



## Perspective

## Addressing the burden of epilepsy: Many unmet needs



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## ABSTRACT

Epilepsy is a heterogeneous clinical condition characterized by recurrent unprovoked seizures, their causes and complications. The incidence, prevalence and mortality of epilepsy vary with age, place and time contributing to a variable extent to the burden of the disease. Diagnostic misclassification may have strong impact on personal and societal reflections of the disease in light of its clinical manifestations and the need for chronic treatment. Epilepsy accounts for a significant proportion of the world's disease burden ranking fourth after tension-type headache, migraine and Alzheimer disease. Among neurological diseases, it accounts for the highest disability-adjusted life year rates both in men and in women. Although epilepsy is self-remitting in up to 50% of cases, variable long-term prognostic patterns can be identified based on the response to the available treatments. Epilepsy carries an overall increased risk of premature mortality with variable estimates across countries. Premature mortality predominates in patients aged less than 50 years, with epilepsies due to structural/metabolic conditions, with generalized tonic-clonic seizures, and seizures not remitting under treatment. Among deaths directly attributable to epilepsy or seizures, included are sudden unexpected death in epilepsy (SUDEP), status epilepticus, accidents, drowning, unintentional injuries, and suicide. Somatic and psychiatric disorders prevail in patients with epilepsy than in people without epilepsy. Asthma, migraine and cerebral tumors tend to occur more frequently in younger adults while cardiovascular disorders, stroke, dementia and meningioma predominate in the elderly. As being a fairly common clinical condition affecting all ages and requiring long-term (sometimes lifelong) treatment, epilepsy carries high health care costs for the society. Direct costs peak in the first year after diagnosis and then vary according to the severity of the disease, the response to treatment, and the presence of comorbidity. Although in several countries the costs of epilepsy are met by the national health systems, out-of-pocket costs may be a relevant fraction of the overall costs, especially in countries where the public management of health care is suboptimal or non-existent. Epilepsy strongly affects patients' independence, psychological health and emotional adjustment. Epilepsy impairs all aspects of health-related quality of life. Awareness and attitudes of the public about epilepsy may significantly affect the burden of the disease. All these factors add to the burden of the disease. However, many of the factors implicated in the onset of epilepsy, its course and treatment can be favorably addressed with appropriate strategic plans. More research is needed to investigate and manage the medical and psychosocial implications of epilepsy.

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## 1. Introduction

Epilepsy is a highly heterogeneous clinical condition characterized by recurrent unprovoked seizures with their causes and biological, psychological and social complications. All these factors add to the burden of the disease and represent a relevant source of needs for patients, caregivers and caring physicians, and have a heavy economic impact at the societal level. The incidence, prevalence and mortality of epilepsy vary with age, place and time contributing to the variability of the burden of the disease.

The observed differences can be explained by diagnostic misclassification, the population's and patient's genetic background, the distribution of some environmental risk factors, the socio-cultural context, the access to treatments and, not least, the definitions used for the diagnosis of the disease.

## 2. Definitions of seizures and epilepsy

One of the problems with the burden of epilepsy is represented by misdiagnosis. Diagnostic misclassification is one possible explanation for the inconsistencies between incidence and lifetime prevalence of epilepsy when comparing developed and developing countries [1]. The absence of diagnostic aids (laboratory tests, EEG and imaging studies) in developing countries may result in

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**Table 1**  
Age-standardized and absolute DALYs for epilepsy and proportion of DALYs attributable to epilepsy.

Variable	Value
Age-standardized DALYs (per 100,000), 1990, men	261.6
Age-standardized DALYs (per 100,000), 1990, women	226.0
Age-standardized DALYs (per 100,000), 2010, men	269.3
Age-standardized DALYs (per 100,000), 2010, women	232.9
Absolute DALYs	17,400,000
Proportion of total (all cause) DALYs (%)	0.7
Proportion of mental, neurological, and substance use DALYs (%)	6.8

Source: Whiteford et al. [8].  
DALYs, disability-adjusted life years.

erroneously classifying as epileptic seizures psychogenic non-epileptic seizures (PNES) and other paroxysmal events. Even in countries where the diagnostic resources are fully available, misdiagnosis is not uncommon. Interrater reliability for the diagnosis of PNES by video-EEG monitoring is only moderate [2]. Misclassification may also refer to seizure type. Acute symptomatic seizures, defined as clinical seizures occurring at the time of a systemic insult or in close temporal association with a documented brain insult [3], are sometimes included in epidemiological studies, leading to the increase of all epidemiological indexes, and inevitably lead to overtreatment and to avoidable negative attitudes and stigma. The burden of epilepsy may also vary depending on the inclusion of single unprovoked seizures. Although the International League Against Epilepsy (ILAE) has recently included single unprovoked seizures in the definition of epilepsy [4,5], the risk of recurrence of a single unprovoked seizure is significantly lower than the risk of recurrence of a second seizure [6,7].

### 2.1. Epilepsy as part of the global burden of disease

Historically, health policy has been informed by mortality statistics. Although premature mortality has been an important source for the understanding of clinical conditions leading to premature mortality, only recently the focus on the burden of diseases has been moved to chronic disabling disorders. Epilepsy is one such disease. Chronic neurological disorders, including epilepsy, account for a significant proportion of the world's disease burden [8].

The Global Burden of Disease Study is a comprehensive analysis of the burden of 291 diseases and injuries and 67 risk factors in 187 countries and 21 world regions comparing the years 1990, 2005 and 2010 [9]. In this comprehensive review, burden estimates were obtained from all available epidemiological data using published reports and statistical methods to model the epidemiological data when unavailable, to quantify disability, and to adjust for comorbidities. The burden of disease was measured by disability-adjusted life years (DALYs), a health metric capturing the years lived with disability (LDs), the non-fatal component, and the years of life lost (YLLs) due to premature mortality. Mental, neurological and substance use disorders were the fifth cause of DALYs and the leading cause of YLDs [10]. Neurological disorders accounted for 3% of DALYs and 5.6% of YLDs [11].

As with other diseases, disability weights were calculated for epilepsy based on the availability of treatments and the presence of seizures [8]. With reference to published reports and modeling, a total of 28,300,000 prevalent cases are expected to live with epilepsy in the entire world. The disease ranks fourth after tension-type headache (1,432,500,000), migraine (1,014,000), and Alzheimer disease (43,000,000). The DALYs attributable to epilepsy are illustrated in Table 1. Among neurological diseases, epilepsy accounts for the highest age-standardized DALY rates both in men and in women, followed by migraine and Alzheimer disease. The disease accounts for 0.7% of total DALYs and for 6.8% of DALYs due

mental, neurological and substance use disorders. A 16% increase of DALYs has been observed both in men and in women when comparing the years 1990 and 2010 (Table 1). This increase was largely due to changes in population growth and aging.

### 2.2. Prevalence of epilepsy

The prevalence of epilepsy varies substantially between developed and developing countries. In a systematic review and meta-analysis of published reports, the median lifetime prevalence for developed countries was 5.8 per 1000 compared to 15.4 per 1000 for rural and 10.3 per 1000 for urban studies in developing countries [12]. The median prevalence of active epilepsy, i.e. having experienced seizures in the previous five years and/or being treated, was 4.9 per 1000 for developed countries and 12.7 per 1000 and 5.9 per 1000 in rural and urban studies in developing countries. Along with sample size and age of study participants, poor health care and lack of specialized medical personnel and diagnostic equipment can explain the differences between developed and developing countries and between urban and rural areas. The higher lifetime prevalence of epilepsy in developing countries can be also due to higher incidence [13], which could in turn be attributable to traumatic brain injury (TBI) and infectious etiology, particularly in rural areas [14,15]. Rural areas of developing countries also have a large proportion of untreated patients possibly due to stigma, beliefs and attitudes towards epilepsy. Furthermore, recall of seizure events over a 5-year period may be poorer in rural areas due to low literacy levels and may lead to underestimation of prevalence [16].

### 2.3. Incidence of epilepsy

The estimated median worldwide incidence of epilepsy is 50.4 per 100,000 population per year [12]. However, significant differences can be found when comparing developing to developed countries (incidence, 81.7 vs. 45.0). The differences can be explained, at least in part, by the level of income in the country. The higher incidence of TBI, infections and infestations of the CNS in developing countries contribute to the increased incidence of the disease [14,15]. Familial clustering and differences in polymorphisms between developing and developed countries should be also considered [13].

The incidence of epilepsy varies with age with peaks in children under one year and predominantly in the elderly [17]. Annual incidence rates as high as 180 per 100,000 population in patients aged 85 years or older have been calculated [17]. The increase in the incidence of epilepsy with age is largely explained by the increased incidence of common clinical conditions in the elderly, like stroke and neurodegenerative disorders [18]. Silent strokes may also account for the occurrence of unprovoked seizures and epilepsy in this age group. Even acute symptomatic seizures predominate in the elderly [19], adding to the burden of the disease. Thus, with the increase of life expectancy, the number of individuals with epilepsy is going to increase in the future [18].

### 2.4. Prognosis and mortality of epilepsy

Epilepsy is a self-remitting clinical condition in up to 50% of cases [20]. Seizure remission is the main explanation for the difference between lifetime prevalence and incidence. However, when incidence and lifetime prevalence are compared in the same study, other factors need to be considered. These include premature mortality, socioeconomic factors, and stigma [1].

Epilepsy carries an overall increased risk of premature mortality. However, variable estimates have been provided across countries. The variability in such estimates can be attributed principally to

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