Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

GBD 2016 Epilepsy Collaborators*

Summary

Background Seizures and their consequences contribute to the burden of epilepsy because they can cause health loss (premature mortality and residual disability). Data on the burden of epilepsy are needed for health-care planning and resource allocation. The aim of this study was to quantify health loss due to epilepsy by age, sex, year, and location using data from the Global Burden of Diseases, Injuries, and Risk Factors Study.

Methods We assessed the burden of epilepsy in 195 countries and territories from 1990 to 2016. Burden was measured as deaths, prevalence, and disability-adjusted life-years (DALYs; a summary measure of health loss defined by the sum of years of life lost [YLLs] for premature mortality and years lived with disability), by age, sex, year, location, and Socio-demographic Index (SDI; a compound measure of income per capita, education, and fertility). Vital registrations and verbal autopsies provided information about deaths, and data on the prevalence and severity of epilepsy largely came from population representative surveys. All estimates were calculated with 95% uncertainty intervals (UIs).

Findings In 2016, there were 45·9 million (95% UI 39·9–54·6) patients with all-active epilepsy (both idiopathic and secondary epilepsy globally; age-standardised prevalence 621·5 per 100 000 population; 540·1–737·0). Of these patients, 24·0 million (20·4–27·7) had active idiopathic epilepsy (prevalence 326·7 per 100 000 population; 278·4–378·1). Prevalence of active epilepsy increased with age, with peaks at 5–9 years (374·8 [280·1–490·0]) and at older than 80 years of age (545·1 [444·2–652·0]). Age-standardised prevalence of active idiopathic epilepsy was 329·3 per 100 000 population (280·3–381·2) in men and 318·9 per 100 000 population (271·1–369·4) in women, and was similar among SDI quintiles. Global age-standardised mortality rates of idiopathic epilepsy were 1·74 per 100 000 population (1·64–1·87; 1·40 per 100 000 population [1·23–1·54] for women and 2·09 per 100 000 population [1·96–2·25] for men). Age-standardised DALYs were 182·6 per 100 000 population (149·0–223·5; 163·6 per 100 000 population [130·6–204·3] for women and 201·2 per 100 000 population [166·9–241·4] for men). The higher DALY rates in men were due to higher YLL rates compared with women. Between 1990 and 2016, there was a non-significant 6·0% (–4·0 to 16·7) change in the age-standardised prevalence of idiopathic epilepsy, but a significant decrease in age-standardised mortality rates (24·5% [10·8 to 31·8]) and age-standardised DALY rates (24·0% [9·0 to 27·6]). A third of the difference in age-standardised DALY rates between low and high SDI quintile countries was due to the greater severity of epilepsy in low-income settings, and two-thirds were due to a higher YLL rate in low SDI countries.

Interpretation Despite the decrease in the disease burden from 1990 to 2016, epilepsy is still an important cause of disability and mortality. Standardised collection of data on epilepsy in population representative surveys will strengthen the estimates, particularly in countries for which we currently have no or sparse data and if additional data is collected on severity, causes, and treatment. Sizeable gains in reducing the burden of epilepsy might be expected from improved access to existing treatments in low-income countries and from the development of new effective drugs worldwide.

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Causes of secondary epilepsy include, among others, inflammatory disorders, brain tumours, traumatic brain injuries, and congenital anomalies. However, these aggregated data do not explain in detail the burden due to epilepsy by age, sex, location, and socioeconomic status. For GBD 2016, we estimated global, regional, and country-specific prevalence, and years lived with disability for active epilepsy from 1990 to 2016. 317 studies on the prevalence of epilepsy, 81 studies on incidence, and 23 studies on mortality were selected on the basis of the quality of evidence. Additional studies on the severity of the disease were selected for the calculation of disability weights (appendix).

Evidence before this study

We searched PubMed, without language restrictions, using the terms (((epilepsy AND epidemiology) AND (“2011/01/01”[PDat] : “2015/12/31”[PDat]) AND ((epilepsy AND epidemiology)))) to identify articles published between Jan 1, 2011, and Oct 17, 2016. The 2015 estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) suggested that epilepsy contributes to 0.5% of disability-adjusted life-years (DALYs) due to all diseases and injuries and 5.0% of DALYs attributable to neurological disorders. However, these aggregated data do not explain in detail the burden due to epilepsy by age, sex, location, and socioeconomic status. For GBD 2016, we estimated global, regional, and country-specific prevalence, and years lived with disability for active epilepsy from 1990 to 2016. 317 studies on the prevalence of epilepsy, 81 studies on incidence, and 23 studies on mortality were selected on the basis of the quality of evidence. Additional studies on the severity of the disease were selected for the calculation of disability weights (appendix).

Added value of this study

This systematic analysis for GBD 2016 is specifically aimed at informing epilepsy researchers and clinicians who might not have seen the general publications on this global public health resource. We present results on the burden of active idiopathic epilepsy (ie, epilepsy of genetic or unknown origin), exploring variation by age, sex, location, and year, as well as the association between epilepsy burden and development status of a country, as measured by the Socio-demographic Index (SDI), a compound measure of income per capita, education, and fertility. About the same number of people globally have idiopathic and secondary epilepsy. There is little variation by SDI in prevalence of idiopathic epilepsy, with rates in the five SDI quintiles of countries indistinguishable from the global age-standardised rate of 326·7 per 100,000 population (278·4–378·1) in 2016. Two-thirds of the gap in burden from idiopathic epilepsy between SDI quintiles is due to longer survival in people with epilepsy, and another third is from lesser severity of disease in high SDI quintile countries.

Implications of all the available evidence

From 1990 to 2016, significant changes in the burden of idiopathic epilepsy have been observed. These changes resulted from reduction in the case fatality rate and severity of disease rather than a change in prevalence. The low mortality rate in high SDI countries suggests that further gains can still be made in low and middle SDI countries because deaths from idiopathic epilepsy are largely avoidable with adequate management of the disease. Similarly, improved access to treatment can reduce burden by shifting people with epilepsy out of the state of recurrent seizures. The causes of secondary epilepsy are more amenable to prevention; although treatments can lead to the same successful control of seizures, they have less successful treatment overall because they do not address the often-severe comorbid disabilities from motor or intellectual impairments. In future GBDs, it would be advisable to explicitly aggregate all of the causes of secondary epilepsy that are currently estimated as sequelae (consequences) of underlying diseases and often in combined sequelae with motor, cognitive, or sensory impairments.

possible explanations for the heterogeneous frequency, course, and consequences of the disease in the world. Causes of secondary epilepsy include, among others, stroke, neurodegenerative disorders, infectious and inflammatory disorders, brain tumours, traumatic brain injuries, and congenital anomalies. However, these conditions were not considered risks in the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), but rather quantified as sequelae, or consequences, of the underlying causes of secondary epilepsy.

The recurrence of seizures and their physical and psychological consequences make epilepsy a burdensome neurological disorder. However, medical treatment of epilepsy with first-line antiepileptic drugs can render up to 70% of patients seizure free when adequately treated. According to a 2006 WHO report, 50 million people had epilepsy. The proportion of all disability-adjusted life-years (DALYs) attributed to epilepsy was 0.5%, but these findings are no longer comparable to current GBD estimates because of major differences in assumptions underpinning the DALY implemented after the WHO report. Comparative findings from different countries are scarce, and meta-analyses of prevalence or incidence studies do not take time of study into account, do not use predictive covariates, and are unable to predict estimates by country.

The GBD collaboration provides a systematic, comparable method of quantifying health loss in detail by disease, age, sex, year, location, and sociodemographic status. In a recent GBD report on the burden of neurological diseases, idiopathic epilepsy (ie, epilepsy of genetic origin or without a definite structural, metabolic, infective, or immune cause) accounted for 5.0% of total neurological DALYs and 1.3% of all deaths. Globally, idiopathic epilepsy ranked fifth among neurological disorders after stroke, migraine, dementia, and meningitis. Idiopathic epilepsy ranked second among neurological disorders in southern sub-Saharan Africa. When comparing the trends from 1990 to 2015, there was, however, a significant decrease in death and DALY rates attributable to idiopathic epilepsy, whereas the age-standardised prevalence rate remained stable globally. A more detailed assessment of DALYs in each country and over time was thus needed to verify if and to what extent the overall trends can be confirmed at the country level and, where available, at the regional level to identify discrepancies and, consequently, areas of intervention. A detailed account of the GBD estimates for epilepsy
(including age-specific, sex-specific, time-specific, and geographical trends, and the sociodemographic context) was needed to make the information more accessible to researchers, clinicians, and planners of neurological services. We aimed to quantify health loss due to epilepsy by age, sex, year, and location using data from the GBD collaboration in 195 countries and territories from 1990 to 2016.

Methods
Overview
Details of the general GBD methodology are reported in the appendix, including the guiding principles to assess health loss, the selection and assessment of the quality of the data sources, the input data and modelling strategies to assess epilepsy mortality and impairment, and a list of key articles used for reference.

Mortality
To assess premature mortality, we adhered to the underlying cause of death recorded in vital registration systems, as assigned by a physician on a death certificate. We made extensive corrections to cause of death data by redistributing deaths that were assigned to unspecified or intermediary causes on the basis of the International Classification of Diseases (ICD). The ICD-9 code for epilepsy is 345 and the ICD-10 codes for epilepsy are G40 and G41. Mortality from epilepsy was modelled with the Cause of Death Ensemble model, a tool developed for GBD cause of death analysis. The Cause of Death Ensemble model has the ability, through out-of-sample predictive validity testing, to determine which combination of covariates produces estimates that best cover the input data. This approach is different from analyses done to prove causality between a covariate or risk and an outcome. The data inputs in the model included 16 533 site-years of vital registration and 1093 site-years of verbal autopsy data; a site-year is a unique combination of location and calendar year. The model also included predictive covariates on pigs per capita and pig meat consumption as a proxy for neurocysticercosis infection, systolic blood pressure, cholesterol, a measure of health-care access and quality, and a summary exposure measure of alcohol consumption. Additional details on calculations can be found in the GBD 2016 risk factor overview paper and in the appendix.

Non-fatal disease modelling
The reference definition for epilepsy was based on the International League Against Epilepsy (ILAE) Guidelines for Epidemiologic Studies on Epilepsy, which defined an epilepsy case as someone with an active, recurrent condition of epileptic seizures (two or more) unprovoked by an immediate cause and who has had at least one epileptic seizure in the past 5 years regardless of antiepileptic drug treatment.

Systematic review of the literature yielded 319 unique sources of data on prevalence covering 20 of the 21 world regions, 82 unique sources of data on incidence covering 15 of the 21 world regions, and three unique sources of data on remission covering three of the 21 world regions. We also added 3 years of medical claims data from the USA. These data were defined in ICD-9 terms. The other sources of prevalence and incidence data were surveys stating case definitions independent of ICD codes.

Oceania was the only region for which no data were available. All data sources reported on all epilepsy (idiopathic and secondary combined). Where datapoints spanned an age group of more than 20 years, we split these data points into 5-year age bands by applying the age pattern from the USA, for which we had the most detailed data by age.

We modelled overall epilepsy prevalence and incidence using DisMod-MR 2.1, the Bayesian meta-regression tool developed for GBD. Study covariates were included to adjust US claims data to the reference epidemiological definition and to adjust studies with data on lifetime history of epilepsy to our active epilepsy definition. Additionally, we used a summary exposure measure of alcohol consumption and pig meat consumption per capita as predictive covariates on prevalence, as well as lag-distributed income as a predictive covariate on the excess mortality rate, or the excess rate of dying in cases of epilepsy in comparison with the general population.

Idiopathic and secondary epilepsy
The overall epilepsy prevalence derived from this model was split into idiopathic epilepsy (ie, epilepsy due to a genetic cause or when diagnostic assessment did not reveal a causative factor) and secondary epilepsy (ie, epilepsy due to structural, metabolic, infective, or immune cause).

The term idiopathic is in accordance with the 1985 ILAE proposal for classification of epilepsies and epileptic syndromes. Although this terminology has been questioned in the latest ILAE classification of the epilepsies, we retained the old term because most of the epidemiological studies used as data sources adopted the old classification.

From a systematic review, we identified 89 unique sources of data reporting on the proportion of epilepsy that is due to genetic or unknown causes, covering 18 of the 21 world regions. We found, however, that not all the sources identified used advanced diagnostic methods (CT or MRI scans in addition to electroencephalograms) to diagnose secondary epilepsy, and that sources that did not use advanced diagnostic methods reported systematically lower proportions for secondary epilepsy. Therefore, we added a covariate to adjust the studies with less comprehensive diagnostic procedures to those that used all available methods to diagnose secondary epilepsy. We used these data in a linear mixed-effects model, with fixed effects on under-5 mortality rate, log-transformed pig
| Region                  | Deaths       | Prevalence       | DALYs         |
|-------------------------|--------------|------------------|---------------|
|                         | 2016 counts  | Percentage change in age-standardised rates, 1990–2016 | 2016 counts  | Percentage change in age-standardised rates, 1990–2016 |
| Global                  | 126 055      | -24.5% (-31.8 to -10.8) | 22 962 448    | 6.0% (-4.0 to 16.7) |
| High SDI                | 12 744       | -2.7% (-7.2 to 4.8)   | 3 357 612     | 10.6% (-11.6 to 39.1) |
| High-middle SDI         | 10 938       | -39.2% (-45.8 to -27.6) | 3 374 755     | 3.0% (-19.6 to 34.0) |
| Middle SDI              | 36 153       | -31.7% (-38.8 to -22.5) | 7 864 730     | 8.9% (-5.4 to 26.5) |
| Low-middle SDI          | 48 802       | -30.6% (-40.3 to -13.5) | 6 832 353     | 1.6% (-19.3 to 26.1) |
| Low SDI                 | 17 360       | -12.1% (-23.3 to 10.3) | 2 479 921     | 4.5% (-24.9 to 45.4) |
| High-income North America | 239 1 (2090 to 2475) | -12.3% (-15.7 to -8.9) | 1 266 669     | 10.7% (-13.5 to 44.8) |
| Canada                  | 34 1 (288 to 345) | -28.9% (-35.2 to -21.7) | 84 838 917     | 2.0% (-78.3 to 36.1) |
| Greenland               | 2 1 (1 0 2)  | -29.9% (-46.7 to -6.0) | 191 96 320     | -11.5% (-81.3 to 33.2) |
| USA                     | 20 76 (2002 to 2150) | -9.7% (-13.2 to -6.0) | 1 181 207 (927 479 to 1 429 263) | 11.4% (-14.3 to 47.4) |
| Australasia             | 346 (319 to 375) | -15.1% (-22.6 to -7.0) | 65 797 (24 377 to 109 378) | -1.5% (-67.2 to 191.5) |
| Australia               | 293 (268 to 320) | -11.8% (-20.6 to -2.3) | 55 674 (14 412 to 97 939) | 0.4% (-75.5 to 297.9) |
| New Zealand             | 53 (47 to 60) | -27.6% (-36.7 to -16.7) | 1 023 (24 676 to 1 7892) | -10.2% (-81.3 to 252.2) |
| High-income Asia Pacific | 1239 (1076 to 1427) | -18.6% (-30.8 to -3.0) | 364 894 (264 943 to 478 045) | -0.4% (-30.7 to 48.0) |
| Brunei                  | 8 (6 to 10) | -13.7% (-35.5 to 17.4) | 1 234 (346 to 2090) | -15.7% (-79.5 to 258.1) |
| Japan                   | 681 (640 to 752) | -10.3% (-16.1 to -0.8) | 247 249 (196 641 to 306 896) | 4.3% (-16.3 to 30.9) |
| Singapore               | 16 (13 to 20) | -28.4% (-43.1 to -9.0) | 8590 (219 615 to 22 222) | 1.9% (-73.7 to 272.6) |
| South Korea             | 525 (389 to 705) | -30.0% (-49.6 to -5.1) | 1 072 821 (26 860 to 188 231) | -10.0% (-79.0 to 299.2) |
| Western Europe          | 7842 (7407 to 8435) | 10.7% (4.4 to 20.0) | 1 525 168 (1 026 982 to 20 406 466) | 12.0% (-25.7 to 74.4) |
| Andorra                 | 1 (1 to 1) | -8.8% (-35.0 to 20.8) | 237 (61 to 411) | -8.9% (-77.0 to 347.6) |
| Austria                 | 88 (78 to 99) | -12.1% (-23.0 to 0.4) | 23 424 (48 912 to 42 084) | 0.4% (-79.1 to 376.7) |
| Belgium                 | 282 (248 to 321) | 45.4% (27.5 to 66.5) | 419 171 (10 360 to 74 029) | 12.5% (-76.6 to 397.4) |
| Cyprus                  | 8 (7 to 9) | -30.0% (-40.6 to -12.9) | 2 314 (5 123 to 4097) | -0.5% (-77.0 to 354.5) |
| Denmark                 | 88 (75 to 105) | 38.6% (14.6 to 70.1) | 14 926 (40 160 to 26 083) | 9.2% (-73.7 to 380.3) |
| Finland                 | 77 (68 to 90) | -13.1% (-25.8 to 5.7) | 14 276 (32 312 to 24 707) | 2.4% (-79.8 to 416.5) |
| France                  | 1703 (1542 to 1879) | 4.9% (-5.4 to 16.7) | 304 489 (76 321 to 531 242) | 11.7% (-75.2 to 413.6) |
| Germany                 | 2308 (2062 to 2583) | 51.6% (34.5 to 71.9) | 429 596 (109 560 to 761 662) | 51.9% (-66.6 to 637.2) |
| Greece                  | 75 (68 to 84) | -9.7% (-20.0 to 2.0) | 28 256 (648 810 to 49 284) | -0.2% (-77.4 to 315.3) |

(Number of deaths, prevalence and DALYs)
| Country          | 2016 counts | Percentage change in age-standardised rates, 1990–2016 | Prevalence | Percentage change in age-standardised rates, 1990–2016 | DALYs | Percentage change in age-standardised rates, 1990–2016 |
|------------------|-------------|------------------------------------------------------|------------|-----------------------------------------------|-------|------------------------------------------------------|
| (Continued from previous page) |             |                                                      | (166 to 608) | 319                                           | -0.2% (59.9 to 165.4) |                   |
| Iceland          | 4 (4 to 5)  | 45.8% (29.5 to 64.0)                                 | 908        | 3.7% (-74.0 to 297.5)                          | 319   | -0.2% (59.9 to 165.4)                                 |
| Ireland          | 60 (51 to 70)| -12.8% (-26.0 to 2.3)                                | 1315       | 1.0% (-75.6 to 379.3)                          | 523   | -14.4% (-63.9 to 107.9)                              |
| Israel           | 91 (77 to 111)| 20.8% (-3.3 to 47.2)                                | 20176      | 6.8% (-72.3 to 304.2)                          | 8069  | -1.1% (-56.0 to 132.1)                               |
| Italy            | 730 (648 to 826)| 11.4% (-1.2 to 28.2)                                | 163995     | -14.1% (-81.3 to 300.9)                        | 5278  | -23.8% (-75.4 to 131.9)                             |
| Luxembourg       | 11 (10 to 13) | -0.9% (-15.2 to 16.2)                               | 1813       | -0.9% (-78.6 to 342.7)                         | 79    | -18.3% (-65.3 to 96.4)                              |
| Malta            | 4 (3 to 5)   | 22.0% (-0.6 to 47.7)                                 | 1096       | 7.4% (-75.2 to 368.2)                          | 385   | 0.9% (-65.8 to 188.5)                               |
| Netherlands      | 268 (246 to 299)| 2.0% (-10.4 to 15.2)                               | 51678      | 6.2% (-76.8 to 353.4)                          | 18651 | -8.1% (-61.8 to 126.9)                              |
| Norway           | 79 (70 to 90) | -17.3% (-28.7 to -3.8)                               | 18119      | 4.8% (-74.1 to 339.6)                          | 6549  | -16.6% (-65.3 to 100.0)                             |
| Portugal         | 169 (152 to 190)| -15.9% (-25.7 to -4.1)                              | 24437      | 3.0% (-78.8 to 345.6)                          | 10049 | -27.0% (-66.9 to 64.3)                              |
| Spain            | 452 (405 to 515) | 1.7% (-10.0 to 20.1)                               | 105520     | 8.2% (-76.7 to 357.3)                          | 33847 | -14.5% (-70.6 to 131.2)                             |
| Sweden           | 111 (98 to 126) | -20.5% (-30.5 to -8.9)                              | 22010      | -8.7% (-67.2 to 164.7)                         | 8370  | -22.9% (-59.0 to 44.7)                              |
| Switzerland      | 107 (84 to 134)| -40.3% (-53.9 to -22.9)                             | 19797      | -8.0% (-80.3 to 272.2)                         | 6923  | -33.1% (-72.5 to 51.0)                              |
| UK               | 112 (108 to 1172)| -6.9% (-10.5 to -2.3)                              | 221727     | -0.3% (-14.8 to 16.3)                          | 9240  | -12.3% (-22.0 to -1.3)                              |
| Southern Latin America | 592 (522 to 670) | -19.7% (-29.4 to -8.2)                              | 184053     | 1.8% (-57.6 to 140.4)                          | 78384 | -17.9% (-55.4 to 49.3)                              |
| Argentina        | 284 (260 to 312) | -20.6% (-28.7 to -11.1)                             | 101909     | 4.2% (-73.2 to 270.6)                          | 44400 | -13.2% (-64.2 to 116.1)                             |
| Chile            | 256 (198 to 327) | -25.5% (-43.0 to -3.2)                              | 71432      | -2.6% (-81.3 to 264.9)                         | 29085 | -25.9% (-72.5 to 72.8)                              |
| Uruguay          | 52 (47 to 56)   | -3.1% (-14.0 to 8.1)                                 | 10704      | 3.7% (-75.8 to 336.2)                          | 4897  | -11.7% (-61.4 to 101.5)                             |
| Eastern Europe   | 1869 (1512 to 2347)| -40.4% (-51.6 to -26.3)                             | 413632     | -7.0% (-64.1 to 149.9)                         | 204537| -31.5% (-63.2 to 23.2)                              |
| Belarus          | 141 (110 to 188) | -24.3% (-41.9 to 0.0)                                | 21587      | -0.6% (-79.9 to 419.2)                         | 12079 | -22.4% (-62.5 to 49.0)                              |
| Estonia          | 33 (28 to 41)   | -1.1% (-19.8 to 23.9)                                | 3813       | 4.8% (-84.4 to 362.2)                          | 2186  | -12.9% (-55.8 to 68.8)                              |
| Latvia           | 40 (33 to 48)   | 21.0% (-1.0 to 48.1)                                 | 4820       | -1.0% (-80.7 to 404.5)                         | 2814  | -3.0% (-52.0 to 109.0)                              |
| Lithuania        | 63 (56 to 72)   | -12.8% (-22.8 to 0.1)                                | 7858       | 0.2% (-79.9 to 371.3)                          | 4587  | -15.0% (-56.3 to 70.0)                              |
| Moldova          | 68 (59 to 79)   | -37.9% (-47.5 to -25.6)                              | 7935       | -12.3% (-80.5 to 427.0)                        | 5216  | -36.9% (-64.6 to 15.7)                              |
| Russia           | 882 (636 to 1209)| -54.9% (-67.9 to -37.7)                             | 289899     | -8.7% (-83.1 to 404.8)                         | 120960| -38.4% (-76.1 to 50.0)                              |
| Ukraine          | 642 (464 to 886) | -10.9% (-36.6 to 25.5)                               | 96220      | -3.6% (-81.4 to 425.8)                         | 56695 | -14.6% (-58.1 to 83.5)                              |
| Central Europe   | 1848 (1715 to 2013) | -14.6% (-21.3 to -4.5)                              | 358718     | 7.3% (-35.7 to 81.3)                           | 159221| -18.2% (-41.2 to 14.8)                              |
| Albania          | 53 (45 to 64)   | -11.3% (-25.4 to 8.7)                                | 11093      | 1.2% (-78.7 to 409.2)                          | 5572  | -12.1% (-56.6 to 82.2)                              |

(Table 1 continues on next page)
### Deaths

| Country                        | 2016 counts (CIs) | Percentage change in age-standardised rates, 1990–2016 |
|-------------------------------|------------------|-------------------------------------------------------|
| Armenia                       | 17 (15 to 20)    | -33·7% (–78·5 to 69·4)                                |
| Azerbaijan                    | 260 (199 to 339) | 6·8% (–45·2 to 70·0)                                  |
| Georgia                       | 40 (33 to 48)    | -35·9% (–75·4 to 68·0)                                |
| Kazakhstan                    | 316 (239 to 452) | 1·6% (–58·5 to 138·3)                                 |
| Kyrgyzstan                    | 195 (120 to 228) | 1·6% (–51·6 to 111·9)                                 |
| Mongolia                      | 83 (64 to 100)   | 22·8% (–37·3 to 151·2)                                |
| Tajikistan                    | 398 (318 to 514) | -1·3% (–43·4 to 69·4)                                 |
| Turkmenistan                  | 128 (103 to 156) | 1·6% (–51·6 to 111·9)                                 |
| Uzbekistan                    | 179 (154 to 203) | 54·4% (–9·3 to 162·2)                                 |
| Central America               | 3858 (3612 to 4192) | -25·4% (–40·2 to 66·8)                          |

### Prevalence

| Country                        | 2016 counts (CIs) | Percentage change in age-standardised rates, 1990–2016 |
|-------------------------------|------------------|-------------------------------------------------------|
| Armenia                       | 17 (15 to 20)    | -33·7% (–78·5 to 69·4)                                |
| Azerbaijan                    | 260 (199 to 339) | 6·8% (–45·2 to 70·0)                                  |
| Georgia                       | 40 (33 to 48)    | -35·9% (–75·4 to 68·0)                                |
| Kazakhstan                    | 316 (239 to 452) | 1·6% (–58·5 to 138·3)                                 |
| Kyrgyzstan                    | 195 (120 to 228) | 1·6% (–51·6 to 111·9)                                 |
| Mongolia                      | 83 (64 to 100)   | 22·8% (–37·3 to 151·2)                                |
| Tajikistan                    | 398 (318 to 514) | -1·3% (–43·4 to 69·4)                                 |
| Turkmenistan                  | 128 (103 to 156) | 1·6% (–51·6 to 111·9)                                 |
| Uzbekistan                    | 179 (154 to 203) | 54·4% (–9·3 to 162·2)                                 |
| Central America               | 3858 (3612 to 4192) | -25·4% (–40·2 to 66·8)                          |

### DALYs

| Country                        | 2016 counts (CIs) | Percentage change in age-standardised rates, 1990–2016 |
|-------------------------------|------------------|-------------------------------------------------------|
| Armenia                       | 17 (15 to 20)    | -33·7% (–78·5 to 69·4)                                |
| Azerbaijan                    | 260 (199 to 339) | 6·8% (–45·2 to 70·0)                                  |
| Georgia                       | 40 (33 to 48)    | -35·9% (–75·4 to 68·0)                                |
| Kazakhstan                    | 316 (239 to 452) | 1·6% (–58·5 to 138·3)                                 |
| Kyrgyzstan                    | 195 (120 to 228) | 1·6% (–51·6 to 111·9)                                 |
| Mongolia                      | 83 (64 to 100)   | 22·8% (–37·3 to 151·2)                                |
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| Central America               | 3858 (3612 to 4192) | -25·4% (–40·2 to 66·8)                          |

(Table 1 continues on next page)
| Country       | Deaths 2016 | Percentage change in age-standardised rates, 1990–2016 | Prevalence 2016 | Percentage change in age-standardised rates, 1990–2016 | DALYs 2016 | Percentage change in age-standardised rates, 1990–2016 |
|---------------|-------------|------------------------------------------------------|-----------------|------------------------------------------------------|------------|------------------------------------------------------|
| Honduras      | 202         | -22.9% (-44.2 to 5.9)                                | 42,165          | -2.4% (-78.7 to 330.6)                                | 23,678     | -20.8% (-65.5 to 70.6)                                |
| Mexico        | 1989        | -31.8% (-34.7 to -28.3)                              | 727,028         | -8.7% (-31.6 to 23.5)                                | 306,444    | -27.9% (-42.5 to -10.3)                                |
| Nicaragua     | 77          | -35.9% (-47.1 to -21.3)                              | 29,296          | -2.8% (-76.5 to 303.2)                                | 12,233     | -30.5% (-70.0 to 56.1)                                |
| Panama        | 54          | -10.3% (-25.6 to 8.8)                                | 16,256          | 4.7% (-75.8 to 367.2)                                | 6,927      | -9.7% (-63.2 to 116.6)                                |
| Venezuela     | 513         | -19.8% (-37.1 to 3.3)                                | 164,964         | -6.0% (-77.9 to 313.9)                                | 71,516     | -19.1% (-66.7 to 106.4)                                |
| Andean Latin America | 605 (541 to 695) | -57.3% (-63.9 to -47.3)                             | 261,097         | -5.3% (-58.0 to -110.2)                              | 104,271    | -40.6% (-66.1 to 4.3)                                 |
| Bolivia       | 172 (135 to 212) | -51.3% (-63.8 to -31.8)                             | 32,455          | -25.0% (94.6 to 268.8)                                | 18,729     | -47.9% (-73.9 to 4.0)                                 |
| Ecuador       | 248 (222 to 277) | -54.6% (-59.9 to -49.0)                             | 88,466          | -8.4% (-80.5 to 319.4)                                | 39,919     | -38.8% (-74.8 to 34.2)                                |
| Peru          | 185 (144 to 265) | -64.8% (-73.8 to -44.5)                             | 140,175         | 2.6% (-79.1 to 355.7)                                 | 46,613     | -39.8% (-80.6 to 58.6)                                |
| Caribbean     | 770 (664 to 898) | -30.5% (-39.7 to -18.8)                             | 136,726         | -7.5% (-48.4 to 59.4)                                 | 75,882     | -26.2% (-46.9 to 9.1)                                 |
| Antigua and Barbuda | 3 (3 to 3)     | -25.3% (-36.5 to -11.4)                             | 428             | -5.6% (-77.8 to 328.7)                                | 242        | -19.8% (-60.1 to 52.6)                                |
| The Bahamas   | 6 (5 to 7)   | -30.2% (-40.5 to -17.8)                              | 1375            | -8.1% (-80.6 to 282.8)                                | 663        | -26.2% (-69.2 to 60.6)                                |
| Barbados      | 6 (6 to 7)   | -23.3% (-34.2 to -9.7)                               | 1075            | 0.1% (-75.6 to 340.1)                                 | 511        | -17.5% (-60.9 to 77.6)                                |
| Belize        | 7 (6 to 8)   | 0.6% (-16.1 to 21.1)                                 | 1228            | 6.1% (-78.0 to 384.2)                                 | 724        | -8.4% (-54.3 to 80.1)                                 |
| Bermuda       | 1 (1 to 1)   | -57.6% (-64.9 to -48.6)                              | 270             | -12.6% (-80.4 to 304.4)                               | 86         | -44.2% (-79.4 to 42.1)                                |
| Cuba          | 95 (85 to 106) | -34.1% (-41.7 to -24.0)                             | 32,247          | -0.8% (-76.3 to 312.7)                                | 12,063     | -23.4% (-70.1 to 78.6)                                |
| Dominica      | 3 (3 to 4)   | -12.4% (-24.8 to 3.3)                                | 302             | -2.2% (-77.6 to 340.5)                                | 217        | -9.3% (-48.3 to 63.3)                                 |
| Dominican Republic | 101 (84 to 123) | -41.9% (-52.7 to -27.3)                             | 31,056          | 4.9% (-78.7 to 450.1)                                 | 13,842     | -27.6% (-71.2 to 71.8)                                |
| Grenada       | 3 (2 to 4)   | -3.1% (-22.7 to 19.1)                                | 416             | 3.0% (-76.8 to 352.5)                                 | 261        | -6.6% (-52.8 to 80.4)                                 |
| Guyana        | 23 (19 to 26) | -24.7% (-36.9 to -11.0)                              | 2827            | -1.1% (-76.9 to 336.1)                                | 2013       | -20.5% (-55.1 to 40.1)                                |
| Haiti         | 345 (235 to 473) | -29.6% (-47.7 to 4.1)                               | 24,380          | -15.2% (-88.4 to 494.0)                               | 27,515     | -32.9% (-61.9 to 30.9)                                |
| Jamaica       | 52 (42 to 66) | -28.0% (-43.6 to -5.5)                               | 11,018          | -3.6% (-75.9 to 283.8)                                | 5,336      | -22.9% (-63.2 to 62.5)                                |
| Puerto Rico   | 59 (53 to 67) | -48.4% (-56.0 to -39.9)                              | 14,581          | -15.3% (-77.7 to 243.8)                               | 5,711      | -39.7% (-73.8 to 34.9)                                |
| Saint Lucia   | 5 (5 to 6)   | -35.0% (-42.7 to -27.0)                              | 705             | -7.1% (-80.1 to 405.7)                                | 423        | -28.6% (-62.3 to 37.6)                                |
| Saint Vincent and the Grenadines | 4 (3 to 4)     | -0.2% (-14.9 to 15.7)                                | 428             | 5.0% (-76.2 to 336.0)                                 | 291        | -4.4% (-47.1 to 77.4)                                 |
| Suriname      | 15 (14 to 18) | -13.8% (-25.7 to 0.6)                                | 1920            | -10.0% (-83.5 to 280.3)                               | 175        | -21.0% (-57.9 to 50.0)                                |
| Trinidad and Tobago | 39 (34 to 45) | -23.2% (-34.6 to -10.7)                              | 5970            | -5.3% (-77.4 to 365.2)                                | 3389       | -19.1% (-57.9 to 57.5)                                |
| Virgin Islands | 2 (2 to 2)     | -25.0% (-43.3 to -2.9)                               | 440             | -3.5% (-80.4 to 326.5)                                | 176        | -20.8% (-66.7 to 83.7)                                |

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| Articles |
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### Prevalence

| Tropical Latin America | Deaths | Percentage change in age-standardised rates, 1990–2016 | Prevalence | Percentage change in age-standardised rates, 1990–2016 | DALYs | Percentage change in age-standardised rates, 1990–2016 |
|------------------------|--------|--------------------------------------------------------|------------|--------------------------------------------------------|-------|--------------------------------------------------------|
| Brazil                 | 35,798 | (-1.1% (-1.3 to -0.8))                                  | 228,479    | (-1.2% (-1.3 to -0.9))                                  | 12,267| (-1.2% (-1.3 to -0.9))                                  |
| Paraguay               | 14,838 | (-1.5% (-1.7 to -1.3))                                  | 201,137    | (-1.5% (-1.7 to -1.3))                                  | 12,604| (-1.5% (-1.7 to -1.3))                                  |
| East Asia              | 29,092 | (-1.8% (-2.0 to -1.6))                                  | 253,122    | (-1.9% (-2.1 to -1.7))                                  | 13,388| (-1.9% (-2.1 to -1.7))                                  |
| China                  | 24,038 | (-2.1% (-2.3 to -1.8))                                  | 216,755    | (-2.2% (-2.4 to -2.0))                                  | 13,499| (-2.2% (-2.4 to -2.0))                                  |
| North Korea            | 20,078 | (-2.4% (-2.6 to -2.1))                                  | 211,146    | (-2.5% (-2.7 to -2.2))                                  | 13,509| (-2.5% (-2.7 to -2.2))                                  |
| Taiwan (province of China) | 24,038 | (-2.1% (-2.3 to -1.8))                                  | 216,755    | (-2.2% (-2.4 to -2.0))                                  | 13,499| (-2.2% (-2.4 to -2.0))                                  |

### Oceania

| Oceania | Deaths | Percentage change in age-standardised rates, 1990–2016 | Prevalence | Percentage change in age-standardised rates, 1990–2016 | DALYs | Percentage change in age-standardised rates, 1990–2016 |
|---------|--------|--------------------------------------------------------|------------|--------------------------------------------------------|-------|--------------------------------------------------------|
| American Samoa | 2 | 101.3% (45.0 to 157.7)                                  | 302        | 25.5% (58.6 to 206.1)                                  | 186   | 46.9% (20.9 to 204.0)                                  |
| Federated States of Micronesia | 2 | 71.7% (25.9 to 48.3)                                  | 308        | 8.6% (65.3 to 279.6)                                  | 207   | 2.0% (44.5 to 91.7)                                  |
| Fiji | 2 | 28.6% (26.8 to 46.8)                                  | 2990       | 5.5% (69.5 to 228.8)                                  | 2307  | 5.1% (41.4 to 85.0)                                  |
| Guam | 1 | 51.5% (20.8 to 92.8)                                  | 516        | 10.3% (66.6 to 290.6)                                  | 234   | 17.6% (50.1 to 224.1)                                  |
| Kiribati | 4 | 1.4% (15.9 to 30.0)                                  | 342        | 6.1% (73.0 to 305.4)                                  | 382   | 2.5% (37.7 to 61.3)                                  |

**Table 1 continues on next page**
### Deaths

| Country            | 2016 counts | Percentage change in age-standardised rates, 1990–2016 |
|--------------------|-------------|--------------------------------------------------------|
| Marshall Islands   | 1 (1 to 1)  | 14.4% (−13.8 to 45.1)                                  |
| Northern Mariana Islands | 1 (1 to 1)  | 0.6% (−26.9 to 38.8)                                   |
| Papua New Guinea   | 128 (R3 to 192) | 2.5% (−19.3 to 31.3)                                  |
| Samoa              | 2 (2 to 3)  | −2.6% (−23.7 to 24.1)                                  |
| Solomon Islands    | 11 (7 to 15)| 22.5% (−6.7 to 62.6)                                   |
| Tonga              | 1 (1 to 1)  | −2.9% (−25.7 to 29.8)                                  |
| Vanuatu            | 5 (4 to 7)  | 22.0% (−3.9 to 58.6)                                   |
| **North Africa and Middle East** | **7356 (6392 to 8157)** | **−29.0% (−38.5 to −7.2)** |

### Prevalence

| Country            | 2016 counts | Percentage change in age-standardised rates, 1990–2016 |
|--------------------|-------------|--------------------------------------------------------|
| Afghanistan        | 997 (462 to 1585) | −5.0% (−2.6 to 20.1)                                  |
| Algeria            | 440 (348 to 574)  | −27.3% (−44.5 to −4.7)                                |
| Bahrain            | 19 (15 to 23)   | −21.7% (−39.2 to 3.2)                                 |
| Egypt              | 498 (389 to 657) | −30.2% (−44.3 to −8.9)                                |
| Iran               | 765 (627 to 937) | −29.3% (−46.3 to −3.1)                                |
| Iraq               | 506 (388 to 632) | −13.6% (−37.5 to 14.7)                                |
| Jordan             | 62 (48 to 78)    | −28.9% (−46.4 to −1.6)                                |
| Kuwait             | 22 (17 to 29)   | −16.7% (−37.9 to 8.1)                                 |
| Lebanon            | 41 (30 to 56)   | −52.1% (−66.7 to −24.3)                               |
| Libya              | 65 (52 to 78)   | −19.1% (−31.5 to −1.2)                                |
| Morocco            | 923 (471 to 1887)| −18.0% (−40.4 to 16.7)                               |
| Oman               | 37 (30 to 45)   | −39.8% (−53.6 to −15.7)                               |
| Palestine          | 99 (87 to 118)  | −18.6% (−32.8 to −0.3)                                |
| Qatar              | 11 (8 to 15)    | −65.9% (−75.6 to −51.7)                               |
| Saudi Arabia       | 211 (182 to 253) | −35.2% (−47.6 to −11.9)                               |
| Sudan              | 630 (412 to 899) | −23.5% (−40.7 to 7.9)                                 |
| Syria              | 83 (71 to 95)   | −32.0% (−45.1 to −3.3)                                |
| Tunisia            | 112 (81 to 149) | −33.1% (−47.5 to −10.3)                               |
| Turkey             | 1316 (1106 to 1544) | −47.9% (−61.7 to −12.9)                              |

### DALYs

| Country            | 2016 counts | Percentage change in age-standardised rates, 1990–2016 |
|--------------------|-------------|--------------------------------------------------------|
| Marshall Islands   | 207 (74 to 122) | 9.7% (−66.1 to 284.3)                                  |
| Northern Mariana Islands | 355 (120 to 543) | 1.8% (−68.0 to 221.1)                                  |
| Papua New Guinea   | 16 671 (4342 to 30406) | 11.5% (−73.5 to 415.7)                                |
| Samoa              | 586 (197 to 869)  | 7.7% (−67.0 to 227.1)                                  |
| Solomon Islands    | 1599 (485 to 2499) | 14.0% (−63.3 to 212.0)                                |
| Tonga              | 295 (88 to 453)   | 7.7% (−68.6 to 234.5)                                  |
| Vanuatu            | 689 (186 to 3344) | 11.8% (−72.8 to 337.5)                                |
| **North Africa and Middle East** | **11 112 639 (835 154 to 1428 785)** | **−22.0% (−39.3 to −0.2)** |

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| Articles |  |  |  |
| --- | --- | --- | --- |
| United Arab Emirates | 115 (82 to 151) | –20.3% (–41.7 to –11.8) | 34,858 (12,413 to 52,207) | –1.3% (–67.5 to 228.3) |
| Yemen | 404 (274 to 568) | –26.8% (–42.5 to 6.5) | 78,302 (21,865 to 132,676) | 7.3% (–73.0 to 426.7) |
| South Asia | 42,009 (39,131 to 47,849) | –33.0% (–42.2 to –15.9) | 5,272,409 (4,221,404 to 6,351,648) | –1.9% (–22.0 to –23.9) |
| Bangladesh | 4,449 (3,566 to 5,468) | –55.3% (–66.6 to –37.3) | 530,689 (176,781 to 816,118) | –18.2% (–74.5 to 194.1) |
| Bhutan | 18 (13 to 24) | –44.3% (–60.2 to –16.7) | 2,808 (909 to 4,471) | –7.1% (–70.5 to 250.4) |
| India | 34,253 (31,491 to 37,479) | –31.4% (–40.7 to –13.5) | 3,934,737 (2,176,019 to 4,766,534) | –1.9% (–20.1 to 21.4) |
| Nepal | 709 (560 to 896) | –31.6% (–50.0 to –6.7) | 113,530 (35,311 to 174,642) | 11.7% (–65.6 to 341.8) |
| Pakistan | 3,580 (2,853 to 4,286) | –8.9% (–27.8 to 13.4) | 6,906,645 (204,907 to 11,698,229) | 9.5% (–69.4 to 412.5) |
| Southern sub-Saharan Africa | 56,930 (52,166 to 62,454) | –5.1% (–18.2 to 9.1) | 3,832,628 (2,850,596 to 4,986,977) | 1.4% (–30.4 to 45.5) |
| Botswana | 171 (76 to 271) | 1.8% (–48.5 to 65.0) | 13,791 (4,748 to 21,418) | 13.7% (–63.1 to 317.0) |
| Lesotho | 199 (143 to 261) | 30.6% (–21.2 to 90.3) | 7,471 (1,509 to 14,829) | 30.5% (–81.0 to 734.2) |
| Namibia | 159 (101 to 234) | –20.9% (–44.3 to 5.8) | 11,753 (2,022 to 20,350) | –2.9% (–7.3 to 30.6) |
| South Africa | 4,420 (4,005 to 4,946) | –12.1% (–25.4 to 2.6) | 294,558 (201,182 to 388,082) | 0.6% (–34.5 to 54.8) |
| Swaziland | 100 (67 to 138) | 5.2% (–27.0 to 43.9) | 6,593 (1,618 to 11,383) | 9.8% (–71.4 to 356.8) |
| Zimbabwe | 635 (509 to 780) | 81.5% (34.3 to 206.5) | 49,362 (12,760 to 87,483) | 4.7% (–75.1 to 314.2) |
| Western sub-Saharan Africa | 8,732 (6,967 to 11,218) | 7.3% (–7.6 to 24.3) | 1,376,947 (760,842 to 2,178,156) | 7.1% (–43.9 to 123.2) |
| Benin | 274 (229 to 327) | 42.0% (17.1 to 73.8) | 51,645 (11,420 to 39,962) | 13.0% (–75.5 to 512.3) |
| Burkina Faso | 395 (328 to 480) | –7.7% (–25.2 to 16.6) | 49,576 (7,985 to 124,301) | 1.4% (–84.7 to 617.9) |
| Cameroon | 663 (466 to 897) | 61.2% (24.4 to 105.8) | 107,382 (20,059 to 229,080) | 22.6% (–80.9 to 661.9) |
| Cape Verde | 17 (14 to 22) | –4.0% (–28.7 to 29.4) | 338 (911 to 5671) | 15.8% (–72.4 to 389.1) |
| Chad | 357 (274 to 435) | 48.8% (22.6 to 82.5) | 44,949 (7,136 to 105,860) | 24.8% (–83.8 to 808.7) |
| Côte d’Ivoire | 693 (535 to 855) | 60.0% (31.0 to 93.5) | 81,378 (18,215 to 168,075) | 18.7% (–76.2 to 478.1) |
| The Gambia | 38 (30 to 47) | 39.8% (15.1 to 68.7) | 825 (2371 to 13,718) | 11.6% (–69.4 to 334.0) |
| Ghana | 412 (342 to 493) | 46.2% (17.0 to 88.0) | 137,757 (34,792 to 240,697) | 25.9% (–71.4 to 439.9) |
| Guinea | 232 (264 to 382) | 45.4% (17.4 to 79.4) | 40,217 (7,713 to 89,091) | 8.7% (–81.2 to 651.8) |
| Guinea-Bissau | 64 (48 to 78) | 36.4% (9.4 to 71.2) | 4,710 (762 to 12,028) | 15.1% (–84.8 to 848.2) |
| Liberia | 95 (78 to 116) | 34.2% (10.5 to 64.7) | 20,420 (4,697 to 41,125) | 1.1% (–81.3 to 366.6) |

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Table 1 continues on next page
| Country                | Deaths 2016 | Percentage change in age-standardised rates, 1990–2016 | Prevalence 2016 | Percentage change in age-standardised rates, 1990–2016 | DALYs 2016 | Percentage change in age-standardised rates, 1990–2016 |
|------------------------|-------------|--------------------------------------------------------|----------------|--------------------------------------------------------|------------|--------------------------------------------------------|
| (Continued from previous page) |             |                                                        |                |                                                        |            |                                                        |
| Mali                   | 377         | 14.5% (-16.4 to 58.1)                                   | 41309          | 28.9% (-82.0 to 861.8)                                  | 3767       | 7.0% (-48.0 to 1069)                                    |
| Mauritania             | 73          | 14.0% (-20.4 to 64.7)                                   | 22889          | 8.7% (-72.5 to 300.4)                                  | 12189      | 0.8% (-55.5 to 134.5)                                  |
| Niger                  | 451         | 28.3% (-4.4 to 79.2)                                   | 59803          | 12.6% (-81.0 to 599.0)                                  | 49820      | 6.7% (-48.8 to 119.6)                                  |
| Nigeria                | 3722        | -17.0% (-42.6 to 13.9)                                  | 577948         | -2.8% (-85.1 to 499.3)                                  | 428168     | -17.2% (-65.2 to 73.0)                                 |
| Sao Tome and Principe  | 3           | 25.2% (-5.2 to 59.3)                                   | 1050           | 17.0% (-67.6 to 374.3)                                  | 568        | 8.7% (-50.9 to 147.3)                                  |
| Senegal                | 378         | 45.1% (13.7 to 68.7)                                   | 74912          | 10.4% (-72.3 to 296.9)                                  | 49079      | 13.1% (-43.3 to 130.2)                                 |
| Sierra Leone           | 162         | 38.6% (16.3 to 67.4)                                   | 18035          | 13.7% (-85.1 to 776.9)                                  | 16196      | 15.5% (-45.7 to 138.6)                                 |
| Togo                   | 188         | 46.1% (19.8 to 72.7)                                   | 31210          | -5.3% (-81.8 to 435.8)                                  | 22342      | 6.0% (-52.7 to 154.1)                                  |
| Eastern sub-Saharan Africa | 8580       | -24.7% (-37.1 to -2.9)                                 | 1520359        | 2.5% (-32.9 to 55.0)                                   | 1058588    | -17.6% (-36.3 to 9.3)                                  |
| Burundi                | 279         | -26.0% (-44.5 to 11.7)                                  | 41575          | -5.5% (-83.7 to 405.0)                                  | 32995      | -21.6% (-60.2 to 58.3)                                 |
| Comoros                | 18          | -22.7% (-41.4 to 3.8)                                  | 3500           | -7.3% (-76.4 to 254.9)                                  | 2307       | -21.3% (-60.0 to 11.1)                                 |
| Djibouti               | 24          | -9.2% (-34.9 to 20.5)                                  | 4357           | 1.9% (-75.7 to 344)                                    | 2979       | -8.9% (-55.4 to 84.2)                                  |
| Eritrea                | 134         | -21.8% (-41.8 to 7.6)                                  | 20890          | 2.4% (-77.7 to 364.6)                                   | 15943      | -14.8% (-56.7 to 60.8)                                 |
| Ethiopia               | 2671        | -42.3% (-59.0 to -12.7)                                 | 371758         | -5.8% (-75.4 to 300.5)                                  | 286089     | -35.3% (-65.0 to 20.3)                                 |
| Kenya                  | 554         | -1.6% (-17.4 to 17.4)                                  | 200780         | 4.1% (-12.1 to 26.9)                                   | 102527     | -3.5% (-17.6 to 12.4)                                  |
| Madagascar             | 560         | -13.3% (-32.9 to 14.5)                                  | 79682          | -4.3% (-81.3 to 392.8)                                  | 62449      | -14.3% (-56.8 to 67.4)                                 |
| Malawi                 | 431         | -9.7% (-35.3 to 25.9)                                  | 55657          | 2.2% (-83.0 to 473.1)                                   | 45071      | -11.0% (-55.8 to 27.1)                                 |
| Mozambique             | 508         | -22.9% (-42.1 to 4.6)                                  | 112389         | 16.1% (-79.8 to 499.2)                                  | 73287      | -9.4% (-61.6 to 104.0)                                 |
| Rwanda                 | 246         | -26.1% (-48.0 to 19.5)                                  | 51061          | 8.5% (-74.4 to 413.2)                                   | 33209      | -18.2% (-60.4 to 80.0)                                 |
| Somalia                | 304         | -10.4% (-29.6 to 15.3)                                  | 28138          | 4.5% (-84.1 to 694.3)                                   | 28587      | -8.5% (-51.5 to 79.8)                                  |
| South Sudan            | 298         | 0.4% (-23.3 to 33.8)                                   | 35504          | 3.3% (-84.5 to 623.6)                                   | 31096      | -3.0% (-52.8 to 110.0)                                 |
| Tanzania               | 1162        | -18.5% (-35.2 to 3.9)                                  | 246200         | 6.2% (-75.3 to 380.8)                                   | 155696     | -10.8% (-56.1 to 82.6)                                 |
| Uganda                 | 936         | -11.5% (-29.3 to 19.2)                                  | 194280         | 5.1% (-80.2 to 434.2)                                   | 130523     | -5.2% (-55.9 to 119.3)                                 |
| Zambia                 | 455         | 24.2% (-15.6 to 67.9)                                  | 73796          | 13.0% (-76.4 to 521.1)                                  | 54989      | 14.5% (-44.9 to 143.7)                                 |
| Central sub-Saharan Africa | 2393       | -13.8% (-30.3 to 12.8)                                 | 272787         | 3.7% (-59.6 to 162.7)                                   | 253262     | -11.5% (-41.2 to 42.1)                                 |
| Angola                 | 530         | -18.9% (-47.3 to 36.2)                                  | 71859          | 6.6% (-80.3 to 474.3)                                   | 61288      | -15.6% (-57.1 to 74.7)                                 |
| Central African Republic | 149         | -0.5% (-20.8 to 25.5)                                  | 7078           | -0.7% (-86.4 to 827.7)                                  | 11901      | -2.1% (-40.9 to 65.6)                                  |

(Table 1 continues on next page)
meat consumption, access to sanitation, and the study quality covariate, as well as random effects for super-regions (ie, seven aggregates of 21 world regions defined in GBD). We obtained predictions for the proportion of idiopathic epilepsy from this model for every location and year, and applied them to the prevalence and incidence results of the DisMod-MR 2.1 model to calculate the prevalence and incidence of idiopathic epilepsy.

Secondary epilepsy was quantified as long-term consequences of meningitis, tetanus, malaria, cysticercosis, cystic echinococcosis, perterm birth complications, neonatal encephalopathy, neonatal sepsis, and neonatal haemolytic disease. Secondary epilepsy from other causes, such as brain cancer, traumatic brain injury, congenital anomalies, or stroke, was not quantified explicitly but assumed to be subsumed in the severity distributions and anomalies, or stroke, was not quantified explicitly but assumed to be subsumed in the severity distributions and corresponding disability weights for those conditions.\(^{a}\)

Severity distributions and years lived with disability

Three health states were defined as sequelae of idiopathic epilepsy: severe epilepsy, defined as an average seizure frequency of more than or equal to once per month; less severe epilepsy with a seizure frequency of less than once a month, or no seizures in the past year while untreated but still fulfilling the criteria of active epilepsy; and seizure-free, treated epilepsy, defined as not having seizures in the past year while on treatment. All the data informing these splits were identified through systematic review. The data included 29 unique sources on the proportion of epilepsy that is treated, covering 16 of the 21 world regions; 68 unique sources on the proportion of epilepsy that is severe, covering 12 of the 21 world regions; and ten unique sources on the proportion of treated patients with epilepsy who do not have seizures, covering six of the 21 world regions. The distributions of cases across these three health states were quantified in three additional linear models. The first two splits, to derive the proportion of less severe epilepsy and then to calculate the proportion of less severe epilepsy that is treated, used linear models with a fixed effect on the index of health-care access and quality and random effects on super-region. To determine the proportion of treated epilepsy where patients had not reported seizures in the previous year, we ran a linear regression with a fixed effect on the index of health-care access and quality. We split out the prevalence and incidence for these categories by sequentially applying the proportions to the prevalence and incidence of idiopathic epilepsy. The final category of less severe epilepsy was calculated as the overall less severe epilepsy category, excluding treated epilepsy without seizures. Each one of the three severity categories has a specific disability weight, and years lived with disability (YLDs) were calculated as prevalence multiplied by the category-specific disability weight. Further details on the methodology are provided in the appendix.

Socio-demographic Index

The frequency and severity of epilepsy were also assessed with reference to the Socio-demographic Index (SDI), a composite measure developed to provide a comparable metric of overall socioeconomic development in each country and represented by the gross domestic product per capita, the average years of education in the population older than 15 years of age, and the total fertility rate.\(^{a}\)

Risk estimation

Alcohol use was the only risk of the 84 risks included in GBD 2016 for which there was deemed to be sufficient evidence for a causal relationship with idiopathic epilepsy as an outcome. Population-attributable fractions were estimated using data for exposure, relative risk, and a theoretical-minimum exposure level. Additional details on calculations can be found in the GBD 2016 risk factor overview paper.\(^{a}\)

Compilation of results

Years of life lost (YLLs) were calculated by multiplying the number of deaths at each age group by the remaining life expectancy at that age, which was derived from the
GBD standard life table.21 DALYs were then calculated by summing YLLs and YLDs. We propagated uncertainty at each step of the analytical process by sampling 1000 draws at each computational step. Uncertainty intervals (UIs) were defined as the 25th and 975th values of the ordered draws. The term rate was used to indicate the number of cases per 100,000 population, in keeping with the other GBD reports. Differences in rates and counts between 1990 and 2016 are presented as significant if more than 950 of 1000 draws were all negative, or all positive. The study is compliant with the Guidelines for Accurate and Transparent Health Estimates Reporting (appendix).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results
In 2016, there were 45·9 million (95% UI 39·9–54·6) individuals with active epilepsy of idiopathic or secondary nature globally. Of these individuals, 24·0 million (20·4–27·7) had active idiopathic epilepsy. There were 126 055 epilepsy-related deaths (118 632–135 517) and 13·5 million DALYs (11·0–16·5; table 1), and there were 5·9 million (5·6–6·4) YLLs and 7·5 million (5·1–10·5) YLDs. Idiopathic epilepsy accounted for 0·23% (0·22–0·25) of deaths and 0·56% (0·48–0·66) of DALYs from all causes. Global age-standardised mortality rates of idiopathic epilepsy were 1·74 per 100 000 population (1·64–1·87; 1·40 per 100 000 population [1·23–1·54] for women and 2·09 per 100 000 population [1·96–2·25] for men).

Globally, in 2016, there were 1·4 million (95% UI 1·2–1·6) idiopathic epilepsy cases in men and 1·3 million (1·1–1·6) cases in women, with age-standardised incidence rates of 38·9 per 100 000 person-years (32·7–45·7) for men and 37·1 per 100 000 person-years (30·8–44·1) for women. Between 1990 and 2016, there were no significant changes in both age-standardised incidence rates (35·8 per 100 000 person-years [30·1–42·0] in 1990 and 38·0 per 100 000 person-years [31·7–45·1] in 2016) and absolute number of people (2·1 million [1·7–2·4] in 1990 and 2·8 million [2·3–3·3] in 2016) with incident idiopathic epilepsy. There were four times geographical variations in the age-standardised incidence rates of idiopathic epilepsy, with the highest rates observed in Ecuador (70·9 per 100 000 person-years [22·3–112·5]) and Mexico (56·0 per 100 000 person-years [41·0–72·0]) and the lowest rates in North Korea (17·0 per 100 000 person-years [5·7–28·2]) and China (19·7 per 100 000 person-years [14·2–25·6]).

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**Figure 1:** Age-standardised prevalence per 100 000 of idiopathic epilepsy for both sexes, 2016

ATG=Antigua and Barbuda. FSM=Federated States of Micronesia. Isl=Islands. LCA=Saint Lucia. TLS=Timor-Leste. TTO=Trinidad and Tobago. VCT=Saint Vincent and the Grenadines.
In 2016, the global age-standardised prevalence of all active epilepsy (idiopathic and secondary) was 621.5 per 100,000 population (95% UI 540.1–737.0). It varied from a low of 311.0 per 100,000 population (253.4–370.5) in Japan to a high of 1287.7 per 100,000 population (754.4–1791.3) in Cape Verde. The prevalence of idiopathic epilepsy was 326.7 per 100,000 population (278.4–378.1). The prevalence was 329.3 per 100,000 population (280.3–381.2) in men and 318.9 per 100,000 population (271.1–369.4) in women. Highest prevalence was found in eastern, western, and southern sub-Saharan Africa regions, central Asia, central and Andean Latin America, and southeast Asia (figure 1). Prevalence increased with age, with peaks at ages 5–9 years (374.8 [280.1–490.0]) and at older than 80 years (545.1 [444.2–652.0]). Prevalence was similar in men and women (figure 2).

Global age-standardised DALY rates of idiopathic epilepsy were 182.6 per 100,000 population (95% UI 149.0–223.5; 163.6 per 100,000 population [130.6–204.3] for women and 201.2 per 100,000 population [166.9–241.4] for men). The higher DALY rates in men were due to a higher YLL rate of 96.1 per 100,000 population (89.4–104.2) in men than in women (63.5 per 100,000 population [56.6–70.1]). Global age-standardised YLD rates in 2016 were similar between men (105.1 per 100,000 population [70.8–145.5]) and women (100.1 per 100,000 population [68.0–138.6]). YLLs peaked at age under 5 years and at ages of 15–19 years and then decreased progressively with age (figure 3). YLDs peaked at 5–9 years of age, decreased until 40–49 years, and increased progressively to the oldest age group.

Between 1990 and 2016, age-standardised prevalence of idiopathic epilepsy did not change (6.0% [95% UI 4.0 to 16.7]), but a significant decrease was found in age-standardised mortality rates (24.5% [10.8 to 31.8]) and in age-standardised DALY rates (19.4% [9.0 to 27.6]). For further details on prevalence, incidence, deaths, DALYs, YLLs, and YLDs for both sexes, all ages, countries, and territories, please refer to the GBD Results Tool.
and north Africa and the Middle East (table 1). However, in individual countries, a significant decrease was found only in the UK, Mexico, China, Bangladesh, and India.

Because of the wide Uls around prevalence, no country experienced a significant change between 1990 and 2016 (table 1). By contrast, the reduction of age-standardised deaths varied by SDI quintiles, with large reductions in the three middle SDI quintiles, but no significant change in the low and high SDI quintiles. Expected values of age-standardised DALY rates decreased from an SDI value of 0·3 upward (figure 4). Most regions saw a steady decrease over time, with values close to the expected line. Rates in Oceania and western sub-Saharan Africa remained mostly unchanged over the estimation period. Rates in central Asia and southern sub-Saharan Africa rose to a peak halfway through the estimation period and then declined.

About two-thirds of the gap in age-standardised DALY rates between low SDI quintile countries (249·2 per 100 000 population [95% UI 202·3–307·6]) and high SDI quintile countries (110·6 per 100 000 population [84·2–143·7]) were due to a difference in YLL rates (126·92 per 100 000 population [114·81–140·13] for low SDI countries and 34·05 per 100 000 population [32·48–36·28] for high SDI countries), and one-third was due to lesser severity of disease as measured in YLDs. Prevalence of idiopathic epilepsy was similar among the quintiles of SDI. In 2016, there was a strong gradient in the prevalence of idiopathic epilepsy by severity. Low SDI quintile countries had the highest age-standardised prevalence of severe epilepsy and the lowest age-standardised prevalence of treated epilepsy without seizures, with the opposite being the case in high SDI countries (table 2).

The only risk quantified in GBD for idiopathic epilepsy was alcohol use, estimated to be responsible for 18·9% (95% UI 14·6–23·1) of global DALYs from epilepsy in 2016. About two thirds of the gap in age-standardised DALY rates in high SDI countries and about one third in low SDI countries were due to lower deaths in the high SDI group compared with the low SDI group. About two thirds of the gap in age-standardised DALY rates in high SDI countries and about one third in low SDI countries were due to lower deaths in the high SDI group compared with the low SDI group.

Discussion

Between 1990 and 2016, a significant reduction was observed in the mortality rate in people with idiopathic epilepsy and, to a lesser extent, a reduction was found in DALY rates, a comprehensive measure of the burden of the disease, when adjusted for age. This finding probably reflects improvements in access to treatment leading to a lower risk of death and lesser severity of the disease. Nevertheless, a substantial treatment gap remains (due to insufficient financial resources, misconceptions, and stigma) that can explain the larger proportion of severe epilepsy and higher case fatality when comparing high SDI with middle and low SDI countries.

Our estimate of 45·9 million cases of idiopathic active and secondary epilepsy in 2016 is higher than the 32·7 million cases reported from a meta-analysis of 65 prevalence studies,7 but it seems that the estimate of the number of cases of active epilepsy in rural populations in low-income countries was reported as 17 million in the meta-analysis, whereas our interpretation of the results is that it should have been 37 million. Furthermore, it is not clearly stated for which year the estimate was made in the meta-analysis. However, similar to findings from that meta-analysis, large variations were observed in the prevalence of epilepsy in this study, but there was no clear pattern by development status or by location. This finding raises the question of how much of the variation we estimated between countries is real or an artifact of measurement error we have been unable to control for. The unknown cause of epilepsy, apart from an association with alcohol use, makes it difficult to fit estimates to sparse and heterogeneous data.

In 2016, epilepsy accounted for more than 13 million DALYs, that is 0·56% of total DALYs globally. The numbers are significantly higher than the projected estimates from WHO (7·4 million),9 but the proportion of total DALYs attributable to epilepsy in the WHO report (0·50%) was almost identical despite multiple measurement differences making results incomparable. In that report, epilepsy was defined in accordance with the 2005 ILAE and International Bureau for Epilepsy definition as...
a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures. This definition in keeping with the definition used in the present study. Other population-based studies addressed the burden of epilepsy using the DALY metrics. These studies were done in China,24 India,25 and South Africa.26 However, the results of these studies cannot be compared with ours because of the different methodology and the regional perspective.

Apart from the major changes in how DALYs are defined since GBD 2010 (no more discounting or age-weighting, a prevalence instead of incidence approach to measuring non-fatal outcomes, and disability weights derived from large population surveys rather than a small panel of health experts), the largest difference is that in the past decade, we have developed statistical models that can evaluate all available epidemiological evidence rather than relying on an analyst to determine a single data source to describe prevalence or incidence in a country.

Variables such as race or ethnicity and socioeconomic level might be also inter-related. Our and others’ findings support the concept that epilepsy and poverty might have a bidirectional association. The inverse association between the burden of epilepsy and sociodemographic status is in line with other neurological disorders and with published reports from low-income countries and from people with low incomes in high-income countries.22,23 Inequalities in health might also vary among members of the same population.24 Low socioeconomic status is also associated with risk factors for epilepsy.25 We should, however, argue that if we find an important link between the development status of countries and epilepsy outcomes, it is likely that much larger variation in outcomes exists at the individual level depending on a person’s socioeconomic attributes.

The major strength of this study is the worldwide assessment of the burden of all major diseases, including epilepsy, using the same methodology and modelling measures. Another strength is the continuous refinement of the available data through input from new original sources and the use of more sophisticated statistical methods as these develop. There are, however, some general and disease-specific limitations. First, as original epidemiological data were not available for all countries, Bayesian statistical models were used to estimate deaths and disease prevalence for countries with missing information. The inclusion of data sources from new original studies in countries for which no data were available in a previous iteration of GBD can lead to more precise estimates that might vary considerably from previous predicted values. The annual updates of GBD provide an opportunity to improve on estimates as new data or new methods become available. Second, the disability weights used for the calculation of DALYs might not be uniform across populations and sociodemographic levels. However, population surveys in nine countries did not find systematic variation in disability weights across populations or within the same population as a function of education.27,28,29 Third, the 95% UI used to define the precision of the estimates are wide, reflecting the overall uncertainty of the estimates and, as a consequence, limiting the ability to find differences across countries. This finding can explain why few countries showed a significant change in DALY rates. The main source of uncertainty around the incidence and prevalence estimates of idiopathic epilepsy comes from the sparse and heterogeneous data about the proportion of people with idiopathic as opposed to secondary epilepsy and, for idiopathic epilepsy, on the distribution of (presumed) genetic and cryptogenic forms. Likewise, deaths as part of idiopathic epilepsy might include deaths of people with secondary epilepsy. Further uncertainty comes from our definition of severity and the estimates of the proportion of people with severe epilepsy, people with less severe epilepsy, and those with no seizures while on treatment. A third source of uncertainty for the YLD estimates comes

Table 2: Age-standardised prevalence per 100 000 population and YLDs of idiopathic epilepsy in 2016, and its sequelae globally and by SDI quintiles

| Source | Prevalence (YLDs) | Seizure-free, treated idiopathic epilepsy (YLDs) | Less severe idiopathic epilepsy (YLDs) | Severe epilepsy (YLDs) |
|--------|------------------|----------------------------------------------|-------------------------------------|---------------------|
|        |                  |                                              |                                     |                     |
| Global | 326.7 (278.4–378.1) | 102.6 (69.5–142.0) | 65.9 (50.6–83.0) | 3.1 (1.8–4.8) |
| High SDI | 209.2 (247.4–372.3) | 76.5 (50.3–109.7) | 137.9 (99.7–177.8) | 6.5 (3.6–10.0) |
| High-middle SDI | 295.6 (231.4–359.5) | 86.7 (56.0–124.8) | 83.4 (57.0–112.5) | 3.9 (2.2–6.3) |
| Middle SDI | 348.3 (294.6–409.9) | 109.4 (73.8–150.4) | 65.5 (46.4–87.4) | 3.1 (1.7–5.0) |
| Low-middle SDI | 326.6 (256.9–400.7) | 108.3 (69.8–154.6) | 34.5 (22.5–49.0) | 1.6 (0.9–2.8) |
| Low SDI | 325.3 (242.3–416.4) | 122.5 (76.8–178.0) | 15.1 (7.4–25.8) | 0.7 (0.3–1.4) |

95% uncertainty intervals are in parentheses. Severe epilepsy is defined as more than one seizure per month; less severe epilepsy is defined as those who have 1–11 seizures per year or did not have a seizure in the past year while untreated but still fulfilling criteria of active epilepsy. SDI=Socio-demographic Index. YLDs=years lived with disability.
from the wide uncertainty bounds around the disability weights. New data collection on these various proportions that determine the sequence of epilepsy would have the greatest bearing on reducing Uls. Fourth, epilepsy is correlated with somatic and psychiatric comorbidities and injuries, as well as a host of diseases associated with stigma and poverty. Here, the correction for comorbidity was based on the assumption that diseases and their sequence are independent. Future improvements of the GBD modelling should include dependent comorbidity.

Fifth, the use of medical claims data could introduce a systematic bias as people who are not under treatment or are excluded from health insurance would not be counted. For the 3 years of claims data from the USA, we applied a correction based on a comparison with representative survey data. In coming years, we hope to include claims data from other countries and more comprehensive claims data from the USA that are less biased towards individuals with private health insurance only. The challenge will be to find representative survey data in those countries to make credible adjustments. Sixth, the peak in DALY rates in southern sub-Saharan Africa coincides with the peak in deaths as a result of HIV or AIDS in 2005 and suggests that despite an effort to correct deaths miscoded to non-HIV causes in the South African vital registration data, we might have left some remaining deaths that should have been reassigned to HIV or AIDS. However, even if the peak is an artifact, these regions still have much higher than expected DALY rates for idiopathic epilepsy. The reason for the recorded increase and then decrease in deaths in vital registration data from central Asia is less clear. Seventh, the higher mortality rate of idiopathic epilepsy in some western European countries than in low-income and middle-income countries cannot be easily explained and might reflect differences in cause of death certification practices. Last, epilepsy in this report be easily explained and might reflect differences in cause and DALY rates in patients with epilepsy between 1990 and 2016 is encouraging, but the changes varied across geographical areas and, where data were available, within countries. Furthermore, changes were linked to the sociodemographic development status, which should prompt more action in economically deprived areas. The success of reducing the burden of idiopathic epilepsy relies mostly on access to treatment. Health service planners and providers also need to be aware that patients with epilepsy are more often poor and marginalised because of stigma, requiring a greater effort to reach them than might be the case for most other diseases.

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