction of preventable etiologies in children, with median estimated fractions of 17% in LMIC and 15% in HIC. Stroke was the most common preventable etiology among older adults with epilepsy, both in LMIC and in HIC, accounting for half or more of all new onset cases. TBI was the attributed cause in nearly 5% of epilepsy cases in HIC and LMIC. CNS infections were a more common attributed cause in LMIC, accounting for about 5% of all epilepsy cases. Among some rural LMIC communities, the median proportion of epilepsy cases attributable to endemic neurocysticercosis was 34%. A large proportion of the overall public health burden of epilepsy is attributable to preventable causes. The attributable fraction for perinatal causes, infections, TBI, and stroke in sum reaches nearly 25% in both LMIC and HIC. Public health interventions addressing maternal and child health care, immunizations, public sanitation, brain injury prevention, and stroke prevention have the potential to significantly reduce the burden of epilepsy.

Keywords

central nervous system infection; epidemiology; etiology; perinatal brain injury; prevalence; stroke; traumatic brain injury

1 Introduction

Estimates suggest that 50-70 million people worldwide have epilepsy,^{1,2} and 4.6 million develop the condition each year.³ These global burden estimates fall more heavily on populations of low- and middle-income countries (LMIC), where a pooled estimate of the annual incidence of epilepsy is considerably greater (139 per 100 000 population) than that for high income-countries (HIC; 49 per 100 000).³

Irrespective of country income, the public health burden of epilepsy carries with it high risks of disability, social isolation, economic loss, and premature mortality. The World Health Organization has therefore identified the condition as a priority, calling for the development of national health care plans of action for epilepsy management, not only to ensure the availability of effective care, but also to prevent its causes.⁴

Prevention may be considered in 3 stages. *Primary prevention* averts the occurrence of a disorder, usually by reducing or eliminating underlying causes and risk factors. *Secondary prevention* involves early detection or interventions to arrest or minimize the development of the condition. *Tertiary prevention* mitigates existing disease and its consequences through appropriate treatment and rehabilitation.⁵ Under this paradigm, most of the attention of the epilepsy community—researchers, care providers, patients, and advocates—has involved tertiary prevention: research on antiepileptic drugs and other treatments and the employment of these treatments in clinical care. Some limited epilepsy research has focused on secondary prevention: early treatment interventions, as well as attempts to identify agents that may interrupt epileptogenesis following brain insults such as traumatic brain injury (TBI).^{6,7} The importance of these efforts in tertiary and secondary prevention cannot be overstated. But the epilepsy community has given rather less attention to primary prevention:

the elimination (where possible) or reduction of underlying causes and risk factors of epilepsy.

The causes of epilepsy are manifold. The International League Against Epilepsy (ILAE) Commission on Classification and Terminology has defined causal categories broadly as structural, genetic, infectious, metabolic, immune, and unknown.⁸ Specific etiologies within these categories vary in their potential for primary prevention. Within the group of structural and infectious causes are specific etiologies—especially birth injuries, central nervous system (CNS) infections, traumatic brain injuries, and stroke—amenable to primary prevention. The first 3 of these specific etiologies may account in large measure for the higher incidence of epilepsy in LMIC compared to HIC.⁹

The purpose of this review is to summarize the public health burden of epilepsy arising from these specific causes and thereby to derive priorities for primary epilepsy prevention.

2 Materials and Methods

This systematic review addresses reports describing the burden of epilepsy from preventable causes, and employs methods recommended under Preferred Reporting Items for Systematic Reviews and Meta-Analyses.¹⁰ We searched the online publication databases of MEDLINE (Ovid), Embase, and PsycINFO for reports published since 1990, the year that the ILAE introduced a definition of epilepsy for epidemiological studies. Primary search terms included epilepsy, combined with cause, etiology, risk factor, or prevention, and also combined with epidemiology, incidence, prevalence, or population-based. Among the retrieved references, we required mention of terms and synonyms suggesting any brain trauma, stroke, infection, parasite, or pre- or perinatal insult listed among any of the key words, titles, and abstracts. Details of this search strategy are described in Table S1.

We screened the retrieved titles and abstracts to identify references representing original epidemiologic studies of populations or samples representative of people with epilepsy that addressed any of 4 preventable categories of epilepsy etiology—pre- or perinatal insults, TBI, CNS infection, or stroke—and indicated any measures of comparable risk (eg, relative proportions, attributable fractions, relative risk, odds ratios).

For references meeting these criteria, we retrieved full reports, each of which was evaluated independently by 2 reviewers who rated report quality on a scale of 1 (best) to 4 (worst) using a standard form that included the following criteria (Table S2):

- Sensitivity of epilepsy case-finding, if population-based;
- Accuracy of epilepsy diagnoses;
- Sensitivity or completeness of epilepsy cause determinations;
- Accuracy of epilepsy cause determination;
- Representativeness of study population, where best representativeness was indicated by population-based studies of incidence, followed by population-

based studies of prevalence, followed by referral clinic populations or special subpopulations of people with epilepsy.

Initially discordant quality ratings were resolved by consensus through correspondence between the reviewers.

We extracted data from reports rated 3 or better, including study population source descriptions, demographic data, attributed etiologic fractions, and comparative risk measures. Findings were summarized across studies as median and interquartile range (IQR).

In determining categories of epilepsy etiology used in our analysis, it was necessary for us to define these broadly and to accept inexact and variable terminologies—often not further defined—used in the reports we reviewed. Pre- and perinatal insults were indicated by general synonymous terms such as birth injury or complications during or following delivery. If studies listed numbers for multiple subcategories of pre- or perinatal etiologies treated as mutually exclusive (eg, fetal distress or asphyxia, prematurity, cerebral palsy, and neonatal infection), we summed these. TBI was indicated by nearly synonymous terms such as head injury or a history thereof. Few studies indicated a threshold of severity or other more precise criteria by which to define TBI (eg, loss of consciousness, hospitalization, or specific craniocerebral trauma). CNS infection was indicated by histories of meningitis or encephalitis, not necessarily specified by type of agent, whether bacterial, viral, parasitic, or fungal. If studies listed numbers of cases in these subcategories separately, we summed these. We identified no studies providing specific information on the distribution of specific bacterial or viral agents reported. When studies addressed specific parasitic agents such as *Taenia solium*, we treated these separately in our review. Finally, we assigned to the category of stroke cases described as such or with terms indicating cerebral infarction or hemorrhage, and if the latter categories were included in the same study, cases were summed.

3 Results

Our searches were conducted through October 2016 and yielded 1217 unduplicated references. Among these, after examining titles and abstracts, we found 294 articles eligible for full review. Of the latter, 99 contained relevant information and had quality ratings of “3” or better, including 53 that represented HIC and 46 that represented LMIC (Figure 1). Quality ratings and evidence obtained from these studies are listed in Table S3, and their full bibliographic references are listed in Table S4.

Among population-based studies rated “2” or better, the median estimated prevalence of active epilepsy for all ages was 11.1 per 1000 population (IQR = 7.8-16.8 per 1000) in LMIC,^{11–22} compared to 7.0 per 1000 (IQR = 6.6-8.1) in HIC.^{23–28} Applied to 2016 World Bank population estimates (6.2 billion in LMIC and 1.2 billion in HIC), this implies a public health burden of epilepsy affecting 68 million people in LMIC and 8.4 million in HIC.

3.1 Pre- and perinatal brain insults

Among children with epilepsy, pre- and perinatal brain insults were the largest attributable fraction of preventable etiologies, with median estimated fractions of 17.4% in LMIC and

14.8% in HIC (Table 1). Pre- and perinatal brain insults also were the largest fraction in LMIC populations of all ages or all adults (median = 11.4%). In 3 LMIC studies, odds ratios ranging from 3.0 to 5.9 indicate an increased risk of epilepsy in persons with a history of pre- and perinatal problems compared to those without (Table 2).^{29–31}

Most studies provided few details to define particular perinatal risk factors, with exceptions among some comparative studies (Table 2). Four studies of the risk of epilepsy in premature versus full-term infants yielded rate ratios of 1.9 and 4.1,^{32,33} and odds ratios of 1.6 and 2.0.^{34,35} Lower Apgar scores (<7) in infants 5 minutes after delivery also indicated higher risk of epilepsy, with reported rate ratios among 4 studies ranging from 4.3 to 5.6.^{32,33,36,37} Studies of epilepsy risk in children born to mothers with eclampsia yielded somewhat inconsistent results, with rate ratios of 14.2³³ and 1.4.³⁸ A study addressing neonatal infection found an increased risk with a rate ratio of 1.6.³³

3.2 Stroke

In HIC populations of all ages or all adults, stroke was the most common attributed preventable etiology, with a median estimated fraction of 11.9% (Table 1). Among older adults with epilepsy, both in LMIC and HIC, etiology was attributed to stroke in 19%–24% of prevalent cases^{39–41} and half or more of all new-onset cases.^{42,43}

The comparative risk of epilepsy among persons with and without diagnoses of stroke or cerebrovascular disease is indicated by odds ratios of 3.1 and 3.5^{44,45} as well as rate ratios of 2.3 and 9.3^{46,47} (Table 2).

3.3 TBI

Median estimates of the proportion of epilepsy attributable to TBI appeared somewhat higher in children in LMIC compared to HIC, 6.6% versus 2.6%, respectively. In contrast, corresponding median estimates for all-age or adult populations suggested slightly higher proportions in HIC compared to LMIC, 5.3% versus 4.2%, respectively (Table 1).

The risks of epilepsy or unprovoked seizures among persons with and without TBI diagnoses are compared in studies showing a rate ratio of 3.1⁴⁸ and odds ratios of 9.2,²⁹ 1.6,³¹ and 2.1⁴⁵ (Table 2).

3.4 CNS infections

In LMIC, the median estimates of the proportion of epilepsy attributable to CNS infections (sometimes further defined as meningitis and encephalitis) were about 5% both in children and across all ages. The corresponding median estimates appeared somewhat lower in studies of HIC: 3.8% of children and 2.4% of all ages (Table 1). An increased risk of epilepsy in persons with a history of CNS infection compared to persons without such history is indicated by odds ratios of 2.6 and 5.1 (Table 2).^{29,30}

3.5 CNS parasitosis

Some studies in rural communities of LMIC with endemic cysticercosis separately reported fractions of epilepsy cases attributable to neurocysticercosis (NCC), yielding a median

estimate of 34.4% (Table 1). Odds ratios comparing risks of epilepsy in persons seropositive and seronegative for *T. solium* antibodies were 2.0⁹ and 2.8⁴⁹ (Table 2).

Two studies compared risks of epilepsy in persons with and without evidence of cerebral malaria, reporting odds ratios for malaria hospitalization as 2.3⁹ and for cerebral malaria diagnosis as 4.4 and 3.4 (Table 2).^{50,51} The risk of epilepsy associated with onchocerciasis was assessed in a study examining *Onchocerca volvulus* antibody seropositivity (odds ratio = 2.2)⁹ and a study comparing endemic and nonendemic localities (rate ratio = 2.9).⁵²

4 Discussion

A large proportion of the overall public health burden of epilepsy may be ascribed to preventable causes. Among populations of children, the sums of median estimated fractions we found attributable to pre- and perinatal insults, infections, and TBI are 29% in LMIC and 21% in HIC. Among all-age or adult populations, the corresponding sums for pre- or perinatal insults, infections, TBI, and stroke reach nearly 24% in LMIC and 25% in HIC. These estimates are imprecise. As noted below, we believe they may undercount some etiologic fractions, especially among LMIC, where the overall incidence of epilepsy is greatest.³ Nevertheless, the burden of epilepsy here ascribed to preventable causes provides evidence of the substantial potential value of primary prevention programs.

Foremost among the attributed causes of epilepsy are pre- and perinatal brain insults. In principle, public health programs to ensure adequate prenatal and intrapartum care could prevent a substantial proportion of epilepsy arising from these causes. Some disparities in access to prenatal care persist even in HIC, indicating needs for program improvement.^{53,54} However, the unmet need for such programs is greatest in LMIC, where >80% of the world population resides and where there are marked inequalities in the distribution of health care resources within and among countries.^{53,55} Consequences are illustrated by estimates that in 2010 the incidence of neonatal encephalopathy was 14.9 per 1000 live births in sub-Saharan Africa, and 10.4 per 1000 in South Asia, compared to 1.5 per 1000 in HIC.⁵⁶ Few studies estimate the population attributable fraction (PAF) of perinatal problems associated with epilepsy. One study across 5 countries in sub-Saharan Africa estimated that the PAF of antenatal and perinatal problems for active convulsive epilepsy in children was 0.33 (95% confidence interval [CI] = 0.21-0.43), whereas that in adults was 0.06 (95% CI = 0.04-0.08).⁹

CNS infections, particularly malaria, NCC, meningitides, and encephalitides, are important causes of epilepsy. The burden is much greater in LMIC, according to the estimates we derived, as well as other estimates of the global burden of disease, including disability-adjusted life years for CNS infections.⁵⁷ Prevention strategies may include improved health care infrastructure enabling early diagnosis and treatment, environmental change to reduce exposure, and immunizations. Immunization programs for vulnerable populations deserve special emphasis. There have been significant reductions in the global burden of meningitis and encephalitis from 1990 to 2015, probably due to increased vaccination against bacterial and viral diseases.⁵⁷

In some LMIC, nearly one-third of epilepsy cases have been ascribed to NCC. This high proportion should be interpreted with some caution, as most of these studies examined prevalent cases of epilepsy where temporal relationships between NCC infection and seizure onset could not be determined. Coupled with less availability of diagnostic tools to detect other causes of epilepsy in the communities studied, these limitations could result in the misclassification of some fraction of cases attributed to NCC.^{58,59} In any event, this is a highly prevalent cause in some communities and a highly preventable condition. There is potential for its full eradication through relatively simple measures involving collaboration of professionals in public health, sanitary engineering, and human and veterinary medicine. In a Honduras community, a public health intervention begun in 1997 to interrupt the transmission of *T. solium* included an education and media program, training pig farmers in animal husbandry, improved sewage disposal, deworming of school students with albendazole, and surveillance of *Taenia* in people's stool. The proportion of cases of epilepsy attributed to NCC was reduced from 37% among those diagnosed before the intervention to 14% among those diagnosed following the intervention ($P = .02$).⁶⁰ More recently a study in Peru has demonstrated a significant reduction in *Taenia* cysts in pigs, but there has been insufficient time to demonstrate a reduction in epilepsy.⁶¹ In Africa, community-directed ivermectin programs have significantly reduced transmission of *O. volvulus* by black flies,⁶² but none has examined the impact on epilepsy incidence or prevalence. There has been a significant reduction in malaria with the introduction of insecticide-treated bed nets and antimalarial agents that prevent transmission, with a 57% reduction in childhood mortality in sub-Saharan Africa.⁶³ These studies demonstrate that existing public health interventions can reduce parasitic risk factors of epilepsy, and thus its occurrence. They warrant high priority among health ministries and other public health agencies.

TBI likewise represents a substantial fraction of preventable epilepsy, and again the burden appears higher in LMIC, at least in children. Other reviews have indicated that TBI incidence, irrespective of subsequent epilepsy development, is substantially higher in LMIC and most commonly due to road traffic injuries or falls.^{64,65} Among the many adverse consequences of TBI, including death and disability, the consequence of epilepsy adds additional weight to arguments for enhanced prevention strategies and programs. Multifaceted programs to improve vehicle and traffic safety have effected major reductions in rates of injury in HIC, and there is a critical need to adapt and implement such measures in LMIC.⁶⁶ Likewise, there is need for further development and implementation of fall prevention programs that address specific risks highest in young children, older adults, and particular occupations.^{67,68}

Finally, an appreciable fraction of preventable epilepsy may be attributable to stroke. Our analysis points to a comparatively greater burden in HIC, likely due at least in part to the larger proportion of older adults in HIC populations. Other analysis indicates that the burden of stroke is substantially increasing in LMIC.⁶⁹ Primary prevention programs addressing cardiovascular risk factors—smoking, hypertension, hyperlipidemias, and metabolic syndromes—deserve further emphasis in HIC and, increasingly, in LMIC.⁷⁰ Secondary stroke prevention—improving access to early thrombolytic or reperfusion therapies of acute stroke and cerebral ischemia—likewise deserves increased emphasis as resources permit,

although studies of the effect of these procedures on later epilepsy occurrence have not yet been reported.

The increasing effectiveness and availability of some general secondary prevention interventions—especially early treatments to save lives among persons acutely ill with stroke, TBI, birth injuries, or CNS infection—could yield an increased number of survivors at risk of epilepsy. This paradoxical potential reinforces the urgency of efforts to promote primary preventions as described above, as well as efforts to develop specific secondary preventions that interrupt epileptogenesis.

There are limitations to the conclusions of this review. Etiologic categories were often imprecisely defined, not only the broad category of pre- or perinatal brain insults, but also TBI, CNS infections, and stroke. Again, these potential inconsistencies among applied definitions could limit the accuracy of summaries across studies.

Many of the studies we reviewed—especially older studies, as well as many throughout LMIC—had limited tools with which to investigate epilepsy etiologies in depth. This could have resulted in inaccurate etiologic fraction estimates for some causes. The majority of studies were conducted on prevalent epilepsy populations in which less etiologic information was available—either from clinical records or recall—for longer-duration epilepsy cases. Again, this may have led to misclassified etiologies and inaccurate estimates. More so in LMIC, we suspect these challenges in data collection may have yielded underestimations of the true burden of preventable etiologies.

The representativeness of the studies we reviewed deserves comment. Few studies could be considered nationally representative; most represented local communities or limited regions. For describing etiologic fractions, we considered mainly population-based studies, although some clinic populations were included when the reviewers judged that these included most people with epilepsy referred for diagnosis and treatment within communities. We encountered large variability in the reported measures of epilepsy occurrence and reported etiologic fractions and risk, even among studies grouped within HIC or LMIC. Although some variability may be attributed to differences in study design and methods, much is likely due to true differences in epilepsy occurrence and cause across different countries and communities. Furthermore, many studies were conducted in areas with a high incidence of the risk factor or putative cause, or high occurrence of epilepsy. Generalizations from the summary estimates we obtained should therefore be made with caution.

More research on preventable causes of epilepsy is needed, employing consistent definitions that describe these causes and important subcategories with more specificity. This applies especially in LMIC, where large regions of the world are still represented by few studies and where risks may vary greatly according to local health care infrastructure, economies, culture, and technology. The information gained from such studies can help to establish priorities for primary, secondary, and tertiary prevention programs within community health systems and prioritize primary prevention targets based on local needs and conditions: programs to improve prenatal, obstetrical, and infant care, reduce head injury risks, reduce CNS infection and parasitic risks, and reduce cardiovascular risks.

While acknowledging the limitations of published studies and the need for further research, the data we have reviewed clearly establish that a substantial proportion of epilepsy is potentially preventable. Therefore, the primary prevention of epilepsy warrants critical attention and action from the community of epilepsy care providers, researchers, advocates, and policymakers through ministries of health, and other public and private health organizations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Ngugi AK, Bottomley C, Kleinschmidt I, et al. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia*. 2010; 51:883–90. [PubMed: 20067507]
2. World Health Organization. Neurological disorders: public health challenges. Geneva, Switzerland: World Health Organization; 2006.
3. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology*. 2017; 88:296–303. [PubMed: 27986877]
4. World Health Organization Executive Board 136th Session. [cited 2018 Jan 13] Global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications. 2015. Available from <https://www.ilae.org/files/dmfile/WHO-Epilepsy-2015.pdf>
5. World Health Organization. [cited 2017 June 29] Health promotion glossary. 1998. Available from <http://www.who.int/healthpromotion/about/HPR%20Glossary%201998.pdf>
6. Mani R, Pollard J, Dichter MA. Human clinical trials in antiepileptogenesis. *Neurosci Lett*. 2011; 497:251–6. [PubMed: 21439351]
7. Thompson K, Pohlmann-Eden B, Campbell LA, et al. Pharmacological treatments for preventing epilepsy following traumatic head injury. *Cochrane Database Syst Rev*. 2015; (8):CD009900. [PubMed: 26259048]
8. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017; 58:512–21. [PubMed: 28276062]
9. Ngugi AK, Bottomley C, Kleinschmidt I, et al. Prevalence of active convulsive epilepsy in sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. *Lancet Neurol*. 2013; 12:253–63. [PubMed: 23375964]
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009; 151:264–9, W264. [PubMed: 19622511]
11. Cruz ME, Schantz PM, Cruz I, et al. Epilepsy and neurocysticercosis in an Andean community. *Int J Epidemiol*. 1999; 28:799–803. [PubMed: 10480714]
12. Del Brutto OH, Santibanez R, Idrovo L, et al. Epilepsy and neurocysticercosis in Atahualpa: a door-to-door survey in rural coastal Ecuador. *Epilepsia*. 2005; 46:583–7. [PubMed: 15816956]
13. Goel D, Dhanai JS, Agarwal A, et al. Neurocysticercosis and its impact on crude prevalence rate of epilepsy in an Indian community. *Neurol India*. 2011; 59:37–40. [PubMed: 21339656]
14. Guekht A, Hauser WA, Milchakova L, et al. The epidemiology of epilepsy in the Russian Federation. *Epilepsy Res*. 2010; 92:209–18. [PubMed: 21035312]
15. Khedr EM, Shawky OA, Ahmed MA, et al. A community based epidemiological study of epilepsy in Assiut Governorate/Egypt. *Epilepsy Res*. 2013; 103:294–302. [PubMed: 22948127]
16. Ma GY, Li ZQ, Lu S, et al. Survey of etiological factors of epilepsy in Mudanjiang rural population by randomly cluster sampling. *Chin J Clin Rehab*. 2004; 8:3178–9.
17. Matuja WB, Kilonzo G, Mbena P, et al. Risk factors for epilepsy in a rural area in Tanzania. A community-based case-control study. *Neuroepidemiology*. 2001; 20:242–7. [PubMed: 11684900]

18. Medina MT, Duron RM, Martinez L, et al. Prevalence, incidence, and etiology of epilepsies in rural Honduras: the Salama Study. *Epilepsia*. 2005; 46:124–31. [PubMed: 15660778]
19. Moyano LM, Saito M, Montano SM, et al. Neurocysticercosis as a cause of epilepsy and seizures in two community-based studies in a cysticercosis-endemic region in Peru. *PLoS Negl Trop Dis*. 2014; 8:e2692. [PubMed: 24551255]
20. Mwape KE, Blocher J, Wiefek J, et al. Prevalence of neurocysticercosis in people with epilepsy in the eastern province of Zambia. *PLoS Negl Trop Dis*. 2015; 9:e0003972. [PubMed: 26285031]
21. Njamnshi AK, Sini V, Djientcheu VDP, et al. Risk factors associated with epilepsy in a rural area in Cameroon: a preliminary study. *Afr J Neurol Sci*. 2007; 26:18–26.
22. Rajshekhar V, Raghava MV, Prabhakaran V, et al. Active epilepsy as an index of burden of neurocysticercosis in Vellore district, India. *Neurology*. 2006; 67:2135–9. [PubMed: 17190933]
23. Ablah E, Hesdorffer DC, Liu Y, et al. Prevalence of epilepsy in rural Kansas. *Epilepsy Res*. 2014; 108:792–801. [PubMed: 24613507]
24. Fernandez-Suarez E, Villa-Estebanez R, Garcia-Martinez A, et al. Prevalence, type of epilepsy and use of antiepileptic drugs in primary care. *Rev Neurol*. 2015; 60:535–42. [PubMed: 26062825]
25. Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. *Epilepsia*. 1991; 32:429–45. [PubMed: 1868801]
26. Josipovic-Jelic Z, Sonicki Z, Soljan I, et al. Prevalence and socioeconomic aspects of epilepsy in the Croatian county of Sibenik–Knin: community-based survey. *Epilepsy Behav*. 2011; 20:686–90. [PubMed: 21402499]
27. Syvertsen M, Nakken KO, Edland A, et al. Prevalence and etiology of epilepsy in a Norwegian county—a population based study. *Epilepsia*. 2015; 56:699–706. [PubMed: 25810072]
28. Wright J, Pickard N, Whitfield A, et al. A population-based study of the prevalence, clinical characteristics and effect of ethnicity in epilepsy. *Seizure*. 2000; 9:309–13. [PubMed: 10933984]
29. Cansu A, Serdaroglu A, Yuksel D, et al. Prevalence of some risk factors in children with epilepsy compared to their controls. *Seizure*. 2007; 16:338–44. [PubMed: 17391991]
30. Kanno S, Unnikrishnan JP, Santhosh Kumar T, et al. Risk factors for epilepsy: a population-based case–control study in Kerala, southern India. *Epilepsy Behav*. 2009; 16:58–63. [PubMed: 19660989]
31. Wagner RG, Ngugi AK, Twine R, et al. Prevalence and risk factors for active convulsive epilepsy in rural northeast South Africa. *Epilepsy Res*. 2014; 108:782–91. [PubMed: 24582322]
32. Vestergaard M, Pedersen CB, Sidenius P, et al. The long-term risk of epilepsy after febrile seizures in susceptible subgroups. *Am J Epidemiol*. 2007; 165:911–8. [PubMed: 17267419]
33. Whitehead E, Dodds L, Joseph KS, et al. Relation of pregnancy and neonatal factors to subsequent development of childhood epilepsy: a population-based cohort study. *Pediatrics*. 2006; 117:1298–306. [PubMed: 16585327]
34. Hesdorffer DC, Ludvigsson P, Olafsson E, et al. ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. *Arch Gen Psychiatry*. 2004; 61:731–6. [PubMed: 15237085]
35. Murphy DJ, Libby G, Chien P, et al. Cohort study of forceps delivery and the risk of epilepsy in adulthood. *Am J Obstet Gynecol*. 2004; 191:392–7. [PubMed: 15343212]
36. Ehrenstein V, Sorensen HT, Pedersen L, et al. Apgar score and hospitalization for epilepsy in childhood: a registry-based cohort study. *BMC Public Health*. 2006; 6:23. [PubMed: 16451724]
37. Sun Y, Vestergaard M, Pedersen CB, et al. Apgar scores and long-term risk of epilepsy. *Epidemiology*. 2006; 17:296–301. [PubMed: 16570027]
38. Wu CS, Sun Y, Vestergaard M, et al. Preeclampsia and risk for epilepsy in offspring. *Pediatrics*. 2008; 122:1072–8. [PubMed: 18977989]
39. Hussain SA, Haut SR, Lipton RB, et al. Incidence of epilepsy in a racially diverse, community-dwelling, elderly cohort: results from the Einstein aging study. *Epilepsy Res*. 2006; 71:195–205. [PubMed: 16870396]
40. Su CL, Chang SF, Chen ZY, et al. Neuroepidemiological survey in Ilan, Taiwan (NESIT): (4) Prevalence of epilepsy. *Acta Neurol Taiwan*. 1998; 7:75–84.

41. Tabatabaei SS, Delbari A, Salman-Roghani R, et al. Seizures and epilepsy in elderly patients of an urban area of Iran: clinical manifestation, differential diagnosis, etiology, and epilepsy subtypes. *Neurol Sci.* 2013; 34:1441–6. [PubMed: 23232961]
42. Martin RC, Faught E, Richman J, et al. Psychiatric and neurologic risk factors for incident cases of new-onset epilepsy in older adults: data from U.S. Medicare beneficiaries. *Epilepsia.* 2014; 55:1120–7. [PubMed: 24902475]
43. Tchalla AE, Marin B, Mignard C, et al. Newly diagnosed epileptic seizures: focus on an elderly population on the French island of Reunion in the Southern Indian Ocean. *Epilepsia.* 2011; 52:2203–8. [PubMed: 22091708]
44. Li X, Breteler MM, de Bruyne MC, et al. Vascular determinants of epilepsy: the Rotterdam Study. *Epilepsia.* 1997; 38:1216–20. [PubMed: 9579923]
45. Pugh MJ, Knoefel JE, Mortensen EM, et al. New-onset epilepsy risk factors in older veterans. *J Am Geriatr Soc.* 2009; 57:237–42. [PubMed: 19207140]
46. Chung TT, Lin CY, Huang WY, et al. Risks of subsequent epilepsy among patients with hypertensive encephalopathy: a nation-wide population-based study. *Epilepsy Behav.* 2013; 29:374–8. [PubMed: 24090775]
47. Imfeld P, Bodmer M, Schuerch M, et al. Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. *Epilepsia.* 2013; 54:700–7. [PubMed: 23215680]
48. Annegers JF, Coan SP. The risks of epilepsy after traumatic brain injury. *Seizure.* 2000; 9:453–7. [PubMed: 11034867]
49. Singh G, Bawa J, Chinna D, et al. Association between epilepsy and cysticercosis and toxocariasis: a population-based case-control study in a slum in India. *Epilepsia.* 2012; 53:2203–8. [PubMed: 23106145]
50. Carter JA, Neville BGR, White S, et al. Increased prevalence of epilepsy associated with severe falciparum malaria in children. *Epilepsia.* 2004; 45:978–81. [PubMed: 15270766]
51. Ngoungou EB, Koko J, Druet-Cabanac M, et al. Cerebral malaria and sequelar epilepsy: first matched case-control study in Gabon. *Epilepsia.* 2006; 47:2147–53. [PubMed: 17201716]
52. Kaiser C, Asaba G, Leichenring M, et al. High incidence of epilepsy related to onchocerciasis in West Uganda. *Epilepsy Res.* 1998; 30:247–51. [PubMed: 9657652]
53. Moller A-B, Petzold M, Chou D, et al. Early antenatal care visit: a systematic analysis of regional and global levels and trends of coverage from 1990 to 2013. *Lancet Glob Health.* 2017; 5:e977–83. [PubMed: 28911763]
54. Ruwe M, Capitman J, Bengiamin M, et al. A systematic review and meta-analysis of racial disparities in prenatal care in California: how much? Does insurance matter? *Soc Work Public Health.* 2010; 25:550–71. [PubMed: 21058214]
55. Mahendran M, Speechley KN, Widjaja E. Systematic review of unmet healthcare needs in patients with epilepsy. *Epilepsy Behav.* 2017; 75:102–9. [PubMed: 28843210]
56. Lee AC, Kozuki N, Blencowe H, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. *Pediatr Res.* 2013; 74(suppl 1):50–72. [PubMed: 24366463]
57. Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.* 2017; 16:877–97. [PubMed: 28931491]
58. Carpio A, Escobar A, Hauser WA. Cysticercosis and epilepsy: a critical review. *Epilepsia.* 1998; 39:1025–40. [PubMed: 9776322]
59. Tellez-Zenteno JF, Hernandez-Ronquillo L. Epidemiology of neurocysticercosis and epilepsy, is everything described? *Epilepsy Behav.* 2017; 16:30770–3.
60. Medina MT, Aguilar-Estrada RL, Alvarez A, et al. Reduction in rate of epilepsy from neurocysticercosis by community interventions: the Salama, Honduras study. *Epilepsia.* 2011; 52:1177–85. [PubMed: 21275975]
61. Garcia HH, Gonzalez AE, Tsang VC, et al. Elimination of *Taenia solium* transmission in northern Peru. *N Engl J Med.* 2016; 374:2335–44. [PubMed: 27305193]

62. Tekle AH, Zoure HG, Noma M, et al. Progress towards onchocerciasis elimination in the participating countries of the African Programme for Onchocerciasis Control: epidemiological evaluation results. *Infect Dis Poverty*. 2016; 5:66. [PubMed: 27349645]
63. Gething PW, Casey DC, Weiss DJ, et al. Mapping *Plasmodium falciparum* mortality in Africa between 1990 and 2015. *N Engl J Med*. 2016; 375:2435–45. [PubMed: 27723434]
64. Hyder AA, Wunderlich CA, Puvanachandra P, et al. The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation*. 2007; 22:341–53. [PubMed: 18162698]
65. Thurman, DJ, Coronado, V, Selassie, A. The epidemiology of TBI implications for public health. *Brain injury medicine: principles and practice*. Zasler, ND, Katz, DI, Zafonte, RD, editors. New York, NY: Demos Medical Publishing; 2007. 45–55.
66. Staton C, Vissoci J, Gong E, et al. Road traffic injury prevention initiatives: a systematic review and metasummary of effectiveness in low and middle income countries. *PLoS ONE*. 2016; 11:e0144971. [PubMed: 26735918]
67. WHO global report on falls prevention in older age. Geneva, Switzerland: World Health Organization; 2007.
68. World report on child injury prevention. Geneva, Switzerland: World Health Organization; 2008.
69. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health*. 2013; 1:e259–81. [PubMed: 25104492]
70. Norrving B, Davis SM, Feigin VL, et al. Stroke prevention worldwide—what could make it work? *Neuroepidemiology*. 2015; 45:215–20. [PubMed: 26505459]
71. Ehrenstein V, Pedersen L, Holsteen V, et al. Postterm delivery and risk for epilepsy in childhood. *Pediatrics*. 2007; 119:e554–61. [PubMed: 17332175]

Key Points

- We investigated 4 preventable etiologic categories—pre- or perinatal insults, stroke, traumatic brain injury, and central nervous system infections—that account for about one-fourth of all epilepsy cases
- The burden of preventable epilepsy appears higher in low- and middle-income countries
- Public health interventions addressing maternal and child health care, immunizations, public sanitation, brain injury prevention, and stroke prevention have the potential to significantly reduce the burden of epilepsy

Figure 1. Flowchart of literature search and inclusion process

Table 1
Percentage attributed etiologies in populations of people with epilepsy by country income

Etiologic category											
Pre-/perinatal		CNS infection		TBI		Stroke		NCC			
Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n		
Children											
HIC	14.8 (9.1-19.4)	13	3.8 (2.7-6.1)	12	2.6 (1.4-3.4)	9	0.5 (0.4-5.2)	3	—		
LMIC	17.4 (14.7-18.9)	6	5.3 (4.7-6.0)	5	6.6 (6.1-7.4)	4	—		—		
All ages or mainly adults											
HIC	5.4 (4.4-6.2)	9	2.4 (1.6-3.4)	17	5.3 (4.6-8.9)	22	11.9 (7.8-16.3)	22	—		
LMIC	11.4 (7.8-15.4)	13	5.2 (2.8-9.7)	13	4.2 (3.3-7.0)	17	2.7 (2.1-5.2)	12	34.4 (20.1-38.0)	14	

Details and estimates of individual studies are summarized in Table S3. Bibliographic citations for these studies are included in Table S4. CNS, central nervous system; HIC, high-income countries; IQR, interquartile range; LMIC, low- and middle-income countries; n, number of studies providing estimates; NCC, neurocysticercosis; TBI, traumatic brain injury.

Table 2
Comparative risks of epilepsy by preventable cause

Author	Rating	Locality	n	Age, y	Risk factor	Metric	Finding (95% CI)
Pre- or perinatal insults—general							
Cansu 2007 ²⁹	3	Ankara, Turkey	805	<17	Pre-/perinatal insult	OR _{adj}	4.2 (2.7-6.5)
Kannoth 2009 ³⁰	1	Kerala, India	362	All	Pre-/perinatal insult	OR	3.02 (1.99-4.59)
Wagner 2014 ³¹	3	Agincourt, South Africa	292	All	Pre-/perinatal insult	OR	5.93 (1.18-24.58)
Pre- or perinatal insults—specific							
Ehrenstein 2006 ^{36,a}	2	North Jutland, Denmark	815	<13	Apgar < 7	RR	4.9 (2.0-12.3)
Sun 2006 ^{37,a}	2	Denmark	16 455	<24	Apgar < 7	IRR	4.26 (3.88-4.67)
Vestergaard 2007 ^{32,b}	2	Denmark	16 481	<26	Apgar < 7	IRR	4.54 (4.12-5.01)
Whitehead 2006 ³³	1	Nova Scotia, Canada	648	<16	Apgar < 7	RR	5.6 (4.0-7.7)
Hesdorffer 2004 ^{34,c}	1	Iceland	109	<16	Prematurity	OR	1.59 (0.58-4.40)
Murphy 2004 ^{35,a,d}	2	Dundee, UK	603	<54	Prematurity	OR _{adj}	1.95 (1.19-3.19)
Vestergaard 2007 ³²	2	Denmark	16 481	<26	Premature, <37 wk	IRR	1.94 (1.84-2.05)
Whitehead 2006 ³³	1	Nova Scotia, Canada	648	<16	Premature, <34 wk	RR	4.1 (2.9-5.9)
Vestergaard 2007 ^{32,a,d}	2	Denmark	16 481	<26	Birth weight < 2500 g	IRR	2.05 (1.95-2.16)
Ehrenstein 2007 ⁷¹	3	Denmark	657	<13	Gestation 43 wk	IRR	2.0 (1.2-3.5)
Whitehead 2006 ³³	1	Nova Scotia, Canada	648	<16	Eclampsia	RR _{adj}	14.2 (3.5-57.3)
Wu 2008 ³⁸	2	Denmark	20 260	<28	Eclampsia	IRR	1.35 (0.81-2.24)
CNS infection—general							
Cansu 2007 ²⁹	3	Ankara, Turkey	805	<17	CNS infection	OR _{adj}	2.6 (1.0-6.7)
Kannoth 2009 ³⁰	1	Kerala, India	362	All	CNS infection	OR	5.06 (0.59-43.49)
Neurocysticercosis							
Ngugi 2013 ⁹	2	Kenya, South Africa, Uganda, Tanzania, Ghana	1711	All	<i>T. solium</i> seropositivity	OR	1.98 (0.72-5.43)
Singh 2012 ⁴⁹	3	Punjab, India	106	All	<i>T. solium</i> seropositivity	OR	2.8 (1.2-6.8)
Onchocerciasis							
Kaiser 1998 ⁵²	2	West Uganda	40	All	Onchocerciasis endemicity	RR	2.9
Ngugi 2013 ⁹	2	Kenya, South Africa, Uganda, Tanzania, Ghana	1711	All	<i>O. volvulus</i> seropositivity	OR	2.23 (1.56-3.19)
Malaria							
Carter 2004 ⁵⁰	3	Kilifi, Kenya	36	9-Jun	Malaria, cerebral	OR	4.4 (1.4-13.7)
Ngugi 2013 ⁹	2	Kenya, South Africa, Uganda, Tanzania, Ghana	1711	All	Malaria hospitalization	OR	2.28 (1.06-4.92)

Author	Rating	Locality	n	Age, y	Risk factor	Metric	Finding (95% CI)
Ngoungou 2006 ⁵¹	3	Libreville, Gabon	296	<26	Malaria, cerebral	OR	3.4 (1.6-7.4)
TBI							
Annegers & Coan 2000 ^{48, e}	1	Minnesota, USA	75	All	TBI	RR	3.1 (2.5-3.8)
Pugh 2009 ^{45, f}	3	USA	1843	>66	TBI	OR	2.11 (1.41-3.14)
Cansu 2007 ²⁹	3	Ankara, Turkey	805	<17	TBI	OR _{adj}	9.2 (4.5-2420.7)
Wagner 2014 ³¹	3	Agincourt, South Africa	292	All	TBI	OR	1.57 (0.82-2.99)
Stroke and cerebrovascular disease							
Li 1997 ⁴⁴	2	Rotterdam, The Netherlands	104	>55	Stroke	OR	3.1 (0.9-10.6)
Pugh 2009 ^{45, f}	3	USA	1843	>66	Cerebrovascular disease	OR	3.50 (3.13-3.91)
Chung 2013 ^{46, g}	3	Taiwan	473	>20	Hypertensive encephalopathy	RR	2.26
Imfeld 2013 ^{47, h}	3	UK	55	>65	Vascular dementia	IRR	9.3 (5.3-16.5)

adj, adjusted; CI, confidence interval; CNS, central nervous system; IRR, incidence rate ratio; n, number of study participants with epilepsy; OR, odds ratio; RR, rate ratio; TBI, traumatic brain injury.

^aBirth cohort.

^bSame database as Sun 2006³⁸; estimate was calculated from report data by reviewer.

^cUnprovoked seizures.

^dEstimate was calculated from report data by reviewer.

^eCohort of TBI patients.

^fCohort of military veterans.

^gCohort of patients with hypertensive encephalopathy.

^hCohort of patients with dementia.