

**Global, regional, and national burden of disorders affecting the nervous system, 1990-2021
a systematic analysis for the Global Burden of Disease Study 2021**
GBD 2021 Nervous System Disorders Collaborators; Samadzadeh, Sara

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Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021



GBD 2021 Nervous System Disorders Collaborators*

Summary

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*Collaborators listed at the end of the paper

Correspondence to:

Dr Jaimie Steinmetz, Institute for Health Metrics and Evaluation,

University of Washington,

Seattle, WA 98105, USA

jsteinme@uw.edu

Background Disorders affecting the nervous system are diverse and include neurodevelopmental disorders, late-life neurodegeneration, and newly emergent conditions, such as cognitive impairment following COVID-19. Previous publications from the Global Burden of Disease, Injuries, and Risk Factor Study estimated the burden of 15 neurological conditions in 2015 and 2016, but these analyses did not include neurodevelopmental disorders, as defined by the International Classification of Diseases (ICD)-11, or a subset of cases of congenital, neonatal, and infectious conditions that cause neurological damage. Here, we estimate nervous system health loss caused by 37 unique conditions and their associated risk factors globally, regionally, and nationally from 1990 to 2021.

Methods We estimated mortality, prevalence, years lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life-years (DALYs), with corresponding 95% uncertainty intervals (UIs), by age and sex in 204 countries and territories, from 1990 to 2021. We included morbidity and deaths due to neurological conditions, for which health loss is directly due to damage to the CNS or peripheral nervous system. We also isolated neurological health loss from conditions for which nervous system morbidity is a consequence, but not the primary feature, including a subset of congenital conditions (ie, chromosomal anomalies and congenital birth defects), neonatal conditions (ie, jaundice, preterm birth, and sepsis), infectious diseases (ie, COVID-19, cystic echinococcosis, malaria, syphilis, and Zika virus disease), and diabetic neuropathy. By conducting a sequela-level analysis of the health outcomes for these conditions, only cases where nervous system damage occurred were included, and YLDs were recalculated to isolate the non-fatal burden directly attributable to nervous system health loss. A comorbidity correction was used to calculate total prevalence of all conditions that affect the nervous system combined.

Findings Globally, the 37 conditions affecting the nervous system were collectively ranked as the leading group cause of DALYs in 2021 (443 million, 95% UI 378–521), affecting 3·40 billion (3·20–3·62) individuals (43·1%, 40·5–45·9 of the global population); global DALY counts attributed to these conditions increased by 18·2% (8·7–26·7) between 1990 and 2021. Age-standardised rates of deaths per 100 000 people attributed to these conditions decreased from 1990 to 2021 by 33·6% (27·6–38·8), and age-standardised rates of DALYs attributed to these conditions decreased by 27·0% (21·5–32·4). Age-standardised prevalence was almost stable, with a change of 1·5% (0·7–2·4). The ten conditions with the highest age-standardised DALYs in 2021 were stroke, neonatal encephalopathy, migraine, Alzheimer's disease and other dementias, diabetic neuropathy, meningitis, epilepsy, neurological complications due to preterm birth, autism spectrum disorder, and nervous system cancer.

Interpretation As the leading cause of overall disease burden in the world, with increasing global DALY counts, effective prevention, treatment, and rehabilitation strategies for disorders affecting the nervous system are needed.

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Introduction

Conditions can affect the nervous system throughout life, for example by disrupting brain growth; damaging the brain, spinal cord, or peripheral nerves; and impairing cognitive, sensory, socioemotional, and motor function and behaviour. This diverse group of conditions includes congenital and neurodevelopmental disorders,

cerebrovascular and neurodegenerative diseases, neurological infections, neurological-immunological disorders, neuromuscular or peripheral nervous system disorders, traumatic injuries, and cancers of the nervous system, for brevity summarised as neurological disorders or nervous system conditions. These disorders vary in cause, symptoms, and course. Some nervous system

Research in context

Evidence before this study

We searched PubMed between Jan 1, 1980, and Oct 22, 2023, to identify studies that assessed trends in nervous system health loss globally, with the search string (“nervous system”[Title] OR “neurological”[Title]) AND (“prevalen*”[Title/Abstract] OR “inciden*”[Title/Abstract] OR “death*”[Title/Abstract] OR “burden”[Title/Abstract]) AND (“global”[Title] OR “international”[Title]). Results yielded studies that either looked at a small subset of conditions, such as only cancers or COVID-19, looked at single geographies, or used Global Burden of Disease, Injuries, and Risk Factors Study (GBD) results. Previous GBD reports on the global, regional, and national burden of neurological disorders covered a period from 1990 to 2016 and were limited to 15 conditions. In 2016, neurological disorders ranked as the leading cause of DALYs and the second-leading cause of death. The largest contributors to DALYs were stroke, migraine, and Alzheimer’s disease and other dementias. Other research groups used GBD 2019 results to quantify 18 neurological disorders or smaller geographies. Previous analyses excluded neurodevelopmental conditions that frequently cause lifelong disability, and neurological complications from conditions that affect multiple body systems, such as diabetes, syphilis, malaria, or more recently COVID-19 and Zika virus disease.

Added value of this study

This study extends previous evidence by including important neurological and neurodevelopmental disorders that were

previously not considered and by adding consequences of non-neurological conditions that affect the nervous system, bringing the total number of included conditions to 37. This study estimated the proportion of nervous system burden that was potentially avertible by eliminating known risk factors for stroke, Alzheimer’s disease and other dementias, multiple sclerosis, Parkinson’s disease, encephalitis, meningitis, and idiopathic intellectual disability but also emphasises the scarcity of knowledge about risk factors for nervous system conditions.

Implications of all the available evidence

Until recently, the nervous system has not been a focus of global public health discourse. Quantifying the global burden associated with nervous system health loss aids policy making and helps to lift brain health onto the public health agenda. With the adoption of the *Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders 2022–2031* by the World Health Assembly, the prevention, early identification, diagnosis, treatment, and rehabilitation of disorders that affect the nervous system have been brought into focus. This study provides the latest evidence to guide ongoing advocacy and awareness efforts. Additional research on modifiable risks, and support for adequate facilities and workforces in managing nervous system conditions, is necessary for equity and access to quality care. As the leading cause of DALYs, affecting more than 40% of the global population, nervous system health loss should be a public health priority.

conditions cause lifelong disability, whereas others are associated with high fatality rates; some are treatable or preventable, whereas for others there is no cure.

Increased life expectancy is arguably one of the greatest achievements of health systems around the world. However, this increase has also led to increases in age-related neurological disorders, such as Alzheimer’s disease and other dementias, stroke, and Parkinson’s disease, necessitating global health policies not only to focus on survival but also to minimise health loss due to disability by promoting function and independence. Not all neurological burden is associated with population ageing,¹ rendering it important to quantify the overall health loss associated with nervous system conditions throughout the lifespan.²

In response to the growing burden of nervous system disorders and conditions worldwide, the World Health Assembly adopted the *Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders 2022–2031* (IGAP) in May, 2022.³ The action plan aims to “reduce the stigma, impact and burden of neurological disorders, including their associated mortality, morbidity and disability, and to improve the quality of life of people with neurological disorders, their carers and families”.³

In the Global Burden of Disease, Injuries, and Risk Factors Study (GBD), nervous system disorders and

conditions are spread across many disease groupings. The basic GBD grouping of neurological disorders includes Alzheimer’s disease and other dementias, headaches, idiopathic epilepsy, motor neuron disease, multiple sclerosis, Parkinson’s disease, and a residual group of other neurological disorders that includes, for instance, muscular dystrophy and Huntington’s disease. Using GBD 2015 and 2016 estimates, Feigin and colleagues previously provided more comprehensive estimates of neurological health loss than the basic GBD grouping by also including stroke, meningitis, encephalitis, tetanus, traumatic brain injury, spinal cord injury, and brain and CNS cancers.^{1,4} Other researchers used GBD 2019 estimates to look at 18 neurological disorders or specific geographies.^{5,6} However, a proportion of global neurological burden stems from neurodevelopmental disorders, which traditionally have been classified in GBD under mental health or neonatal conditions, and from childhood infections. Both infections and neurodevelopmental disorders are often associated with lifelong disability.⁷ Furthermore, some peripheral neuropathies were not previously captured within the neurological burden.

Additionally, as shown by the COVID-19 pandemic,^{8,9} emerging and re-emerging infectious diseases are becoming an increasing global concern. For example,

vector-borne viruses such as Zika virus,¹⁰ Japanese encephalitis virus,¹¹ and West Nile virus¹² are increasing their geographical spread owing to climate change and constitute a notable global public health threat. These infections, often targeting the nervous system directly, cause both mortality and neurological morbidity, with an especially high burden in low-income and middle-income countries (LMICs).¹³

This Article aims to create an estimate of the burden of disorders and conditions that affect the nervous system using an expanded group of GBD conditions, cause categories, and disease consequences compared with previous analyses. This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.

Methods

Overview

GBD 2021 quantifies health loss for 371 diseases in 204 countries and territories, including measures of prevalence, disease severity, and death that together constitute a comprehensive assessment of disease burden. The analysis presented here groups conditions that affect the CNS and peripheral nervous system for which neurological consequences can be isolated in GBD (table 1). The conditions included here are not an exhaustive list; we were unable to include neurological consequences from some conditions, for example HIV or adrenoleukodystrophy, because they could not be explicitly estimated in GBD at this stage. However, this analysis is the most comprehensive attempt to capture neurological health loss to date. Broadly, and as outlined in the IGAP, these conditions include: neurodevelopmental disorders;¹⁴ neurological disorders (eg, stroke or Alzheimer's disease and other dementias); and neurological consequences of other congenital, neonatal, metabolic, or infectious diseases. Neurological consequences captured in this analysis include intellectual disability, cognitive impairment, motor impairment, epilepsy, microcephaly, neuropathy, and sensory deficits resulting from neonatal insults (described by condition in appendix p 5). For example, persistent cognitive symptoms and Guillain-Barré syndrome after COVID-19 were included in the analysis, but ongoing fatigue or respiratory symptoms due to COVID-19 were not included. Methods that were used to isolate nervous system health loss for conditions with neurological and non-neurological outcomes are described later in this section. Other neurological disorders is a residual category (appendix pp 5–6) that encompasses conditions that affect the CNS and peripheral nervous system but are not explicitly modelled as isolated diseases in GBD because of resource constraints. The category broadly includes unspecified disorders of the nervous system, some degenerative or demyelinating diseases, disorders of the autonomic nervous system, some movement disorders,

spinocerebellar diseases, nerve root and plexus disorders, peripheral nerve disorders, some neuromuscular disorders, and muscle diseases, such as myopathies (appendix pp 5–6, 63–64). Epilepsy estimates exclude epilepsy cases that are captured under other conditions to avoid double counting. A Guidelines for Accurate and Transparent Health Estimates Reporting checklist is included in the appendix (pp 2–5).

Prevalence estimates

GBD attempts to acquire all available population-representative studies, large-scale surveys, censuses, insurance claims, and hospital records that catalogue incidence and prevalence for each condition. The number of data sources that inform non-fatal estimates for each condition are summarised in the appendix (pp 6–7). For each condition, a reference case definition and data collection method was set. Data collected with non-reference methods were adjusted to the reference case definition using regression analyses assessing systematic bias. Case definitions and International Classification of Disease (ICD) codes used in non-fatal analyses are described in the appendix (pp 8–16).

For most conditions, Bayesian models were used to estimate incidence and prevalence across time, geography, age, and sex, on the basis of data and relevant predictive covariates. Modelling details vary by condition but generally use a Bayesian meta-regression tool called Disease Modelling Meta-Regression (DisMod-MR) 2.1.¹⁵ Details of DisMod-MR 2.1 are in the GBD 2019 capstone appendix 1, section 4.5 of reference 9,¹⁵ and described in the appendix (p 16). Predictive covariates included in models for individual conditions and details on geographical categories are also described in the appendix (pp 16–18). By including remission rates in the GBD modelling approach, we counted cases as being prevalent only if they were still a case, and we further accounted for transient versus progressive conditions in the case definition (appendix pp 8–14) and assessment of burden. Details of the modelling approach of three conditions with episodic occurrence (ie, migraine, tension-type headaches, and epilepsy) are in the appendix (p 20).

This Article describes prevalence, which reflects incidence and duration. Duration in turn is determined by mortality and remission rates and reflects disease severity and access to care. Total prevalence for each condition was split into more granular categories, termed sequelae, to capture different levels of severities and different possible health outcomes (appendix pp 21–48). For example, Parkinson's disease prevalence was proportionally split between three sequelae (ie, mild, moderate, and severe).¹⁶ For conditions that are not purely neurological, such as COVID-19, only relevant neurological sequelae were included. Further details on non-fatal methods for these conditions and diseases are shown in the appendix (pp 5–62).

See Online for appendix

Case aggregation and comorbidity corrections

The total number of prevalent cases for each individual condition was calculated by aggregating cases for all underlying sequelae. For wholly neurological conditions, the aggregate of sequela-level cases equalled the total number of cases for the overall condition. For conditions with both non-neurological and neurological health loss, the aggregate number of cases for sequelae with nervous system health loss was a subset of the total number of cases. For example, only a subset of all individuals with long-term consequences of COVID-19 in 2021 had neurological sequelae captured in GBD, such as cognitive impairment or Guillain–Barré syndrome (details of analysis linking Guillain–Barré syndrome as an outcome from COVID-19 infection are shown in appendix p 62). The total cases of cognitive impairment due to COVID-19 included in this analysis equals the total number of people who had cognitive impairment or Guillain–Barré syndrome attributed to COVID-19, but calculation of years lived with disability (YLDs) excludes any additional health loss in these individuals due to acute COVID-19 symptoms, fatigue, or ongoing respiratory problems.

A comorbidity correction was used to calculate total prevalence of all nervous system conditions and disorders combined, assuming independent comorbidity. Without a comorbidity correction, prevalence would be overestimated because individual conditions or disorders would be assumed to be non-overlapping (ie, one condition or disorder per individual). The total number of people with any nervous system health loss was then calculated by multiplying by the number of people in the population: $\text{prevalence}_{\text{total}} = 1 - [(1 - \text{prevalence}_{\text{condition1}}) * (1 - \text{prevalence}_{\text{condition2}}) * \dots (1 - \text{prevalence}_{\text{condition37}})]$.

YLDs due to nervous system health loss

The YLDs measure of non-fatal burden allows for comparison of relative health effects between disparate diseases. Disability refers to the relative health loss from a condition, as reflected in disability weights that grade severity of health loss from none (ie, disability weight of 0) to severe (ie, disability weight of 1, which is equivalent to death).¹⁷ YLDs account for both prevalence and severity of health loss by multiplying sequela prevalence by a sequela-specific disability weight. For example, although tension-type headaches are highly prevalent, the associated disability weight is relatively low compared with those of many other neurological conditions, which is reflected in the final YLD values. As another example, the disability weight for mild multiple sclerosis is 0.183, and that for severe multiple sclerosis is 0.719 (a description of multiple sclerosis disability weights is shown in appendix pp 55–56). These weights are derived from population and internet surveys where respondents were asked to indicate the person that they believed to be healthier between random pairs of hypothetical people, each with a brief

	Included in GBD 2016 analysis by Feigin and colleagues ¹	Mortality included in this analysis
Alzheimer's disease and other dementias	Yes	Yes
Attention deficit hyperactivity disorder	No	No
Autism spectrum disorder	No	No
Cerebral malaria	No	No
Cognitive impairment or Guillain–Barré syndrome due to COVID-19	No	No
Congenital and adult neurosyphilis	No	No
Diabetic neuropathy	No	No
Encephalitis	Yes	Yes
Epilepsy	Yes (idiopathic)	Yes
Epilepsy due to cystic echinococcosis	No	No
Fetal alcohol syndrome	No	No
Guillain–Barré syndrome	No	Yes*
Idiopathic intellectual disability	No	No
Meningitis	Yes	Yes
Migraine	Yes	No
Motor neuron disease	Yes	Yes
Multiple sclerosis	Yes	Yes
Neonatal encephalopathy	No	Yes
Nervous system cancer (ie, CNS cancers, neuroblastoma, and other peripheral nervous cell tumours; includes paediatric and adult primary cases, and excludes metastases)	Yes (CNS)	Yes
Neural tube defects	No	Yes
Neurocysticercosis	No	Yes
Neurological complications due to congenital birth defects	No	No
Neurological complications due to congenital Zika syndrome	No	No
Neurological complications due to Down syndrome	No	No
Neurological complications due to Klinefelter syndrome	No	No
Neurological complications due to neonatal jaundice	No	No
Neurological complications due to neonatal sepsis	No	No
Neurological complications due to other chromosomal anomalies (excluding Down syndrome, Klinefelter syndrome, and Turner syndrome)	No	No
Neurological complications due to preterm birth	No	No
Other neurological disorders (including degenerative diseases, disorders of the autonomic nervous system, some movement disorders, spinocerebellar diseases, nerve root and plexus disorders, peripheral nerve disorders, neuromuscular disorders, and some muscle diseases such as myopathies; appendix pp 5–6)	Yes	Yes
Parkinson's disease	Yes	Yes
Rabies	No	Yes
Spinal cord injury	Yes	No
Stroke (ie, ischaemic stroke, subarachnoid haemorrhage, and intracerebral haemorrhage)	Yes	Yes
Tension-type headache	Yes	No
Tetanus	Yes	Yes
Traumatic brain injury	Yes	No

*Guillain–Barré syndrome deaths not ascribed to an underlying cause are captured in the category of other neurological disorders.

Table 1: Conditions included in our analysis of nervous system health loss

lay description of health states included in GBD. Disability weights and lay descriptions for all health states included in this analysis are described in the appendix (pp 49–61). To account for the fact that individuals can have more than one condition, we did a simulation to produce adjusted disability weights on the basis of the observed combinations of comorbidities generated by the simulation.

For sequelae that include both neurological and non-neurological health loss, YLDs were recalculated to isolate the non-fatal burden attributable to nervous system health loss. For example, sequelae of Down syndrome include severe intellectual disability with congenital heart disease due to Down syndrome (sequela 1) and severe intellectual disability due to Down syndrome (sequela 2). To isolate the neurological component of sequela 1, the adjusted disability weight generated from the comorbidity simulation for sequela 2 was used to recalculate YLDs by multiplying the prevalence of sequela 1 by the adjusted disability weight for sequela 2. This method was used to calculate YLDs for all sequelae with combined neurological and non-neurological health loss to isolate the burden due to nervous system health loss.

Calculating deaths and years of life lost

Deaths were estimated for 15 neurological conditions (table 1). An overview of data and modelling methods is shown in the appendix (pp 62–66). Total sources included for each individual condition are in the appendix (pp 62–63); ICD-9 and ICD-10 mapping for each condition and predictive covariates included in models are in the appendix (pp 63–66).

Causes of death in GBD are mutually exclusive and collectively exhaustive, meaning a given individual is assigned only one underlying cause of death and the sum of all disease-specific deaths adds up to total deaths for a given year. Years of life lost (YLLs) were calculated for each condition by multiplying deaths and remaining standard life expectancy.¹⁵ This measure captures premature death, meaning that a death at a young age, for example from neonatal encephalopathy, leads to more YLLs than a death at older ages, such as from Alzheimer's disease and other dementias. Disability-adjusted life-years (DALYs) were calculated as the sum of YLDs and YLLs by year, age, sex, and location, and represent the combined non-fatal and fatal burden of each condition. For conditions where we did not ascribe deaths (eg, headaches or conditions such as preterm birth where we included only long-term neurological outcomes), DALYs are equal to YLDs. Percentage of deaths and DALYs that occurred in LMICs were calculated using World Bank income levels, which are based on gross national income per capita.

Risk factors

GBD assesses the degree to which risk factors contribute to disease burden by identifying how disease DALYs would change given a theoretical minimum risk exposure level.¹⁷ The contribution of preventable risk factors to

DALYs was quantified for eight conditions: stroke, Alzheimer's disease and other dementias, multiple sclerosis, Parkinson's disease, idiopathic epilepsy, meningitis, encephalitis, and idiopathic intellectual disability. We did not include conditions that are not wholly neurological, for examples diabetes, as we could not ascribe risk contribution specific to neurological health states. The number of risk factors assessed in GBD 2021 varies by condition on the basis of evidence of association and available data. Exposure to a given risk was estimated for each location, age, sex, and year using regression modelling, and relative risk curves were computed by pooling data from studies assessing a given risk–outcome pair, such as intervention, cohort, and case–control studies. For each risk–outcome pair, risk exposure and relative risk analyses were used to calculate population attributable fraction. Attributable DALYs were then calculated, defined as the expected decrease in disease burden if risk exposure had equalled the theoretical minimum risk exposure level. Total attributable burden across all risks for a given outcome accounted for mediation effects but not potential synergistic effects.

Mean estimate, uncertainty, and percentage change calculation

Estimates were calculated 500 times by sampling the posterior distribution of the estimate (termed draws) at each step in the modelling process, and all calculations were performed by draw. Mean estimates for each year, age, sex, and location were taken from the distribution of 100 estimates, and 95% uncertainty intervals (UI) were taken as the 12.5th and 487.5th ordered draws. Age-standardised estimates were calculated using standard GBD population age weights.¹⁵ Percentage change between 1990 and 2021 was calculated by subtracting 1990 estimates from 2021 estimates and dividing the difference by 1990 estimates.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Overview

An estimated 3.40 billion (95% UI 3.20–3.62) individuals had a condition affecting the nervous system in 2021, corresponding to 43.1% (40.5–45.9) of the world population (table 2). These conditions caused 11.1 million (9.75–13.8) deaths and contributed to 168 million (114–243) YLDs and 275 million (247–316) YLLs. With a total of 443 million (378–521) DALYs, this expanded nervous system category was the top-ranked contributor to global DALYs and YLLs in GBD 2021, followed by cardiovascular diseases (excluding stroke; unpublished estimates, GBD 2021 Diseases and Injuries

Collaborators). The grouping of 15 conditions or disorders published in previous analyses¹ contributed 313 million (260–379) DALYs, or 70.5% (66.9–74.6) of the total neurological DALYs reported here for 2021. Newly added neurological conditions contributed 2.14 million (1.53–2.82) DALYs, or 0.5% (0.4–0.6) of total neurological DALYs; neurodevelopmental and paediatric conditions contributed 80.3 million (69.6–92.5) DALYs, or 18.2% (15.3–21.2); and other conditions that include neurological health loss contributed 48.1 million (34.1–64.8) DALYs, or 10.8% (8.1–13.6) of total neurological DALYs. The percentage contribution of original and newly added groups of conditions to total DALYs is shown in the appendix (p 67). The original category of 15 conditions would have still been the top-ranked contributor to global DALYs in GBD 2021 even without the addition of new conditions. The expanded category was also the first-ranked contributor to global YLDs, followed by musculoskeletal disorders (unpublished estimates, GBD 2021 Diseases and Injuries Collaborators).

For total nervous system health loss, global DALY counts increased by 18.2% (95% UI 8.7 to 26.7), from 375 million (339–419) DALYs in 1990 to 443 million (378–521) DALYs in 2021 (table 2). By contrast, age-standardised DALY rates decreased by 27.0% (21.5 to 32.4), from 7712.5 (6965.3 to 8626.0) per 100 000 people in 1990 to 5637.6 (4829.7 to 6587.9) per 100 000 people in 2021. Global YLLs remained almost constant, with a change of –3.1% (–11.8 to 7.7) from 284 million (268 to 302) YLLs in 1990 to 275 million (247 to 316) in 2021. By contrast, age-standardised YLL rates decreased 39.0% (33.2 to 44.3), from 5853.3 (5525.9 to 6272.7) per 100 000 people in 1990 to 3573.3 (3190.9 to 4134.3) per 100 000 people in 2021. Global YLDs increased 85.6% (75.8 to 98.0), from 91.0 million (58.6 to 134) YLDs in 1990 to 168 million (114 to 243) in 2021. Age-standardised YLDs rates increased by 11.2% (7.2 to 16.3), from 1859.4 (1217.7 to 2701.4) per 100 000 people in 1990 to 2064.1 (1390.0 to 2983.1) per 100 000 people in 2021 (table 2; appendix pp 68–69).

Regionally, age-standardised DALY rates were highest in western sub-Saharan Africa (8190.6 [95% UI 6986.0–9548.9] per 100 000 people) and central sub-Saharan Africa (7967.5 [6665.8–9546.6] per 100 000 people) and lowest in Australasia (2882.6 [2253.6–3717.3] per 100 000 people) and high-income Asia Pacific (2984.6 [2359.4–3768.2] per 100 000 people; appendix pp 70–78), with large differences observed for children younger than 5 years. For example, DALY rates for children younger than 5 years were approximately 18-fold higher in western sub-Saharan Africa (29 334.5 [23 721.8–35 170.5]) than in Australasia (1604.1 [1405.5–1846.4]), driven by conditions including neonatal encephalopathy, meningitis, and encephalitis. Age-standardised YLDs were similar between regions, ranging from a minimum in east Asia of 1698.6 (1133.9–2446.0) per 100 000 people to a maximum in the

Caribbean of 2327.5 (1571.2–3295.6) per 100 000 people. Age-standardised YLLs had greater regional variation, ranging from a minimum in Australasia of 1098.9 (910.3–1456.4) to a maximum in western sub-Saharan Africa of 6163.8 (5131.0–7314.6; appendix pp 70–79). Using World Bank income levels, 81.9% (77.5–84.9; 9.10 million of 11.1 million) of deaths and 84.7% (83.1–86.3; 375 million of 443 million) of DALYs attributable to neurological conditions were in LMICs.

The ten conditions that accounted for the greatest nervous system DALYs in 2021 were stroke, neonatal encephalopathy, migraine, Alzheimer's disease and other dementias, diabetic neuropathy, meningitis, epilepsy, neurological complications due to preterm birth, autism spectrum disorder, and nervous system cancer, with stroke being the greatest contributor globally and in 19 of 21 GBD regions (table 2; figure 1). Notably, four of the top ten conditions were not included in our previous analyses of neurological burden: neonatal encephalopathy, diabetic neuropathy, neurological complications due to preterm birth, and autism spectrum disorder, which emphasises the effects of early life and childhood conditions on total nervous system health loss and the under-recognised effects on the peripheral nervous system.

Regional rankings across conditions were mostly consistent (figure 1). Exceptions included regional variation for meningitis (regional ranking range: third to 22nd), tetanus (range: 11th to 35th), multiple sclerosis (range: 15th to 31st), and motor neuron disease (range: 15th to 34th). Some infectious disease rankings reflected their regional pathogen endemicity (eg, cerebral malaria, neurocysticercosis, and neurological complications due to congenital Zika syndrome).

For children younger than 5 years, the three leading causes of DALYs globally were neonatal encephalopathy (8316.7 [95% UI 7072.6–9991.8] per 100 000 people), meningitis (1234.9 [869.5–1741.7] per 100 000 people), and neural tube defects (722.6 [580.8–899.4] per 100 000 people). For older children and adolescents aged 5–19 years, the three leading causes of DALYs were migraine (380.0 [24.7–946.6] per 100 000 people), neurological complications due to preterm birth (234.3 [168.4–305.2] per 100 000 people), and epilepsy (185.1 [137.0–261.7] per 100 000 people). For adults aged 20–59 years, the leading causes were stroke (1126.1 [1035.5–1218.4] per 100 000 people), migraine (750.8 [117.3–1617.8] per 100 000 people), and diabetic neuropathy (260.5 [171.9–387.6] per 100 000 people), and for adults aged 60–79 years, the leading causes were stroke (8490.9 [7827.5–9108.6] per 100 000 people), Alzheimer's disease and other dementias (1504.2 [746.6–3345.6] per 100 000 people), and diabetic neuropathy (1397.3 [911.8–1930.8] per 100 000 people). For adults aged 80 years and older, the leading causes were stroke (20 336.1 [17762.6–22 137.4] per 100 000 people), Alzheimer's disease and other

	Counts (thousands)		Age-standardised rate (per 100 000 people)				
	2021	Percentage change, 1990–2021	2021	Percentage change, 1990–2021	Females	Males	Female-to-male ratio*
All neurological conditions							
DALYs	443 000 (378 000 to 521 000)	18.2% (8.7 to 26.7)	5637.6 (4829.7 to 6587.9)	-27.0% (-32.4 to -21.5)	5185.8 (4281.2 to 6262.9)	6101.0 (5320.2 to 6982.7)	0.85 (0.78 to 0.93)
YLDs	168 000 (114 000 to 243 000)	85.6% (75.8 to 98.0)	2064.1 (1390.0 to 2983.1)	11.2% (7.2 to 16.3)	2078.2 (1301.3 to 3133.1)	2043.6 (1439.2 to 2832.7)	1.01 (0.88 to 1.14)
YLLs	275 000 (247 000 to 316 000)	-3.1% (-11.8 to 7.7)	3573.3 (3190.9 to 4134.3)	-39.0% (-44.3 to -33.2)	3107.4 (2755.1 to 3604.8)	4057.2 (3574.4 to 4576.6)	0.77 (0.71 to 0.84)
Prevalence	3 400 000 (3 200 000 to 3 620 000)	58.8% (56.3 to 61.5)	41 204.1 (38 654.3 to 43 869.9)	1.5% (0.7 to 2.4)	43 458.5 (40 796.2 to 46 078.7)	38 949.0 (36 503.4 to 41 604.7)	1.12 (1.10 to 1.14)
Deaths	11 100 (9750 to 13 800)	41.2% (28.1 to 58.8)	139.0 (121.3 to 173.3)	-33.6% (-38.8 to -27.6)	125.0 (105.1 to 161.2)	154.6 (136.0 to 186.7)	0.81 (0.73 to 0.90)
Alzheimer's disease and other dementias							
DALYs	36 300 (17 200 to 77 400)	168.7% (156.3 to 179.9)	450.9 (212.9 to 956.8)	1.7% (-2.8 to 5.1)	504.8 (241.5 to 1062.7)	372.4 (170.8 to 806.4)	1.37 (1.26 to 1.46)
YLDs	11 600 (7960 to 15 300)	162.7% (157.0 to 168.0)	141.9 (97.7 to 187.2)	2.6% (1.1 to 3.6)	161.9 (110.7 to 214.8)	114.4 (78.5 to 151.2)	1.42 (1.33 to 1.49)
YLLs	24 700 (6370 to 65 700)	173.4% (153.2 to 192.5)	308.9 (78.9 to 789.0)	1.4% (-4.1 to 7.4)	342.9 (89.2 to 872.0)	258.0 (62.8 to 674.5)	1.36 (1.22 to 1.47)
Prevalence	56 900 (49 400 to 65 000)	160.8% (156.1 to 165.9)	694.0 (602.9 to 794.1)	3.2% (1.7 to 4.2)	769.9 (670.7 to 877.6)	589.5 (507.5 to 678.8)	1.31 (1.28 to 1.35)
Deaths	1950 (503 to 5080)	198.3% (175.2 to 221.8)	25.2 (6.7 to 64.4)	1.5% (-4.0 to 7.1)	27.9 (7.5 to 70.1)	20.7 (5.2 to 55.1)	1.38 (1.24 to 1.49)
Attention deficit hyperactivity disorder							
YLDs	1030 (572 to 1670)	18.7% (14.8 to 22.8)	13.5 (7.4 to 21.9)	-9.6% (-11.9 to -7.3)	7.7 (4.2 to 12.7)	19.0 (10.4 to 30.7)	0.40 (0.38 to 0.43)
Prevalence	84 800 (63 400 to 117 000)	18.8% (14.9 to 23.2)	1108.9 (828.7 to 1536.2)	-9.7% (-11.8 to -7.4)	636.0 (467.9 to 879.0)	1561.7 (1172.5 to 2151.7)	0.41 (0.39 to 0.43)
Autism spectrum disorder							
YLDs	11 500 (7840 to 16 300)	46.7% (44.5 to 48.5)	147.6 (100.2 to 208.1)	2.1% (0.6 to 3.4)	94.5 (64.6 to 133.1)	199.8 (136.3 to 281.7)	0.47 (0.46 to 0.49)
Prevalence	61 800 (52 100 to 72 700)	47.5% (45.1 to 49.4)	788.3 (663.8 to 927.2)	2.0% (0.4 to 3.1)	508.1 (424.6 to 604.3)	1064.7 (898.5 to 1245.7)	0.48 (0.46 to 0.50)
Cerebral malaria							
YLDs	407 (296 to 514)	109.1% (98.6 to 120.1)	5.3 (3.9 to 6.7)	53.6% (45.6 to 61.5)	5.6 (4.1 to 7.1)	5.0 (3.6 to 6.3)	1.12 (1.08 to 1.16)
Prevalence	996 (923 to 1070)	122.2% (116.4 to 128.1)	12.9 (12.0 to 13.9)	63.0% (58.7 to 67.4)	13.8 (12.7 to 14.9)	12.1 (11.2 to 13.1)	1.14 (1.13 to 1.15)
Congenital birth defects†							
YLDs	1450 (676 to 2750)	53.4% (48.3 to 58.4)	18.7 (8.8 to 35.4)	8.9% (5.5 to 12.4)	15.9 (7.4 to 30.4)	21.4 (10.2 to 39.9)	0.74 (0.69 to 0.80)
Prevalence	13 900 (7980 to 21 600)	56.0% (51.6 to 60.4)	180.2 (104.5 to 278.7)	11.4% (8.6 to 14.5)	157.0 (90.4 to 243.6)	203.0 (118.0 to 315.0)	0.77 (0.73 to 0.81)
Congenital Zika syndrome†							
YLDs	0.100 (0.100 to 0.100)	100.0% (100.0 to 100.0)	0.0 (0.0 to 0.0)	100.0% (100.0 to 100.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.97 (0.93 to 1.02)
Prevalence	0.100 (0.100 to 0.200)	100.0% (100.0 to 100.0)	0.0 (0.0 to 0.0)	100.0% (100.0 to 100.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.97 (0.97 to 0.97)
COVID-19†							
YLDs	2480 (87.2 to 7990)	100% (100 to 100)	29.4 (1.1 to 101.1)	100.0% (100.0 to 100.0)	36.9 (1.0 to 122.8)	19.7 (0.9 to 75.0)	1.84 (0.97 to 3.35)
Prevalence	23 400 (4140 to 72 800)	100% (100 to 100)	288.5 (50.5 to 899.2)	100.0% (100.0 to 100.0)	370.9 (64.3 to 1175.0)	205.7 (35.8 to 608.9)	1.87 (1.32 to 2.61)
Cystic echinococcosis†							
YLDs	4.60 (2.90 to 7.00)	21.1% (-0.3 to 48.3)	0.1 (0.0 to 0.1)	-24.7% (-37.7 to -9.2)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	1.21 (1.14 to 1.27)

(Table 2 continues on next page)

	Counts (thousands)		Age-standardised rate (per 100 000 people)				
	2021	Percentage change, 1990–2021	2021	Percentage change, 1990–2021	Females	Males	Female-to-male ratio
(Continued from previous page)							
Prevalence	15.1 (11.5 to 19.3)	45.2% (27.9 to 60.2)	0.2 (0.1 to 0.2)	-10.7% (-19 to -2.0)	0.2 (0.2 to 0.3)	0.2 (0.1 to 0.2)	1.21 (1.14 to 1.27)
Diabetic neuropathy							
YLDs	26 300 (18 000 to 37 400)	309.1% (296.2 to 320.4)	694.0 (602.9 to 794.1)	91.9% (86.3 to 97.3)	769.9 (670.7 to 877.6)	589.5 (507.5 to 678.8)	0.92 (0.89 to 0.94)
Prevalence	206 000 (171 000 to 249 000)	310.5% (297.4 to 322.3)	301.9 (207.0 to 429.4)	92.2% (86.4 to 97.7)	289.7 (198.4 to 410.9)	315.9 (216.4 to 449.9)	0.95 (0.92 to 0.97)
Down syndrome†							
YLDs	135 (89.8 to 194)	-4.5% (-11.8 to 3.0)	1.8 (1.2 to 2.6)	-24.2% (-29.7 to -18.3)	1.7 (1.2 to 2.5)	1.9 (1.2 to 2.7)	0.93 (0.92 to 0.95)
Prevalence	1490 (1240 to 1780)	-5.4% (-12.6 to 2.3)	20.0 (16.7 to 24.0)	-24.6% (-30.2 to -18.6)	19.3 (16.1 to 22.9)	20.7 (17.2 to 25.0)	0.93 (0.91 to 0.94)
Encephalitis							
DALYs	4950 (4150 to 5700)	-17.8% (-33.4 to 4.0)	67.4 (55.7 to 78.3)	-35.7% (-47.8 to -19.0)	67.2 (58.4 to 78.2)	67.7 (50.6 to 83.5)	1.01 (0.76 to 1.26)
YLDs	497 (354 to 658)	5.0% (0.0 to 10.5)	6.2 (4.4 to 8.2)	-29.9% (-33.2 to -26.6)	6.1 (4.3 to 8.1)	6.3 (4.5 to 8.4)	0.96 (0.93 to 1.00)
YLLs	4460 (3690 to 5280)	-19.7% (-36.4 to 4.6)	61.2 (49.9 to 72.9)	-36.2% (-49.1 to -17.9)	61.2 (51.9 to 71.1)	61.4 (44.2 to 76.2)	1.01 (0.74 to 1.31)
Prevalence	4640 (3250 to 6000)	0.7% (-3.0 to 5.3)	57.3 (40.2 to 73.9)	-35.6% (-38.2 to -3.02)	54.7 (38.7 to 70.3)	59.9 (41.7 to 77.7)	0.91 (0.90 to 0.93)
Deaths	92.0 (79.0 to 108)	9.9% (-8.9 to 36.4)	1.2 (1.0 to 1.4)	-26.1% (-38.0 to -8.3)	1.2 (1.0 to 1.4)	1.2 (0.9 to 1.5)	0.98 (0.69 to 1.27)
Epilepsy							
DALYs	14 400 (11 000 to 18 500)	22.5% (7.7 to 38.7)	183.9 (141.0 to 237.2)	-14.6% (-24.6 to -3.9)	160.4 (118.3 to 212.2)	207.2 (161.9 to 262.2)	0.77 (0.67 to 0.86)
YLDs	7760 (4660 to 11 800)	35.6% (7.1 to 67.6)	98.9 (59.8 to 149.8)	-7.1% (-25.8 to 13.7)	94.4 (57.0 to 142.9)	103.6 (62.4 to 157.5)	0.91 (0.89 to 0.94)
YLLs	6610 (5450 to 7340)	10.7% (-0.6 to 24.4)	85.0 (70.7 to 95.0)	-21.6% (-29.6 to -12.5)	66.0 (47.6 to 76.6)	103.6 (84.2 to 117.2)	0.64 (0.45 to 0.78)
Prevalence	24 400 (18 600 to 30 800)	57.4% (30.6 to 85.6)	308.9 (236.2 to 390.1)	6.2% (-10.5 to 24.1)	294.6 (224.6 to 373.7)	323.8 (249.0 to 406.4)	0.91 (0.89 to 0.93)
Deaths	140 (116 to 153)	34.2% (23.3 to 45.8)	1.7 (1.5 to 1.9)	-15.7% (-22.5 to -8.8)	1.4 (1.0 to 1.5)	2.1 (1.8 to 2.4)	0.64 (0.46 to 0.76)
Fetal alcohol syndrome							
YLDs	23.6 (13.8 to 37.0)	24.0% (14.8 to 32.1)	0.3 (0.2 to 0.5)	-11.1% (-17.4 to -5.4)	0.3 (0.2 to 0.5)	0.3 (0.2 to 0.5)	0.91 (0.84 to 0.99)
Prevalence	517 (374 to 677)	33.7% (28.4 to 37.9)	6.7 (4.9 to 8.8)	-4.7% (-8.2 to -1.8)	6.2 (4.7 to 8.0)	7.1 (5.1 to 9.5)	0.88 (0.83 to 0.99)
Guillain-Barré syndrome							
YLDs	49.0 (31.6 to 72.5)	71.3% (61.4 to 81.9)	0.6 (0.4 to 0.9)	5.7% (3.3 to 8.2)	0.6 (0.4 to 0.8)	0.7 (0.4 to 1.0)	0.86 (0.84 to 0.89)
Prevalence	166 (134 to 201)	71.3% (61.4 to 81.9)	2.0 (1.7 to 2.5)	5.7% (3.3 to 8.2)	1.9 (1.5 to 2.3)	2.2 (1.8 to 2.7)	0.86 (0.84 to 0.89)
Idiopathic intellectual disability							
YLDs	3810 (1760 to 6520)	16.3% (10.5 to 22.3)	49.9 (23.2 to 85.4)	-13.6% (-18.0 to -8.4)	51.5 (25.5 to 85.6)	48.3 (20.8 to 84.7)	1.08 (1.00 to 1.20)
Prevalence	88 300 (47 100 to 129 000)	10.2% (5.7 to 13.7)	1157.2 (620.9 to 1688.1)	-18.0% (-21.1 to -15.7)	1204.4 (688.7 to 1708.4)	1110.5 (554.5 to 1667.2)	1.10 (1.02 to 1.24)
Klinefelter syndrome†							
YLDs	3.00 (1.50 to 5.80)	30.5% (24.1 to 37.3)	0.0 (0.0 to 0.0)	2.7% (-1.7 to 6.7)	NA	0.0 (0.0 to 0.1)	NA
Prevalence	230 (158 to 320)	30.2% (25.7 to 34.6)	3.1 (2.1 to 4.3)	2.7% (1.3 to 4.2)	NA	6.1 (4.2 to 8.4)	NA

(Table 2 continues on next page)

	Counts (thousands)		Age-standardised rate (per 100 000 people)				
	2021	Percentage change, 1990–2021	2021	Percentage change, 1990–2021	Females	Males	Female-to-male ratio
(Continued from previous page)							
Meningitis							
DALYs	14 500 (11 500 to 18 700)	-56.0% (-63.6 to -45.5)	208.5 (163.6 to 270.8)	-62.1% (-68.9 to -52.8)	193.3 (155.1 to 245.0)	223.0 (167.7 to 302.2)	0.87 (0.69 to 1.03)
YLDs	603 (425 to 791)	-31.3% (-34.3 to -28.0)	7.8 (5.5 to 10.2)	-51.7% (-53.8 to -49.4)	7.6 (5.4 to 10.0)	7.9 (5.6 to 10.4)	0.97 (0.95 to 1.00)
YLLs	13 900 (11 000 to 18 000)	-56.7% (-64.2 to -45.8)	200.7 (156.5 to 262.5)	-62.5% (-69.3 to -52.9)	185.7 (146.9 to 236.1)	215.1 (160.0 to 294.1)	0.87 (0.68 to 1.03)
Prevalence	7270 (5930 to 9070)	-35.5% (-38.2 to -32.7)	92.3 (75.2 to 114.8)	-56.8% (-58.6 to -55.1)	88.5 (72.5 to 109.7)	96.1 (78.2 to 120.0)	0.92 (0.91 to 0.93)
Deaths	214 (177 to 266)	-49.0% (-56.6 to -38.2)	2.9 (2.4 to 3.7)	-60.2% (-66.3 to -51.7)	2.7 (2.2 to 3.4)	3.2 (2.5 to 4.1)	0.87 (0.70 to 0.99)
Migraine							
YLDs	43 400 (6740 to 95 100)	58.9% (53.7 to 66.0)	532.7 (80.7 to 1167.8)	0.6% (-4.0 to 2.6)	662.8 (93.8 to 1450.9)	403.9 (67.5 to 872.6)	1.62 (1.39 to 1.79)
Prevalence	1 160 000 (996 000 to 1 330 000)	58.2% (54.4 to 62.6)	14 246.5 (12 194.1 to 16 378.7)	1.6% (0.3 to 2.6)	17 902.6 (15 446.0 to 20 487.0)	10 624.2 (9039.5 to 12 297.3)	1.69 (1.65 to 1.73)
Motor neuron disease							
DALYs	1040 (962 to 1120)	105.8% (87.1 to 125.9)	12.2 (11.2 to 13.2)	8.5% (-0.6 to 18.6)	10.1 (9.3 to 11.1)	14.4 (13.0 to 15.7)	0.70 (0.62 to 0.77)
YLDs	57.9 (40.7 to 78.0)	68.4% (61.6 to 75.9)	0.7 (0.5 to 1.0)	-1.4% (-3.4 to 0.7)	0.6 (0.4 to 0.9)	0.8 (0.5 to 1.0)	0.83 (0.81 to 0.86)
YLLs	983 (903 to 1070)	108.6% (88.7 to 130.2)	11.5 (10.5 to 12.4)	9.2% (-0.5 to 20.0)	9.4 (8.7 to 10.5)	13.7 (12.2 to 15.0)	0.69 (0.61 to 0.77)
Prevalence	273 (236 to 314)	68.6% (61.8 to 76.2)	3.3 (2.9 to 3.8)	-1.3% (-3.3 to 0.9)	3.0 (2.6 to 3.5)	3.6 (3.2 to 4.2)	0.83 (0.81 to 0.85)
Deaths	39.1 (35.6 to 42.4)	156.2% (136.0 to 178.6)	0.5 (0.4 to 0.5)	19.9% (10.9 to 30.1)	0.4 (0.3 to 0.4)	0.5 (0.5 to 0.6)	0.69 (0.62 to 0.77)
Multiple sclerosis							
DALYs	973 (836 to 1130)	69.5% (63.5 to 75.6)	11.4 (9.7 to 13.2)	-11.0% (-14 to -8.0)	14.5 (12.4 to 16.9)	8.1 (7.0 to 9.5)	1.80 (1.72 to 1.87)
YLDs	484 (344 to 631)	86.5% (78.9 to 94.5)	5.7 (4.0 to 7.4)	-0.4% (-3.9 to 3.1)	7.5 (5.3 to 9.7)	3.9 (2.7 to 5.1)	1.93 (1.86 to 2.00)
YLLs	490 (465 to 513)	55.7% (47.3 to 63.9)	5.7 (5.4 to 6.0)	-19.5% (-23.5 to -15.1)	7.1 (6.7 to 7.6)	4.2 (4.0 to 4.5)	1.68 (1.54 to 1.80)
Prevalence	1890 (1690 to 2110)	88.1% (80.8 to 95.5)	22.2 (19.8 to 24.8)	-0.3% (-3.6 to 3.3)	29.3 (26.2 to 32.7)	14.7 (13.0 to 16.6)	1.99 (1.94 to 2.05)
Deaths	16.3 (15.3 to 17.0)	79.1% (69.2 to 88.6)	0.2 (0.2 to 0.2)	-12.7% (-17.4 to -8.3)	0.2 (0.2 to 0.2)	0.1 (0.1 to 0.2)	1.59 (1.46 to 1.70)
Neonatal encephalopathy							
DALYs	58 600 (50 100 to 69 000)	-27.5% (-39.5 to -14.5)	932.1 (797.5 to 1101.7)	-26.5% (-38.9 to -13.0)	795.2 (675.1 to 942.3)	1060.2 (889.7 to 1259.1)	0.75 (0.67 to 0.87)
YLDs	4280 (3100 to 5590)	189.1% (61.5 to 348.9)	55.2 (39.9 to 72.1)	107.0% (16.2 to 220.4)	45.3 (32.5 to 59.5)	64.7 (46.7 to 84.3)	0.70 (0.68 to 0.72)
YLLs	54 300 (46 000 to 64 900)	-31.5% (-43.9 to -17.9)	876.9 (743.6 to 1056.6)	-29.2% (-42.0 to -15.3)	749.9 (627.7 to 895.0)	995.6 (824.7 to 1193.6)	0.76 (0.67 to 0.88)
Prevalence	18 600 (16 100 to 21 100)	175.2% (94.9 to 246.8)	238.1 (206.3 to 269.7)	91.2% (37.2 to 139.8)	188.4 (163.5 to 213.3)	286.6 (248.7 to 325.4)	0.66 (0.65 to 0.67)
Deaths	604 (511 to 722)	-31.5% (-44.0 to -17.9)	9.7 (8.3 to 11.7)	-29.2% (-42.0 to -15.3)	8.3 (7.0 to 10.0)	11.1 (9.2 to 13.3)	0.76 (0.67 to 0.88)
Neonatal jaundice†							
YLDs	718 (517 to 917)	80.0% (69.8 to 90.3)	9.3 (6.7 to 11.9)	31.5% (24.3 to 39.0)	9.5 (6.8 to 12.1)	9.2 (6.6 to 11.8)	1.03 (1.01 to 1.05)
Prevalence	1960 (1800 to 2160)	102.7% (95.8 to 109.0)	25.5 (23.4 to 28.2)	48.8% (43.8 to 53.5)	25.6 (23.5 to 28.2)	25.4 (23.3 to 28.1)	1.01 (1.00 to 1.02)

(Table 2 continues on next page)

	Counts (thousands)		Age-standardised rate (per 100 000 people)				
	2021	Percentage change, 1990–2021	2021	Percentage change, 1990–2021	Females	Males	Female-to-male ratio
(Continued from previous page)							
Neonatal sepsis†							
YLDs	2490 (1570 to 3590)	136.5% (32.3 to 322.0)	32.3 (20.3 to 46.5)	70.4% (-4.5 to 203.1)	27.0 (17.1 to 38.7)	37.3 (23.5 to 54.0)	0.72 (0.71 to 0.74)
Prevalence	7100 (5140 to 9260)	153.8% (51.5 to 332.6)	92.1 (66.8 to 120.1)	83.3% (9.5 to 212.0)	75.2 (54.7 to 97.7)	108.3 (78.3 to 141.4)	0.69 (0.69 to 0.70)
Nervous system cancer							
DALYs	9200 (7890 to 10 600)	50.2% (29.1 to 69.0)	111.8 (95.5 to 129.3)	-8.9% (-20.8 to 1.5)	96.8 (86.4 to 107.3)	127.5 (97.7 to 162.0)	0.77 (0.60 to 1.00)
YLDs	132 (93.8 to 174)	111.8% (89.2 to 133.2)	1.6 (1.1 to 2.1)	22.5% (9.0 to 34.4)	1.5 (1.0 to 2.0)	1.7 (1.2 to 2.3)	0.86 (0.70 to 1.08)
YLLs	9070 (7750 to 10 500)	49.6% (28.4 to 67.8)	110.3 (93.9 to 127.4)	-9.2% (-21.2 to 1.0)	95.3 (85.1 to 105.7)	125.8 (96.3 to 159.7)	0.77 (0.60 to 1.00)
Prevalence	1030 (907 to 1140)	117.1% (92.0 to 140.4)	12.8 (11.2 to 14.2)	37.7% (22.5 to 51.3)	12.5 (11.1 to 13.9)	13.2 (10.4 to 15.9)	0.95 (0.78 to 1.21)
Deaths	264 (226 to 302)	90.3% (67.8 to 110.7)	3.1 (2.7 to 3.6)	1.3% (-9.8 to 11.9)	2.7 (2.4 to 3.0)	3.6 (2.8 to 4.4)	0.75 (0.59 to 0.96)
Neural tube defects							
DALYs	5300 (4310 to 6510)	-47.3% (-59.0 to -24.7)	83.2 (67.8 to 102.5)	-47.7% (-59.5 to -25.1)	88.2 (64.3 to 118.1)	78.5 (61.6 to 104.5)	1.14 (0.72 to 1.61)
YLDs	333 (229 to 456)	11.8% (5.2 to 18.1)	4.5 (3.1 to 6.2)	-11.0% (-16.3 to -6.2)	4.6 (3.1 to 6.2)	4.4 (3.1 to 6.1)	1.03 (1.00 to 1.06)
YLLs	4970 (3980 to 6430)	-49.1% (-61.3 to -26.5)	78.7 (62.8 to 98.6)	-49.0% (-61.1 to -26.2)	83.7 (60.7 to 114.3)	74.1 (56.9 to 100.2)	1.15 (0.71 to 1.65)
Prevalence	1130 (965 to 1310)	11.2% (4.4 to 17.7)	15.2 (13.0 to 17.6)	-12.2% (-17.1 to -7.6)	15.4 (13.2 to 17.8)	15.0 (12.8 to 17.3)	1.03 (1.00 to 1.06)
Deaths	56.4 (45.3 to 72.8)	-48.6% (-60.9 to -25.7)	0.9 (0.7 to 1.1)	-48.8% (-61.0 to -26.0)	0.9 (0.7 to 1.3)	0.8 (0.6 to 1.1)	1.15 (0.71 to 1.66)
Neurocysticercosis							
DALYs	1240 (788 to 1810)	14.2% (-2.4 to 34.5)	14.6 (9.3 to 21.3)	-38.4% (-46.7 to -28.5)	15.6 (9.9 to 22.5)	13.6 (8.8 to 20.0)	1.15 (1.06 to 1.22)
YLDs	1150 (714 to 1730)	18.5% (0.6 to 41.3)	13.6 (8.4 to 20.2)	-37.3% (-46.2 to -27.0)	14.6 (9.1 to 21.5)	12.6 (7.8 to 18.9)	1.17 (1.09 to 1.24)
YLLs	81.3 (54.1 to 119)	-22.0% (-46.6 to 11.3)	1.0 (0.7 to 1.5)	-48.4% (-65.1 to -25.3)	1.0 (0.5 to 1.5)	1.1 (0.6 to 1.7)	0.94 (0.44 to 1.61)
Prevalence	4360 (3150 to 5720)	43.7% (31.2 to 59.2)	51.3 (37.2 to 67.3)	-25.1% (-29.0 to -19.7)	55.5 (40.3 to 71.9)	46.9 (33.7 to 63.1)	1.19 (1.11 to 1.25)
Deaths	1.60 (1.10 to 2.30)	-16.7% (-43.8 to 17.7)	0.0 (0.0 to 0.0)	-50.0% (-66.2 to -28.5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.93 (0.48 to 1.53)
Neurosyphilis							
YLDs	64.9 (42.2 to 93.4)	17.3% (4.8 to 31.0)	0.8 (0.5 to 1.2)	-18.5% (-27.0 to -9.4)	0.8 (0.5 to 1.1)	0.9 (0.6 to 1.3)	0.89 (0.83 to 0.94)
Prevalence	696 (563 to 857)	38.5% (25.0 to 53.3)	8.8 (7.1 to 10.8)	-6.1% (-15.5 to 4.0)	8.6 (6.9 to 10.6)	9.0 (7.3 to 11.0)	0.95 (0.93 to 0.97)
Other chromosomal anomalies†							
YLDs	295 (196 to 417)	7.3% (2.3 to 12.4)	4.1 (2.7 to 5.7)	-12.8% (-16.8 to -8.7)	3.3 (2.2 to 4.7)	4.7 (3.1 to 6.9)	0.71 (0.59 to 0.86)
Prevalence	3280 (2880 to 3760)	6.2% (0.9 to 11.2)	45.2 (39.5 to 52.0)	-13.0% (-17.2 to -9.0)	37.0 (32.4 to 43.0)	52.8 (44.2 to 62.9)	0.71 (0.59 to 0.85)
Other neurological disorders							
DALYs	4360 (3630 to 5270)	131.0% (107.3 to 155.5)	54.8 (45.3 to 66.6)	50.7% (35.4 to 65.5)	51.8 (42.7 to 63.2)	57.8 (48.0 to 69.4)	0.90 (0.84 to 0.96)
YLDs	2010 (1330 to 2870)	153.8% (110.9 to 197.8)	25.5 (16.8 to 36.6)	70.6% (43.8 to 98.8)	25.3 (16.6 to 36.2)	25.6 (16.8 to 36.9)	0.99 (0.96 to 1.02)
YLLs	2330 (2080 to 2510)	116.0% (83.3 to 140.8)	29.0 (25.9 to 31.4)	37.6% (18.3 to 52.7)	26.3 (22.7 to 28.9)	32.0 (29.0 to 34.8)	0.82 (0.74 to 0.93)

(Table 2 continues on next page)

	Counts (thousands)		Age-standardised rate (per 100 000 people)				
	2021	Percentage change, 1990–2021	2021	Percentage change, 1990–2021	Females	Males	Female-to-male ratio
(Continued from previous page)							
Deaths	71.5 (65.0 to 76.4)	189.8% (157.8 to 214.6)	0.9 (0.8 to 0.9)	50.1% (35.1 to 61.2)	0.8 (0.7 to 0.8)	1.0 (0.9 to 1.1)	0.78 (0.71 to 0.85)
Parkinson's disease							
DALYs	7470 (6730 to 8140)	161.8% (145.8 to 177.0)	89.6 (80.7 to 97.5)	10.0% (3.7 to 16.1)	68.6 (60.7 to 75.8)	117.5 (106.2 to 128.5)	0.58 (0.53 to 0.64)
YLDs	1670 (1170 to 2210)	271.2% (256.9 to 284.4)	19.6 (13.9 to 25.9)	60.6% (54.3 to 65.9)	16.1 (11.4 to 21.2)	23.9 (17.0 to 31.5)	0.67 (0.65 to 0.69)
YLLs	5800 (5250 to 6260)	141.4% (124.0 to 158.5)	70.0 (63.0 to 75.2)	1.0% (-5.9 to 7.5)	52.5 (45.4 to 58.0)	93.5 (84.6 to 101.7)	0.56 (0.50 to 0.63)
Prevalence	11 800 (10 400 to 13 400)	273.9% (260.2 to 287.3)	138.6 (123.1 to 157.6)	60.7% (54.9 to 66.2)	114.5 (102.1 to 129.8)	168.2 (148.4 to 191.7)	0.68 (0.67 to 0.69)
Deaths	388 (345 to 419)	162.2% (143.6 to 179.4)	4.8 (4.3 to 5.2)	4.1% (-2.7 to 10.3)	3.6 (3.0 to 4.0)	6.6 (5.9 to 7.1)	0.55 (0.49 to 0.61)
Preterm birth†							
YLDs	13 800 (9950 to 17 900)	74.0% (61.9 to 85.0)	180.7 (130.1 to 233.4)	29.2% (20.3 to 37.7)	169.3 (122.6 to 218.2)	191.4 (137.6 to 247.7)	0.89 (0.87 to 0.90)
Prevalence	97 500 (83 000 to 112 000)	64.1% (53.7 to 74.3)	1256.8 (1073.2 to 1445.9)	16.1% (8.7 to 23.7)	1146.3 (978.2 to 1315.6)	1363.9 (1162.4 to 1572.4)	0.84 (0.83 to 0.85)
Rabies							
DALYs	571 (325 to 826)	-59.0% (-71.8 to -44.1)	7.5 (4.2 to 11.0)	-69.9% (-79.3 to -58.8)	5.6 (3.0 to 9.9)	9.4 (5.0 to 13.6)	0.62 (0.26 to 0.93)
YLDs	0.100 (0.00 to 0.100)	-54.3% (-66.5 to -40.4)	0.0 (0.0 to 0.0)	-69.8% (-77.6 to -61.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.63 (0.28 to 0.91)
YLLs	572 (324 to 832)	-59.0% (-71.9 to -44.0)	7.5 (4.2 to 11.0)	-69.9% (-79.2 to -58.8)	5.6 (3.0 to 9.9)	9.4 (5.0 to 13.6)	0.62 (0.26 to 0.93)
Prevalence	0.400 (0.200 to 0.500)	-54.3% (-66.5 to -40.4)	0.0 (0.0 to 0.0)	-69.8% (-77.6 to -61.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.63 (0.28 to 0.91)
Deaths	10.1 (6.00 to 14.4)	-54.2% (-66.3 to -39.9)	0.1 (0.1 to 0.2)	-69.7% (-77.4 to -60.7)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.2)	0.62 (0.28 to 0.91)
Spinal cord injury							
YLDs	4570 (3200 to 6020)	28.9% (24.0 to 33.9)	54.7 (38.3 to 72.1)	-24.2% (-26.9 to -20.9)	37.9 (26.7 to 49.7)	71.6 (50.5 to 93.6)	0.53 (0.50 to 0.57)
Prevalence	15 400 (14 000 to 17 100)	42.0% (37.7 to 46.5)	183.9 (167.3 to 204.2)	-17.8% (-20.4 to -14.9)	131.5 (118.6 to 146.8)	236.6 (215.0 to 262.3)	0.56 (0.52 to 0.59)
Stroke							
DALYs	160 000 (148 000 to 172 000)	32.2% (21.7 to 42.6)	1886.0 (1740.1 to 2017.3)	-38.7% (-43.4 to -34.0)	1578.2 (1431.4 to 1710.6)	2232.3 (2028.8 to 2449.0)	0.71 (0.64 to 0.78)
YLDs	15 200 (11 000 to 19 400)	89.9% (85.9 to 94.0)	178.7 (128.9 to 227.6)	-7.4% (-9.0 to -5.9)	175.6 (126.7 to 223.1)	183.4 (132.7 to 234.5)	0.96 (0.94 to 0.98)
YLLs	145 000 (134 000 to 157 000)	28.2% (16.9 to 38.9)	1707.4 (1572.6 to 1838.0)	-40.8% (-45.8 to -35.8)	1402.6 (1263.6 to 1527.5)	2048.9 (1866.9 to 2253.8)	0.69 (0.61 to 0.77)
Prevalence	93 800 (89 000 to 99 300)	86.1% (83.0 to 89.4)	1099.3 (1044.2 to 1162.1)	-8.5% (-9.7 to -7.3)	1027.7 (974.4 to 1088.1)	1184.4 (1124.2 to 1252.1)	0.87 (0.85 to 0.88)
Deaths	7250 (6610 to 7820)	44.1% (32.6 to 56.2)	87.4 (78.6 to 94.2)	-39.4% (-44.0 to -34.7)	74.5 (66.0 to 81.7)	103.1 (93.1 to 112.8)	0.72 (0.64 to 0.81)
Tension-type headache							
YLDs	4600 (1350 to 15 000)	63.4% (49.6 to 69.5)	55.7 (16.1 to 185.1)	-3.1% (-4.8 to 0.9)	62.0 (18.8 to 189.0)	49.3 (13.5 to 172.4)	1.34 (0.94 to 1.43)
Prevalence	2 010 000 (1 780 000 to 2 270 000)	56.4% (52.7 to 60.2)	24 764.8 (21 863.6 to 27 954.7)	-0.6% (-1.3 to 0.2)	25 634.4 (22 631.5 to 28 974.3)	23 880.8 (21 046.2 to 26 935.1)	1.07 (1.06 to 1.09)
Tetanus							
DALYs	1340 (633 to 2130)	-91.7% (-94.4 to -86.8)	19.6 (9.1 to 31.9)	-92.6% (-94.9 to -88.0)	18.4 (8.6 to 31.6)	20.8 (8.3 to 36.8)	0.95 (0.49 to 1.69)
YLDs	3.00 (2.20 to 4.00)	-56.1% (-62.3 to -47.8)	0.0 (0.0 to 0.1)	-67.7% (-72.1 to -61.9)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.91 (0.83 to 0.98)

(Table 2 continues on next page)

	Counts (thousands)		Age-standardised rate (per 100 000 people)				
	2021	Percentage change, 1990–2021	2021	Percentage change, 1990–2021	Females	Males	Female-to-male ratio
(Continued from previous page)							
YLLs	1340 (644 to 2180)	-91.8% (-94.4 to -86.3)	19.6 (9.1 to 32.2)	-92.6% (-95.0 to -88.1)	18.4 (8.5 to 31.6)	20.7 (8.3 to 36.8)	0.95 (0.49 to 1.69)
Prevalence	37.7 (28.5 to 49.2)	-62.2% (-66.3 to -58.1)	0.5 (0.4 to 0.6)	-72.8% (-75.5 to -70.1)	0.4 (0.3 to 0.6)	0.5 (0.4 to 0.7)	0.83 (0.79 to 0.87)
Deaths	21.3 (9.90 to 33.2)	-89.7% (-92.8 to -83.8)	0.3 (0.1 to 0.5)	-91.8% (-94.2 to -87.2)	0.3 (0.1 to 0.4)	0.3 (0.1 to 0.6)	0.85 (0.44 to 1.52)
Traumatic brain injury							
YLDs	5490 (3880 to 7340)	52.2% (49.5 to 55.2)	64.8 (45.8 to 86.8)	-16.4% (-17.7 to -15.0)	40.1 (28.5 to 53.7)	90.1 (63.5 to 120.8)	0.45 (0.43 to 0.46)
Prevalence	38 000 (36 400 to 39 800)	52.7% (50.4 to 55.4)	448.6 (429.9 to 470.3)	-16.9% (-18.0 to -15.6)	283.7 (270.2 to 299.2)	617.4 (592.2 to 646.0)	0.46 (0.45 to 0.47)

Data are mean (95% uncertainty interval). Counts are provided to three significant figures, rates and percentages are provided to one decimal place, and ratios are provided to two decimal places. Due to rounding, age-standardised rates for some rare conditions (eg, tetanus, rabies, neurocysticercosis, and congenital Zika syndrome) are shown as 0.0, but the actual values are higher than 0.0. To avoid double-counting cases, epilepsy includes all epilepsy not due to other causes explicitly analysed here (eg, preterm birth), and Guillain-Barré syndrome excludes Guillain-Barré syndrome due to COVID-19, as these estimates are included under COVID-19 estimates. DALYs=disability-adjusted life-years. NA=not applicable. YLDs=years lived with disability. YLLs=years of life lost. *Values higher than 1 indicate higher levels in females. †Neurological complications related to this condition.

Table 2: Global DALYs, YLDs, YLLs, prevalence, and deaths per 100 000 people and age-standardised rates by neurological disorder category, 1990–2021

dementias (13 047.1 [5903.4–27 898.8] per 100 000 people), and Parkinson's disease (1773.2 [1550.8–1925.0] per 100 000 people; table 3).

Temporal and sex patterns

Temporal trends between 1990 and 2021 in age-standardised DALYs for individual conditions varied from a maximum increase of 91.9% (95% UI 86.3–97.3) for diabetic neuropathy to a maximum decrease for tetanus of 92.6% (88.0–94.9) (figure 2). Six conditions had a 25.0% or larger increase in age-standardised DALYs from 1990 to 2021: diabetic neuropathy, neurological complications due to neonatal sepsis, cerebral malaria, other neurological disorders, neurological complications due to neonatal jaundice, and neurological complications due to preterm birth. Eight conditions had a 25.0% or larger decrease in DALYs in this time period: tetanus, rabies, meningitis, neural tube defects, stroke, neurocysticercosis, encephalitis, and neonatal encephalopathy. Congenital Zika syndrome and COVID-19 did not exist in 1990. In 2021, neurological complications due to COVID-19 was the 20th ranked contributor to age-standardised global neurological DALYs (figure 1). Of the 41.5 million (22.1–89.4) cases of neurological health loss with infectious causes, 23.4 million (4.14–72.8) were cases of COVID-19 with long-term cognitive symptoms or Guillain-Barré syndrome. These COVID-19 cases contributed 2.48 million (0.0872–7.99) DALYs.

In 2021, rates of age-standardised DALYs for the total neurological category were lower in females (5185.8 [95% UI 4281.2–6262.9] per 100 000 people) than in males (6101.0 [5320.2–6982.7] per 100 000 people; figure 3; table 2), with a female-to-male ratio of 0.85 (0.78–0.93; figure 2). Age-specific rates show similar or higher DALY burden in males than in females in most

age groups, except for ages 90–94 years and 95 years and older (figure 3). The three conditions with the largest female-to-male ratios were cognitive impairment or Guillain-Barré syndrome due to COVID-19 (1.84, 0.97–3.35), multiple sclerosis (1.80, 1.72–1.87), and migraine (1.62, 1.39–1.79). Conditions with the smallest female-to-male ratios were attention deficit hyperactivity disorder (0.40, 0.38–0.43), traumatic brain injury (0.45, 0.43–0.46), and autism spectrum disorder (0.47, 0.46–0.49).

Risk factor contribution to neurological condition burden

18 risk factors were quantified for stroke, four for encephalitis and meningitis, three for Alzheimer's disease and other dementias, and one each for multiple sclerosis, Parkinson's disease, idiopathic epilepsy, and idiopathic intellectual disability (appendix p 80). Stroke DALYs had the largest attributable burden globally (84.2%, 95% UI 78.2–88.8). The risk factor with the largest all-age population attributable fraction for stroke was high systolic blood pressure (57.3%, 42.7–68.4), and that for Alzheimer's disease and other dementias was high fasting plasma glucose (14.6%, 1.2–29.4). Smoking was associated with increased DALYs from stroke, Alzheimer's disease and other dementias, and multiple sclerosis. The proportion of DALYs associated with idiopathic epilepsy that was attributable to high alcohol use was almost four times higher in males (10.8%, 7.8–13.8) than in females (2.9%, 1.8–4.0). Ambient particulate matter pollution accounted for 16.7% (11.6–21.0) stroke risk, and household air pollution accounted for 11.3% (6.5–19.5) of stroke risk. The largest attributable fraction was for lead exposure, which accounted for 63.1% (33.3–81.1) of DALYs associated with idiopathic intellectual disability burden.

	Global	Central Europe, eastern Europe, and central Asia			High-income				Latin America and Caribbean				South Asia, east Asia, and Oceania			Sub-Saharan Africa						
		Central Asia	Central Europe	Eastern Europe	Australasia	High-income Asia Pacific	High-income North America	Southern Latin America	Western Europe	Andean Latin America	Caribbean	Central Latin America	Tropical Latin America	North Africa and Middle East	South Asia	East Asia	Oceania	Southeast Asia	Central sub-Saharan Africa	Eastern sub-Saharan Africa	Southern sub-Saharan Africa	Western sub-Saharan Africa
Stroke	1	1	1	1	2	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1
Neonatal encephalopathy	2	3	10	8	10	8	9	6	9	3	2	5	5	5	2	4	4	3	2	2	2	2
Migraine	3	2	2	2	1	3	2	2	1	2	4	3	2	2	3	3	3	2	5	6	3	4
Dementia	4	4	3	3	3	2	3	3	3	5	5	4	3	4	5	2	5	4	3	4	5	5
Diabetic neuropathy	5	5	4	4	5	4	4	4	4	4	3	2	4	3	6	5	2	5	6	7	4	6
Meningitis	6	16	21	18	20	20	22	16	21	19	7	17	16	15	8	16	9	6	4	3	6	3
Epilepsy	7	6	7	11	8	6	8	7	7	6	6	6	6	6	7	9	6	9	7	5	7	7
Preterm birth*	8	9	9	14	7	7	6	8	8	9	8	8	8	8	4	11	7	8	10	10	9	10
Autism spectrum disorder	9	8	6	5	4	5	5	5	5	8	9	7	9	9	11	7	10	7	9	9	8	9
Nervous system cancer	10	7	5	6	6	11	7	9	6	7	10	9	7	7	13	6	18	11	19	13	12	21
Parkinson's disease	11	10	11	13	12	13	10	11	11	10	11	12	11	10	12	8	11	10	11	12	11	12
Neural tube defects	12	19	24	22	19	19	19	15	22	18	12	18	15	13	15	18	8	13	8	8	18	8
Encephalitis	13	12	18	17	22	18	24	19	23	13	19	16	22	20	9	15	16	12	22	15	20	13
Traumatic brain injury	14	11	8	7	13	14	14	14	14	11	14	10	10	11	14	10	12	14	15	19	15	17
Tension-type headache	15	13	13	10	14	12	13	13	13	15	16	15	14	14	16	12	13	15	14	16	16	14
Other neurological disorders	16	15	15	9	11	9	11	12	12	12	13	11	12	17	21	14	15	18	18	20	10	11
Spinal cord injury	17	14	12	12	9	10	12	10	10	16	15	13	13	12	18	13	14	16	16	18	19	19
Idiopathic intellectual disability	18	20	22	21	21	27	20	21	18	23	21	24	23	16	10	20	19	19	23	23	21	25
Neonatal sepsis*	19	17	14	15	18	17	23	17	17	21	20	20	19	18	20	19	17	17	21	17	13	20
COVID-19*	20	18	16	16	27	26	18	22	20	17	22	19	17	19	17	34	21	21	13	14	17	16
Tetanus	21	34	32	35	32	30	34	32	31	29	26	30	29	26	22	29	27	20	20	11	26	18
Congenital birth defects*	22	24	25	26	25	24	26	27	25	26	27	26	26	22	19	23	24	22	24	24	23	23
Neurocysticercosis	23	25	20	23	35	25	21	20	27	14	18	14	18	32	23	21	20	25	12	21	14	22
Attention deficit hyperactivity disorder	24	22	23	24	16	16	17	23	19	20	17	21	20	23	26	17	22	23	26	27	24	28
Motor neuron disease	25	27	19	19	15	15	16	18	16	24	24	23	21	25	29	22	33	31	34	34	32	34
Multiple sclerosis	26	23	17	20	17	23	15	24	15	25	25	25	25	21	28	28	31	29	29	30	25	27
Neonatal jaundice*	27	21	26	25	26	29	28	25	28	22	23	22	24	24	25	24	23	24	25	26	22	26
Rabies	28	30	35	33	31	35	31	35	35	37	34	37	37	34	24	27	30	26	31	22	30	24
Cerebral malaria	29	36	36	36	36	36	37	37	36	33	32	33	30	29	33	36	25	33	17	25	28	15
Other chromosomal anomalies*	30	26	27	27	23	21	25	26	24	27	28	27	27	27	27	25	26	27	28	29	27	29
Down syndrome*	31	28	28	28	24	22	27	28	26	28	29	28	28	28	31	26	29	28	30	31	31	31
Neurosyphilis	32	32	33	31	30	31	32	33	32	31	30	31	31	33	30	32	28	30	27	28	29	30
Guillain-Barré syndrome	33	29	29	29	28	28	29	29	29	30	31	29	32	30	32	31	32	32	33	33	33	32
Fetal alcohol syndrome	34	33	31	30	29	32	30	31	30	32	33	32	33	31	34	30	34	34	32	32	34	33
Cystic echinococcosis*	35	31	30	32	34	34	35	30	34	36	37	35	36	35	35	33	36	36	35	35	36	36
Klinefelter syndrome*	36	35	34	34	33	33	33	34	33	35	35	34	35	36	36	35	35	35	36	36	35	35
Congenital Zika syndrome*	37	37	37	37	37	37	36	36	37	34	36	36	34	37	37	37	37	37	37	37	37	37

Figure 1: Ranking of age-standardised DALY rates for all conditions with neurological health loss by GBD region in 2021
Regions are grouped by GBD super-region and alphabetically ordered. Individual conditions are ordered by global ranking from highest age-standardised DALY rates to lowest age-standardised DALY rates. Dementia represents Alzheimer's disease and other dementias. DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries and Risk Factors Study. *Rankings are isolated to disease DALYs due to neurological complications, as opposed to DALYs attributed to the entire condition.

Discussion

In 2021, 3·40 billion individuals had nervous system health loss and 11·1 million individuals died from a nervous system condition. This nervous system category was the leading cause of DALYs and YLLs, emphasising the enormous public health impact of these conditions.

This study builds on previous efforts¹⁴ and provides the most comprehensive estimate of neurological burden globally. The original grouping of conditions published

for GBD 2015⁴ and GBD 2016¹ contributed 313 million DALYs, or 70·5% of the total neurological DALYs reported here for 2021. We added conditions affecting the nervous system that were previously not captured, such as Guillain-Barré syndrome, neurocysticercosis, rabies, and neuroblastoma and other peripheral nervous cell tumours (captured under the nervous system cancer category), which together contributed 2·14 million DALYs, or 0·5% of the total. To improve reflection of the life course in line with the new

	Aged <5 years	Rank	Aged 5–19 years	Rank	Aged 20–59 years	Rank	Aged 60–79 years	Rank	Aged ≥80 years	Rank
All neurological conditions	11 806.6 (10 144.1–13 813.9)	NA	1705.4 (1227.4–2372.8)	NA	3443.1 (2639.2–4531.4)	NA	13 742.8 (12 096.7–15 569.1)	NA	38 329.3 (31 687.1–50 519.4)	NA
Alzheimer's disease and other dementias	0.0 (0.0–0.0)	NA	0.0 (0.0–0.0)	NA	44.2 (21.2–101.5)	13	1504.2 (746.6–3345.6)	2	13 047.1 (5903.4–27 898.8)	2
Attention deficit hyperactivity disorder	2.4 (1.2–4.2)	24	28.3 (14.5–48)	14	10.7 (5.8–17.1)	23	1.0 (0.5–1.9)	29	0.0 (0.0–0.0)	33
Autism spectrum disorder	169.1 (114.9–237.3)	7	161.4 (109.2–227.2)	4	146.2 (99.4–206.3)	6	112.9 (77.4–157.1)	9	59.5 (40.5–83.6)	14
Cerebral malaria	2.8 (2.0–3.6)	23	8.8 (6.4–11.2)	22	5.0 (3.6–6.3)	27	0.8 (0.6–1.0)	30	0.0 (0.0–0.0)	32
Congenital birth defects*	27.2 (15.4–46.4)	14	20.5 (9.4–39.1)	15	17.4 (7.9–33.5)	19	13.1 (5.8–25.5)	23	10.0 (4.3–19.5)	20
Congenital Zika syndrome*	0.0 (0.0–0.0)	30	0.0 (0.0–0.0)	NA	0.0 (0.0–0.0)	NA	0.0 (0.0–0.0)	NA	0.0 (0.0–0.0)	NA
COVID-19*	8.6 (0.5–35.7)	18	15.4 (1.0–65.3)	18	40.1 (1.0–133.9)	16	32.6 (0.9–97.5)	18	30.0 (0.9–79.2)	17
Cystic echinococcosis*	0.0 (0.0–0.0)	31	0.0 (0.0–0.1)	34	0.1 (0.0–0.1)	35	0.1 (0.1–0.1)	35	0.0 (0.0–0.1)	31
Diabetic neuropathy	0.0 (0.0–0.0)	32	1.5 (0.8–2.4)	27	260.5 (171.9–387.6)	3	1397.3 (911.8–1930.8)	3	1493.5 (1026.5–2052.6)	4
Down syndrome*	3.2 (2.1–4.7)	22	3.0 (2.0–4.3)	25	1.3 (0.8–1.8)	31	0.1 (0.1–0.2)	34	0.0 (0.0–0.0)	NA
Encephalitis	270.6 (196.3–342.6)	4	49.6 (41.3–59.1)	11	34.9 (30.5–41.0)	17	63.8 (56.7–73.9)	14	89.6 (74.4–107.0)	10
Epilepsy	211.5 (163.7–268.9)	6	185.1 (137.0–261.7)	3	174.0 (134.1–219.5)	4	176.9 (125.9–247.7)	7	268.5 (186.4–379.7)	5
Fetal alcohol syndrome	0.4 (0.2–0.7)	27	0.4 (0.2–0.6)	32	0.3 (0.2–0.4)	34	0.1 (0.1–0.2)	33	0.1 (0.1–0.2)	30
Guillain-Barré syndrome	0.4 (0.2–0.7)	28	0.5 (0.2–0.8)	31	0.6 (0.3–0.9)	33	1.2 (0.7–2.0)	28	1.4 (0.8–2.2)	25
Idiopathic intellectual disability	68.3 (32.4–118.0)	11	70.4 (33.7–118.7)	7	43.1 (19.4–74.0)	14	17.1 (7.2–30.4)	21	9.8 (4.9–16.7)	21
Klinefelter syndrome*	0.1 (0.1–0.2)	29	0.0 (0.0–0.1)	33	0.0 (0.0–0.0)	36	0.0 (0.0–0.0)	36	0.0 (0.0–0.0)	34
Meningitis	1234.9 (869.5–1741.7)	2	130.4 (111.0–161.3)	5	72.4 (65.0–83.4)	11	69.8 (64.2–77.9)	13	84.1 (75.1–92.4)	11
Migraine	0.0 (0.0–0.0)	NA	380.0 (24.7–946.6)	1	750.8 (117.3–1617.8)	2	451.6 (112.3–953.6)	4	238.3 (65.8–499.5)	6
Motor neuron disease	6.2 (4.9–7.7)	19	1.3 (1.0–1.5)	28	8.7 (8.0–9.6)	24	57.3 (53.2–61.9)	15	48.2 (39.8–54.1)	16
Multiple sclerosis	0.0 (0.0–0.0)	NA	0.5 (0.4–0.7)	30	15.1 (12.7–17.8)	22	31.8 (28.1–35.8)	19	24.4 (20.7–28.3)	18
Neonatal encephalopathy	8316.7 (7072.6–9991.8)	1	64.9 (46.3–85.6)	8	55.4 (40.1–72.0)	12	25.8 (18.8–33.0)	20	2.1 (1.3–3.0)	23
Neonatal jaundice*	13.2 (9.5–16.8)	15	11.6 (8.4–14.8)	21	8.7 (6.3–11.2)	25	3.9 (2.8–5.0)	26	0.4 (0.3–0.6)	28
Neonatal sepsis*	42.3 (27.1–61.1)	13	39.5 (24.7–57.1)	12	31.3 (19.6–45.2)	18	13.5 (8.3–19.3)	22	0.6 (0.3–0.9)	27
Nervous system cancer	94.9 (71.4–121.5)	10	60.2 (50.3–71.7)	10	106.6 (91.2–125.6)	7	280.0 (245.7–316.1)	6	208.8 (174.3–232.0)	8
Neural tube defects	722.6 (580.8–899.4)	3	17.0 (12.5–23.6)	17	4.5 (3.6–5.9)	29	1.6 (1.2–2.1)	27	1.3 (0.9–1.8)	26
Neurocysticercosis	0.8 (0.1–1.9)	25	1.6 (0.8–2.5)	26	16.1 (9.1–23.8)	21	45.7 (24.8–76.2)	17	65.4 (36.1–105.0)	13
Neurosyphilis	0.7 (0.4–1.0)	26	1.1 (0.7–1.6)	29	0.8 (0.5–1.1)	32	0.6 (0.4–0.8)	31	0.4 (0.3–0.6)	29
Chromosomal anomalies*	12.2 (8.1–17.3)	17	5.8 (3.9–8.2)	24	2.3 (1.5–3.3)	30	0.4 (0.2–0.5)	32	0.0 (0.0–0.0)	36

(Table 3 continues on next page)

	Aged <5 years	Rank	Aged 5–19 years	Rank	Aged 20–59 years	Rank	Aged 60–79 years	Rank	Aged ≥80 years	Rank
(Continued from previous page)										
Other neurological disorders	44.6 (36.2–54.4)	12	60.2 (44.2–84.0)	9	41.8 (34.6–49.6)	15	94.7 (84.0–106.8)	11	157.8 (133.9–176.9)	9
Parkinson's disease	0.0 (0.0–0.0)	NA	0.0 (0.0–0.0)	NA	16.2 (13.6–19.1)	20	430.7 (389.5–472.1)	5	1773.2 (1550.8–1925.0)	3
Preterm birth*	264.9 (190.4–344.9)	5	234.3 (168.4–305.2)	2	165.7 (120.5–212.9)	5	56.0 (41.9–71.4)	16	14.1 (9.6–20.9)	19
Rabies	12.8 (4.5–24.6)	16	12.3 (6.6–17.9)	19	4.9 (3.1–6.8)	28	3.9 (2.5–5.4)	25	1.6 (1.1–2.2)	24
Spinal cord injury	3.2 (2.3–4.2)	21	17.6 (11.9–23.5)	16	74.7 (52.3–99.2)	10	103.2 (74.5–132.7)	10	83.0 (57.6–113.0)	12
Stroke	147.5 (109.0–196.8)	8	72.9 (65.0–80.2)	6	1126.1 (1035.5–1218.4)	1	8490.9 (7827.5–9108.6)	1	20336.1 (17762.6–22137.4)	1
Tension-type headache	0.0 (0.0–0.0)	NA	29.7 (4.8–148.1)	13	77.5 (23.3–238.7)	8	75.4 (23.3–224.1)	12	49.4 (12.2–165.8)	15
Tetanus	120.5 (51.4–218.6)	9	7.8 (3.5–13.8)	23	7.5 (3.3–12.2)	26	8.2 (3.7–12.8)	24	4.2 (1.5–7.2)	22
Traumatic brain injury	3.9 (2.6–5.3)	20	11.8 (8.3–16.0)	20	77.5 (54.2–103.7)	9	176.5 (126.5–236.6)	8	226.3 (160.7–298.5)	7

Rates are provided to one decimal place. Due to rounding, values for some rare conditions (eg, tetanus, rabies, neurocysticercosis, and congenital Zika syndrome) are shown as 0.0, but the actual values are higher than 0.0. *Neurological complications related to this condition.

Table 3: Global disability-adjusted life-years per 100 000 people by five broad age categories for all conditions with neurological health loss

IGAP,³ we included neurodevelopmental disorders and paediatric neurological conditions, which represent a large proportion of global disease burden due to premature death and long-lasting disability,⁷ and together these conditions contributed 80.3 million DALYs or 18.2% of the total DALYs attributable to neurological health loss. Cerebral palsy was not listed separately among the 37 included conditions because the relevant GBD sequelae are captured under their causes, for example preterm birth and neonatal encephalopathy. We also quantified the disease burden of conditions that include neurological complications by extracting and accounting for neurological sequelae from a heterogeneous group of conditions with nervous system health loss, together contributing approximately 48.1 million DALYs or 10.8% of the total DALYs attributable to neurological health loss.

Nervous system health loss disproportionately affected people in LMICs, partly due to higher prevalence of conditions affecting neonates and children younger than 5 years (especially birth-related complications and infections). Increased survival in neonates is unfortunately accompanied by an increase in the long-term disability from neurological complications of these conditions.^{18–20} Access to treatment and rehabilitation services for nervous system conditions is limited by little availability or existence of specialised services and workforces, contributing to poor health outcomes and high mortality. For instance, the high proportion of deaths in LMICs compared with high-income countries is probably related to poorer access to high-quality services and nervous system specialists in LMICs.²¹ We showed that YLDs are more consistent between geographical regions than YLLs

(appendix p 79). However, this similarity could partly be because sources directly reporting disease severity for highly disabling outcomes are sparse, and therefore we were unable to take into account potential effects of treatment on severity.

Nervous system conditions contribute to more DALYs in males but higher prevalence in females (mostly attributable to migraine and tension-type headache), and disease burden generally increases with age. Different age patterns emerged for different conditions, including differences in the relative contribution of YLLs and YLDs to total burden, emphasising the need for tailored interventions and prevention strategies across the lifespan.

In line with previous GBD findings,¹ the absolute number of people living with, or dying from, neurological conditions increased over the past three decades. This trend mirrors global demographic and ageing trends and increased exposure to environmental, metabolic, and lifestyle risk factors that are especially relevant for non-communicable neurological conditions, such as stroke and dementia.^{22,23} At the same time, the age-standardised death, DALY, and YLL rates of total neurological conditions decreased. Improved public awareness of stroke, use of statins,²⁴ and blood pressure lowering medications²⁵ have probably contributed to the decreased DALYs associated with stroke, as well as, primarily in high-income countries, the approval of intravenous thrombolytics in the mid-1990s, the increasing availability of endovascular thrombectomy for acute stroke, and growth of comprehensive stroke units.^{26–28} Observed reductions in DALYs were also probably driven by global vaccination and disease-prevention efforts, especially for

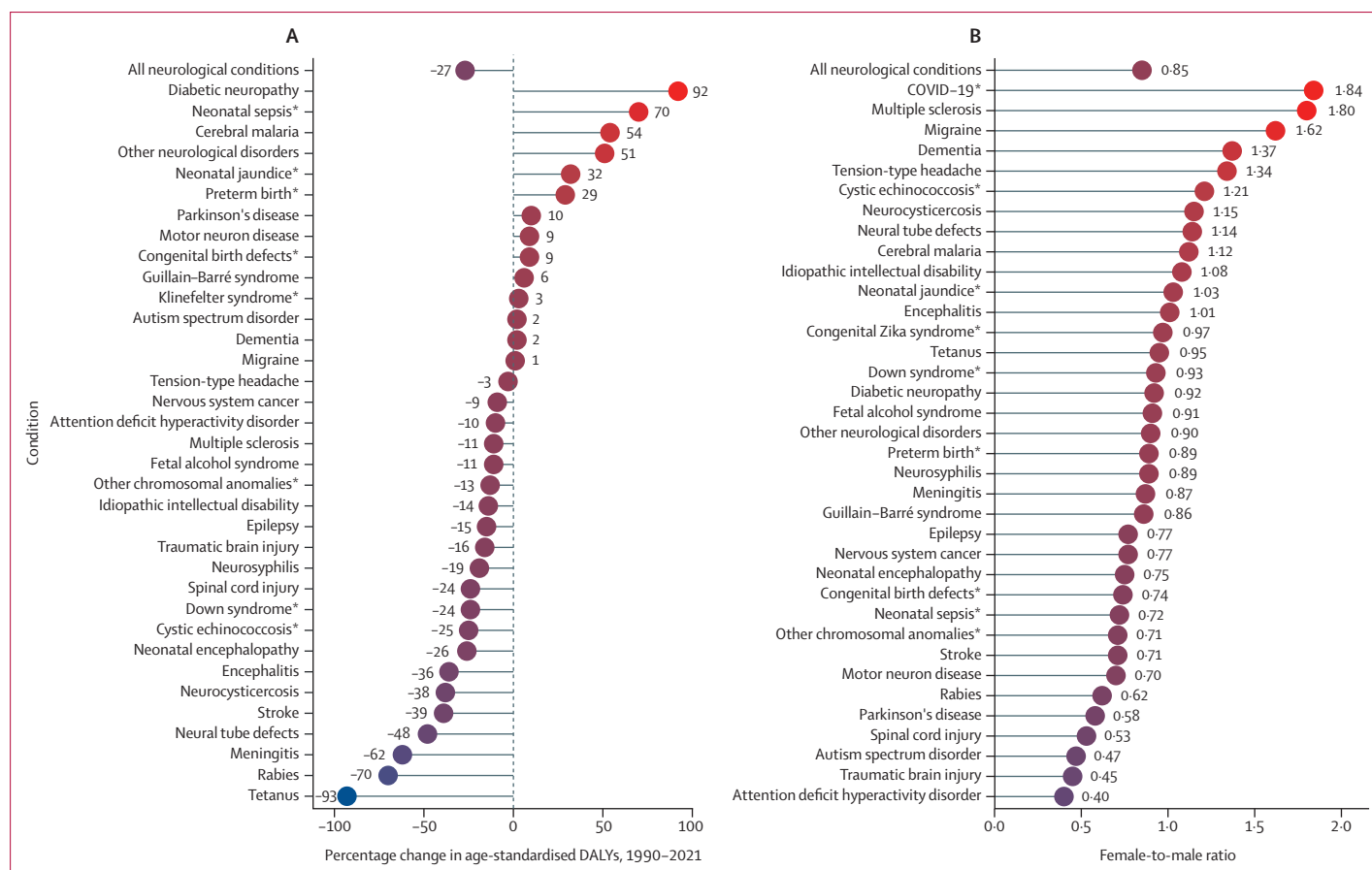


Figure 2: Change in age-standardised DALYs, 1990–2021, and female-to-male ratios in 2021 for each condition

(A) Percentage change from 1990 to 2021 overall and for individual conditions. Colours range from dark blue (largest decrease in age-standardised DALYs) to bright red (largest increases). Cognitive impairment due to COVID-19 and congenital Zika virus disease are not included because they were not documented until after 1990. (B) Female-to-male ratio in 2021, where values higher than 1 indicate higher levels in females (log scale). Colours range from blue (smaller female-to-male ratios) to red (larger female-to-male ratios). Throughout the figure, dementia represents Alzheimer's disease and other dementias. DALYs=disability-adjusted life-years. *Percentage change and female-to-male ratios are isolated to disease DALYs due to neurological complications as opposed to DALYs attributed to the entire condition.

tetanus, rabies, meningitis, neurocysticercosis, and encephalitis,²⁹ and improved access to prevention and treatment. For instance, we estimate an 17·8% reduction in encephalitis DALYs, which could partly reflect Japanese encephalitis vaccination and improved access to health care.³⁰ The substantial decrease in global deaths from tetanus because of vaccination strategies emphasises the profound value of vaccination prevention campaigns. Lastly, the promotion and enforcement of folic acid supplementation and fortification of grain products contributed to the decreases in incidence of neural tube defects in countries that have instituted this basic public health initiative.^{31–33}

The estimate of Guillain–Barré syndrome due to COVID-19 was generated through an analysis of US data from a large sample of approximately 2 million individuals, a finding supported by some other studies³⁴ but requiring further research, because other studies showed no effect of COVID-19 on Guillain–Barré syndrome.^{35,36} A more detailed description of methods used in this analysis to

estimate Guillain–Barré syndrome following COVID-19, including strengths and limitations, is in the appendix (p 2). Parkinson's disease was previously identified as the fastest growing neurological condition,^{4,37} but through the inclusion of additional cause categories and sequelae, other conditions—ie, primarily diabetic neuropathy, neonatal conditions with neurological consequences, and cerebral malaria—are now ranking higher in terms of percentage growth of age-standardised DALYs since 1990 (table 1). Diabetic neuropathy is now the fifth-ranked cause of global age-standardised DALYs due to neurological conditions and its fast-increasing burden is in line with the observed increase in the global prevalence of diabetes,³⁸ particularly type 2 diabetes, which constitutes 96% of all diabetic cases and is a preventable condition. The fast-increasing burden from diabetes, neonatal conditions, and cerebral malaria, which are all largely preventable, indicates poor implementation of effective risk reduction strategies for these health conditions.

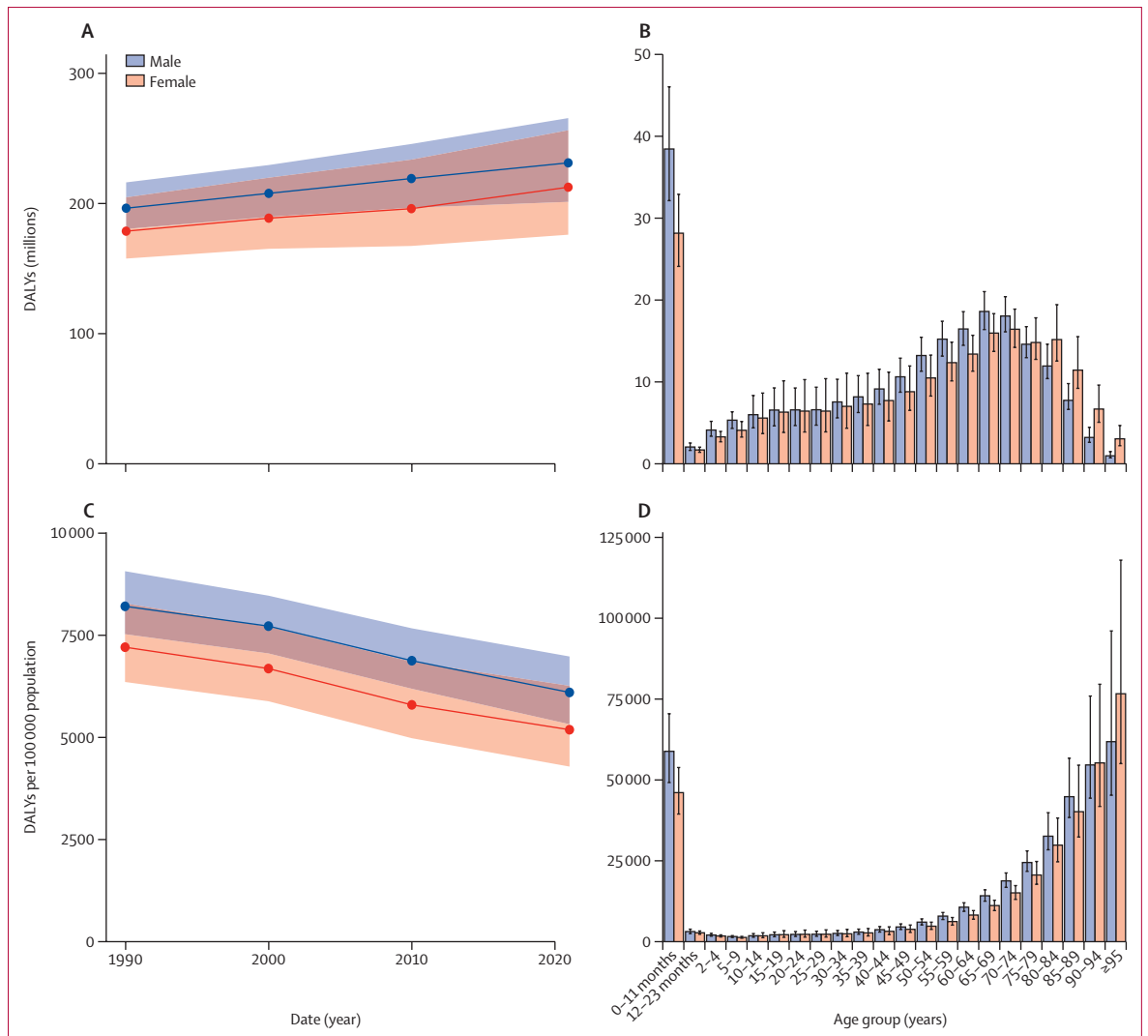


Figure 3: Temporal and age patterns in global DALYs for all neurological conditions combined

DALY counts are shown over time (A) and by age group in 2021 (B). Age-standardised DALYs per 100 000 population are shown over time (C) and age-specific rates are shown in 2021 (D). Shading in panels A and C and black bars in panels B and D depict 95% uncertainty intervals. DALYs=disability-adjusted life-years.

Because cures do not exist for many neurological conditions, and because access to quality medical care can be limited by workforce constraints in some places,³⁹ a comprehensive understanding of modifiable risk factors and the potentially avoidable burden of the neurological conditions they affect is key. This study extends previous estimates of risk factors for neurological disorders that focused on stroke, Alzheimer's disease and other dementias, and idiopathic epilepsy by additionally quantifying risk for multiple sclerosis, Parkinson's disease, encephalitis, meningitis, and idiopathic intellectual disability. Risk factors for stroke are the most comprehensively studied of all neurological conditions in GBD, and in 2021, 84.2% of stroke DALYs were potentially preventable through the reduction of exposure to 18 identified risk factors. Controlling lead exposure could reduce the burden of idiopathic intellectual

disability by 63.1%, and reducing high fasting plasma glucose to typical concentrations (ie, 4.88–5.30 mmol/L³⁸) could reduce the burden of Alzheimer's disease and other dementias by 14.6%. Smoking was identified as a risk factor for stroke,^{22,40} Alzheimer's disease and other dementias,⁴¹ and multiple sclerosis. However, some established risk–outcome pairs (eg, hearing loss and Alzheimer's disease and other dementias;⁴¹ exposure to pesticides and Parkinson's disease) were not assessed in our model. Psychosocial factors, such as sleep, stress, and social isolation, are increasingly recognised as contributors to neurological conditions and should be quantified in future analyses.

This study has limitations. Although we attempted to capture all nervous system health loss modelled in GBD explicitly or in the broad category of other neurological disorders, some conditions that cause nervous system

damage were left out because we could not isolate the neurological component (eg, genetic conditions such as adrenoleukodystrophy or infections such as HIV, which have large effects in many parts of the world and should be explicitly estimated in the future; appendix p 49) or because they are not quantified in GBD (eg, poliomyelitis). Diabetic neuropathy has now been included within the neurological conditions category and its high ranking indicates a considerable burden within the category that has not previously been conveyed or emphasised. The inclusion of diabetic neuropathy calls attention to the scarcity of data for other peripheral neuropathies, such as those associated with alcohol, HIV, and vitamin deficiencies. Thus, our singular representation of diabetic neuropathy in this study is probably a gross underestimation of the total peripheral neuropathy burden.

Neurodevelopmental disorders that are captured in GBD under mental health, such as attention deficit hyperactivity disorder, autism spectrum disorder, and idiopathic intellectual disability, have been added because of their strong links to, and effects on, the nervous system, and because of their ICD-11 classification as neurodevelopmental disorders. Other mental health conditions that were not classified as neurodevelopmental or neurocognitive were excluded. Neurological complications of non-neurological diseases have been added as far as possible. We also assumed independence of disabling sequelae when making comorbidity corrections, which would lead to some overestimation of the non-fatal burden. Future analyses should include an improved evaluation of comorbidities that does not assume independency of co-occurrence. Further, we do not assess comorbidity with other chronic conditions, such as heart disease, that can compound effects on quality of life.

The residual category for other neurological disorders ranked 16th for age-standardised DALYs, emphasising the need to explicitly estimate DALYs for the conditions within this category, including specific movement disorders, myopathies, and non-traumatic spinal cord diseases. For non-fatal estimates of the residual category, we approximated YLDs by assuming the same ratio of YLDs and YLLs that we estimated for the main fatal neurological disorders. This approach, although a reasonable approximation for residual neurological conditions that lead to death, does not capture the burden of any residual neurological conditions that are not a cause of death, such as peripheral neuropathies and neuropathic pain.^{42,43} Some neurological pain quantified in GBD is captured within musculoskeletal conditions—eg, low back pain (including sciatica) or neck pain—and such pain was not included in our current analysis. In GBD 2021, these conditions are defined as pain lasting at least 1 day, making it impossible to distinguish between chronic neurological pain and shorter-term musculoskeletal pain. Our analysis also did not account

for deaths associated with traumatic brain injury and spinal cord injury. Within GBD and the ICD, the underlying cause of death is assigned to the cause of injury (eg, violence or road traffic accident) rather than the nature of the injury.

When quantifying the neurological burden of post-COVID-19 condition, we accounted only for cognitive impairment, using the same disability weights as for mild or moderate dementia, which might not be accurate considering that cognitive impairment following COVID-19 appears to improve with time. As we did not have the resources to conduct disability weight surveys, such an approximation was necessary. We were also unable to analyse non-cognitive long-term neurological outcomes of COVID-19 (with the exception of Guillain–Barré syndrome) due to a dearth of such data for most countries. Some studies have shown that the prevalence of other neurological complications (eg, persistent headache, neuralgia, daytime sleepiness, and stroke) associated with COVID-19 varies widely.^{44–46} We also acknowledge that this analysis was conducted in the first 2 years after the emergence of COVID-19, and longer-term consequences on cognition or other aspects of nervous system health are not fully quantified.

Our study also has general limitations shared by all GBD studies, such as the scarcity of reliable epidemiological data in many countries, especially in LMICs, meaning that country estimates are informed by predictive covariates and data from surrounding countries, and our results are also affected by diagnostic and other biases in the original research. Efforts were made to correct for non-reference case definitions or measurement methods used in GBD source data. Adjusting for measurement bias is a strength of GBD because it allows us to leverage as many data sources as possible across time and geographies. This process is constantly being refined to enhance quality, transparency, and standardisation. However, some standard GBD reference definitions differ from other disease definitions, such as those used in the new ICD-11. Finally, because this is a global analysis, we could not capture the nuances of how these conditions affect specific geographies.

In summary, acute and chronic conditions affecting the nervous system are diverse. These conditions include infectious or vector-borne diseases, non-communicable diseases, and injuries, necessitating different public health strategies for prevention and treatment across the life course. These distinctions emphasise the complexity that health-care systems are facing and the need to balance acute and long-term disease management. For some conditions and disorders, effective treatments are available, whereas for others there is no cure, underscoring the importance of prevention and research into novel interventions.

Resources for nervous system conditions should therefore span the entire care continuum, including prevention, diagnosis, treatment, rehabilitation, long-term

care, and palliation. Improved population-level preventive strategies for neurological infections and birth-related neurological sequelae can affect many lives; such strategies include appropriate sanitation, vaccination, folic acid fortification, improved access to prenatal and perinatal care and education, and early detection and treatment of birth defects. Additionally, zoonotic diseases, such as COVID-19 or Zika virus disease, have increasingly posed challenges to brain health,^{8,47,48} emphasising the importance of close collaboration across sectors and integration of human, animal, social, political, and environmental sciences in joint efforts to optimise brain health.^{2,47,49}

Most nervous system burden occurs in LMICs, where health-care resources are scarce, access to services is limited by availability and workforce constraints, and many countries are insufficiently prepared to address the increasing number of cases or DALYs.³⁹ In 2017, only 46 (24%) of 194 countries had policies with a separate budget dedicated to neurological disorders, and only 69 (55%) of 125 countries who responded to a questionnaire had clinical guidelines for neurological disorders (ie, systematically developed statements or recommendations designed to assist practitioners and patients in making decisions about appropriate health care for neurological disorders). The available neurological workforce is unevenly distributed across the world, with high-income countries having 70 times more neurological professionals per 100 000 individuals in the population compared with LMICs.³⁹ The adoption of IGAP provides a guideline for a decade of concerted multisectoral actions to respond to the growing absolute burden of neurological conditions.^{2,3}

The findings in this study have important health service and policy implications and serve as evidence that global neurological health loss has been under-recognised and is increasing and unevenly distributed geographically and socioeconomically. Elucidating the individual contributions of conditions that affect nervous system health will inform targeted interventions and policy options that can increase nervous system health at individual and population levels.

GBD 2021 Nervous System Disorders Collaborators

Jaimie D Steinmetz*, Katrin Maria Seeher*, Nicoline Schiess, Emma Nichols, Bochen Cao, Chiara Servili, Vanessa Cavallera, Ewerton Cousin, Hailey Hagins, Madeline E Moberg, Max L Mehlman, Yohannes Habtegiorgis Abate, Jaffar Abbas, Madineh Akram Abbasi, Mohammadreza Abbasian, Hedayat Abbastabar, Michael Abdelmasseh, Mohammad Abdollahi, Mozhan Abdollahi, Mohammad-Amin Abdollahifar, Rami Abd-Rabu, Deldar Morad Abdulah, Auwal Abdullahi, Aidin Abedi, Vida Abedi, Roberto Ariel Abeldaño Zuñiga, Hassan Abidi, Olumide Abiodun, Richard Gyan Aboagye, Hassan Abolhassani, Victor Aboyans, Woldu Aberhe Abraha, Ahmed Abualhasan, Eman Abu-Gharbieh, Salahdein Aburuz, Lawan Hassan Adamu, Isaac Yeboah Addo, Oladimeji M Adebayo, Victor Adekanmbi, Tayo Alex Adekiya, Wirawan Adikusuma, Qorinah Estiningtyas Sakilah Adnani, Saryia Adra, Tsion Afework, Aanuoluwapo Adeyimika Afolabi, Ali Afraz, Saira Afzal, Shahin Aghamiri, Antonella Agodi, Williams Agyemang-Duah, Bright Opoku Ahinkorah, Aqeel Ahmad, Danish Ahmad,

Sajjad Ahmad, Amir Mahmoud Ahmadzade, Ali Ahmed, Ayman Ahmed, Haroon Ahmed, Jivan Qasim Ahmed, Luai A Ahmed, Muktar Beshir Ahmed, Syed Anees Ahmed, Marjan Ajami, Budi Aji, Olufemi Ajumobi, Seyed Esma'il Akade, Morteza Akbari, Hossein Akbarialiabad, Shiva Akhlaghi, Karolina Akinosoglou, Rufus Olusola Akinyemi, Maxwell Akonde, Syed Mahfuz Al Hasan, Fares Alahdab, Tareq Mohammed Ali AL-Ahdal, Rasmieh Mustafa Al-amer, Mohammed Albashtawy, Mohammad T AlBataineh, Khalifah A Aldawsari, Hediye Alemi, Sharifullah Alemi, Abdelazeem M Algammal, Adel Ali Saeed Al-Gheethi, Fadwa Alhalaqa Naji Alhalaqa, Robert Kaba Alhassan, Abid Ali, Endale Alemayehu Ali, Liaqat Ali, Mohammed Usman Ali, Musa Mohammed Ali, Rafat Ali, Shahid Ali, Syed Shujait Shujait Ali, Zahid Ali, Sheikh Mohammad Alif, Yousef Alimohamadi, Ahmednur Adem Aliyi, Mohamad Aljofan, Syed Mohamed Aljunid, Suvarna Alladi, Joseph Uy Almazan, Sami Almustanyir, Basem Al-Omari, Jaber S Alqahtani, Ibrahim Alqasmi, Ahmed Yaseen Alqutaibi, Rustam Al-Shahi Salman, Zaid Altaany, Jaffar A Al-Tawfiq, Khalid A Altirkawi, Nelson Alvis-Guzman, Yaser Mohammed Al-Worafi, Hany Aly, Safwat Aly, Kareem H Alzoubi, Reza Amani, Alireza Amindarolzarbi, Sohrab Amiri, Mohammad Hosein Amirzade-Iranag, Hubert Amu, Dickson A Amugsi, Ganiyu Adeniyi Amusa, Jimoh Amzat, Robert Ancuceanu, Deanna Anderlini, David B Anderson, Catalina Liliana Andrei, Sofia Androudi, Dhanalakshmi Angappan, Teklit W Angesom, Abhishek Anil, Alireza Ansari-Moghaddam, Raziqee Anwer, Mosab Arafat, Aleksandr Y Aravkin, Demelash Arede, Hany Ariffin, Hidayat Arifin, Mesay Arkew, Johan Årnlöv, Mahwish Arooj, Anton A Artamonov, Kurnia Dwi Artanti, Raphael Taiwo Aruleba, Ali A Asadi-Pooya, Tilahun Ferede Asena, Mohammad Asghari-Jafarabadi, Muhammad Ashraf, Tahira Ashraf, Kendalem Asmare Atalell, Seyyed Shamsadin Athari, Bantalem Tilaye Tilaye Atinafu, Prince Atorkey, Maha Moh'd Wahbi Atout, Alok Atreya, Avinash Aujayeb, Abolfazl Avan, Beatriz Paulina Ayala Quintanilla, Haleh Ayatollahi, Olatunde O Ayinde, Seyed Mohammad Ayyoubzadeh, Sina Azadnajafabad, Zahra Azizi, Khalil Azizian, Ahmed Y Azzam, Mahsa Babaei, Muhammad Badar, Ashish D Badiye, Soroush Baghdadi, Sara Bagherieh, Ruhai Bai, Atif Amin Baig, Senthilkumar Balakrishnan, Shivanthi Balalla, Ovidiu Constantin Baltatu, Maciej Banach, Soham Bandyopadhyay, Indrajit Banerjee, Mehmet Firat Baran, Miguel A Barboza, Martina Barchitta, Mainak Bardhan, Suzanne Lyn Barker-Collo, Till Winfried Bärnighausen, Amadou Barrow, Davood Bashash, Hamideh Bashiri, Hameed Akande Bashiru, Afisu Basiru, João Diogo Basso, Sanjay Basu, Abdul-Monim Mohammad Batiha, Kavita Batra, Bernhard T Baune, Neeraj Bedi, Ahmet Begde, Tahmina Begum, Babak Behnam, Amir Hossein Behnoush, Maryam Beiranvand, Yannick Béjot, Alehegn Bekele, Melaku Ashagrie Belete, Uzma Iqbal Belgaum, Maryam Bemanalizadeh, Rose G Bender, Bright Benfor, Derrick A Bennett, Isabela M Bensenor, Betyna Berice, Paulo J G Bettencourt, Kebede A Beyene, Abhishek Bhadra, Devidas S Bhagat, Kayleigh Bhangdia, Nikha Bhardwaj, Pankaj Bhardwaj, Ashish Bhargava, Sonu Bhaskar, Ajay Nagesh Bhat, Vivek Bhat, Gurjit Kaur Bhatti, Jasvinder Singh Bhatti, Rajbir Bhatti, Ali Bijani, Boris Bikbov, Mariah Malak Bilalaga, Atanu Biswas, Saeid Bitaraf, Veera R Bitra, Tone Bjørge, Virginia Bodolica, Aadam Olalekan Bodunrin, Archith Boloor, Dejana Braithwaite, Carol Brayne, Hermann Brenner, Andrew Briko, Maria L Bringas Vega, Julie Brown, Christine M Budke, Danilo Buonsenso, Katrin Burkart, Richard A Burns, Yasser Bustanji, Muhammad Hammad Butt, Nadeem Shafique Butt, Zahid A Butt, Lucas Scotta Cabral, Florentino Luciano Caetano dos Santos, Daniela Calina, Ismael R Campos-Nonato, Chao Cao, Héléne Carabin, Rosario Cárdenas, Giulia Carreras, Andre F Carvalho, Carlos A Castañeda-Orjuela, Adriano Casulli, Ferrán Catalá-López, Alberico L Catapano, Arthur Caye, Luca Cegolon, Muthia Cenderadewi, Ester Cerin, Pamela R Uscamaita Chacón-Uscamaita, Jeffrey Shi Kai Chan, Gashaw Sisay Chanie, Jaykaran Charan, Vijay Kumar Chattu, Endeshaw Chekol Abebe, Hui Chen, Jianqi Chen, Gerald Chi, Fatemeh Chichagi, Saravana Babu Chidambaram, Ritesh Chimoriya, Patrick R Ching, Abdulaal Chitheer, Yuen Yu Chong, Hitesh Chopra,

Sonali Gajanan Choudhari, Enayet Karim Chowdhury, Rajiv Chowdhury, Hanne Christensen, Dinh-Toi Chu, Isaac Sunday Chukwu, Eric Chung, Kaleb Coberly, Alyssa Columbus, Josielli Comachio, Joao Conde, Paolo Angelo Cortesi, Vera Marisa Costa, Rosa A S Couto, Michael H Crique, Natália Cruz-Martins, Mohammad Amin Dabbagh Ohadi, Sriharsha Dadana, Omid Dadras, Xiaochen Dai, Zhaoli Dai, Emanuele D'Amico, Hadi A Danawi, Lalit Dandona, Rakhi Dandona, Amira Hamed Darwish, Saswati Das, Subasish Das, Ana Maria Dascalu, Nihar Ranjan Dash, Mohsen Dashti, Fernando Pio De la Hoz, Alejandro de la Torre-Luque, Diego De Leo, Frances E Dean, Amin Dehghan, Azizallah Dehghan, Hiwot Dejene, Daniel Demant, Andreas K Demetriades, Solomon Demissie, Xinlei Deng, Hardik Dineshbhai Desai, Vinoth Gnana Chellaiyan Devanbu, Kuldeep Dhama, Samath Dhamminda Dharmaratne, Meghnath Dhimal, Diana Dias da Silva, Daniel Diaz, Mahmoud Dibas, Delaney D Ding, Monica Dinu, M Ashworth Dirac, Mengistie Diress, Thanh Chi Do, Thao Huynh Phuong Do, Khanh Duy Khanh Doan, Milad Dodangeh, Mohamed Fahmy Doheim, Klara Georgieva Dokova, Deepa Dongarwar, Haneil Larson Dsouza, John Dube, Senbagam Duraisamy, Oyewole Christopher Durojaiye, Sulagna Dutta, Arkadiusz Marian Dziedzic, Hisham Atan Edinur, Negin Eissazade, Michael Ekholuenetale, Temitope Cyrus Ekundayo, Nevine El Nahas, Iman El Sayed, Mohammad Amin Elahi Najafi, Iffat Elbarazi, Noha Mousaad Elemam, Frank J Elgar, Islam Y Elgendy, Hala Rashad Elhabashy, Muhammed Elhadi, Legesse Tesfaye Eliho, Richard G Ellenbogen, Omar Abdelsadek Abdou Elmeligy, Mohamed A Elmonem, Mohammed Elshaer, Ibrahim Elsohaby, Mehdi Emamverdi, Theophilus I Emeto, Matthias Endres, Christopher Imokhuede Esezobor, Sharareh Eskandarieh, Abdolmajid Fadaei, Ademiya Francis Fagbamigbe, Ayesha Fahim, Ali Faramarzi, Jawad Fares, Mohsen Farjoud Kouhanjani, Andre Faro, Farshad Farzadfar, Ali Fatehizadeh, Mobina Fathi, Saeid Fathi, Syeda Anum Fatima Fatima, Alireza Feizkhal, Seyed-Mohammad Fereshtehnejad, Alize J Ferrari, Nuno Ferreira, Getahun Fetensa, Neda Firouraghi, Florian Fischer, Ana Catarina Fonseca, Lisa M Force, Arianna Fornari, Behzad Foroutan, Takeshi Fukumoto, Muktar A Gadanya, Abhay Motiramji Gaidhane, Yaseen Galali, Nasrin Galehdar, Quan Gan, Aravind P Gandhi, Balasankar Ganesan, William M Gardner, Naval Garg, Shuo-Yan Gau, Rupesh K Gautam, Teshome Gebre, Mesfin Gebrehiwot, Gebreamlak Gebremedhn Gebremeskel, Haftay Gebremedhin Gebreslassie, Lemma Getacher, Bardiya Ghaderi Yazdi, Fataneh Ghadirian, Fariborz Ghaffaripasand, Reza Ghanbari, MohammadReza Ghasemi, Ramy Mohamed Ghazy, Sailaja Ghimire, Ali Gholami, Ali Gholamrezanezhad, Elena Ghotbi, Sherief Ghozy, Alessandro Gialluisi, Paramjit Singh Gill, Logan M Glasstetter, Elena V Gnedovskaya, Ali Golchin, Mahaveer Golechha, Pouya Goleji, Davide Golinelli, Mansueto Gomes-Neto, Alessandra C Goulart, Anmol Goyal, Richard J Gray, Michal Grivna, Habtamu Alganesh Guadie, Bin Guan, Giovanni Guarducci, Stefano Guicciardi, Damitha Asanga Gunawardane, Hanbing Guo, Bhawna Gupta, Rajeev Gupta, Sapna Gupta, Veer Bala Gupta, Vivek Kumar Gupta, Reyna Alma Gutiérrez, Farrokh Habibzadeh, Vladimir Hachinski, Rasool Haddadi, Mostafa Hadei, Najah R Hadi, Nils Haep, Teklehaimanot Gereziher Haile, Arvin Haj-Mirzaian, Brian J Hall, Rabih Halwani, Sajid Hameed, Mohammad Hamiduzzaman, Ahmad Hammoud, Hannah Han, Nasrin Hanifi, Graeme J Hankey, Md Abdul Hannan, Junwei Hao, Harapan Harapan, Habtamu Endashaw Hareru, Arief Hargono, Netanja I Harlianto, Josep Maria Haro, Nicholas Nathaniel Hartman, Ahmed I Hasaballah, Faizul Hasan, Hamidreza Hasani, Mohammad Hasanian, Amr Hassan, Shoab Hassan, Soheil Hassanipour, Hadi Hassankhani, Mohammed Bheser Hassen, Johannes Haubold, Simon I Hay, Khezir Hayat, Mohamed I Hegazy, Golnaz Heidari, Mohammad Heidari, Reza Heidari-Soureshjani, Hamed Hesami, Kamal Hezam, Yuta Hiraike, Howard J Hoffman, Ramesh Holla, Kathleen Pillsbury Hopf, Nobuyuki Horita, Md Mahbub Hossain, Md Belal Hossain, Sahadat Hossain, Hassan Hosseinzadeh, Mehdi Hosseinzadeh, Sorin Hostiuc, Chengxi Hu, Junjie Huang, Md Nazmul Huda, Javid Hussain, Nawfal R Hussein, Hong-Han Huynh, Bing-Fang Hwang, Segun Emmanuel Ibitoye, Mehran Ilaghi, Olayinka Stephen Ilesanmi, Irena M Ilic, Milena D Ilic, Mustapha Immurana, Farideh Iranvanpour, Sheikh Mohammed Shariful Islam, Faisal Ismail, Hiroyasu Iso, Gaetano Isola, Masao Iwagami, Chidozie C D Iwu, Mahalaxmi Iyer, Ali Jaan, Louis Jacob, Farhad Jadidi-Niaragh, Mahboobeh Jafari, Morteza Jafarina, Abdollah Jafarzadeh, Kasra Jahankhani, Nader Jahanmeh, Haitham Jahrami, Abhishek Jaiswal, Mihaelo Jakovljevic, Roland Dominic G Jamora, Somnath Jana, Nilofer Javadi, Saad Javed, Saad Javeed, Sathish Kumar Jayapal, Shubha Jayaram, Heng Jiang, Catherine Owens Johnson, Walter D Johnson, Mohammad Jokar, Jost B Jonas, Abel Joseph, Nitin Joseph, Charity Ehimwenma Joshua, Mikk Jürisson, Ali Kabir, Zubair Kabir, Gebisa Guyasa Kabito, Vidya Kadashetti, Fatemeh Kafi, Rizwan Kalani, Farnaz Kalantar, Feroze Kaliyadan, Ashwin Kamath, Sagarika Kamath, Tanuj Kanchan, Amit Kandel, Himal Kandel, Kehinde Kazeem Kanmodi, Mehrdad Karajizadeh, Jafar Karami, Shama D Karanth, Ibraheem M Karaye, André Karch, Aliasghar Karimi, Hanie Karimi, Arman Karimi Behnagh, Hengameh Kasraei, Nicholas J Kassebaum, Joonas H Kaupilla, Harkiran Kaur, Navjot Kaur, Gbenga A Kayode, Foad Kazemi, Leila Keikavoosi-Arani, Cathleen Keller, Mohammad Keykhai, Mohammad Amin Khadembashiri, Yousef Saleh Khader, Morteza Abdullatif Khafae, Himanshu Khajuria, Amirmohammad Khalaji, Faham Khamesipour, Mohammad Khammarnia, Maseer Khan, Moien AB Khan, Yusra H Khan, Mohammed Ziauddin Khan Suheb, Shaghayegh Khanmohammadi, Tripti Khanna, Khaled Khatab, Haitham Khatabeh, Moawiah Mohammad Khatabeh, Sorour Khateri, Mahalauqa Nazli Khatib, Hamid Reza Khayat Kashani, Mohammad Saeid Khonji, Fatemeh khorashadizadeh, Moein Khormali, Jagdish Khubchandani, Saeid Kian, Grace Kim, Jihee Kim, Min Seo Kim, Yun Jin Kim, Ruth W Kimokoti, Adnan Kisa, Sezer Kisa, Mika Kivimäki, Sonali Kochhar, Ali-Asghar Kolahi, Kamrun Nahar Koly, Farzad Kompani, Walter J Koroshetz, Soewarta Kosen, Masoumeh Kourosh Arami, Ai Koyanagi, Michael A Kravchenko, Kewal Krishan, Vijay Krishnamoorthy, Barthelemy Kuate Defo, Md Abdul Kuddus, Ashish Kumar, G Anil Kumar, Manasi Kumar, Nithin Kumar, Netsanet Bogale Kumsa, Satyajit Kundu, Maria Dyah Kurniasari, Dian Kusuma, Ambily Kuttikkattu, Hmwe Hmwe Kyu, Carlo La Vecchia, Muhammad Awwal Ladan, Chandrakant Lahariya, Tri Laksono, Dharmesh Kumar Lal, Tea Lallukka, Judit Lám, Faris Hasan Lami, Iván Landires, Berthold Langguth, Savita Lasrado, Kamaluddin Latief, Kaveh Latifinaibin, Kathryn Mei-Ming Lau, Matthew B Laurens, Basira Kankia Lawal, Long Khanh Dao Le, Thao Thi Thu Le, Caterina Ledda, Munjae Lee, Sang-woong Lee, Seung Won Lee, Wei-Chen Lee, Yo Han Lee, Matilde Leonardi, Temesgen L Lerango, Ming-Chieh Li, Wei Li, Virendra S Ligade, Stephen S Lim, Christine Linehan, Chaojie Liu, Jue Liu, Wei Liu, Chun-Han Lo, Warren David Lo, Stany W Lobo, Giancarlo Logroscino, Graciliana Lopes, Platon D Lopukhov, László Lorenzovici, Stefan Lorkowski, Joana A Loureiro, Jailos Lubinda, Giancarlo Lucchetti, Ricardo Lutzky Saute, Zheng Feei Ma, Mahmoud Mabrok, Monika Machoy, Farzan Madadzadeh, Mohammed Magdy Abd El Razek, Azzam A Maghazachi, Nastaran Maghbouli, Soleiman Mahjoub, Morteza Mahmoudi, Azeem Majeed, Jeadran N Malagón-Rojas, Elaheh Malakan Rad, Kashish Malhotra, Ahmad Azam Malik, Iram Malik, Tauqeer Hussain Mallhi, Deborah Carvalho Malta, Aseer Manilal, Vahid Mansouri, Mohammad Ali Mansournia, Bishnu P Marasini, Hamid Reza Marateb, Seyed Farzad Maroufi, Jose Martinez-Raga, Santi Martini, Francisco Rogerlândio Martins-Melo, Miquel Martorell, Winfried März, Roy Rillera Marzo, João Massano, Yasith Mathangasinghe, Elezebeth Mathews, Richard James Maude, Andrea Maugeri, Pallab K Maulik, Mahsa Mayeli, Maryam Mazaheri, Colm McAlinden, John J McGrath, Jitendra Kumar Meena, Man Mohan Mehndiratta, Max Alberto Mendez Mendez-Lopez, Walter Mendoza, Oliver Mendoza-Cano, Ritesh G Menezes, Mohsen Merati, Atte Meretoja, Alexander Merkin, Abera M Mersha, Tomislav Mestrovic, Tianyue Mi, Tomasz Miazgowski, Irmina Maria Michalek, Ephrem Tesfaye Mihretie, Le Huu Nhat Minh, Reza Mirfakhraie, Andreea Mirica, Erkin M Mirrakhimov,

- Mehdi Mirzaei, Awoke Misganaw, Sanjeev Misra, Prasanna Mithra, Biru Abdissa Mizana, Ashraf Mohamadkhani, Nouh Saad Mohamed, Esmaeil Mohammadi, Hiwa Mohammadi, Shadieh Mohammadi, Soheil Mohammadi, Marita Mohammadshahi, Mustapha Mohammed, Salahuddin Mohammed, Shafiu Mohammed, Syam Mohan, Hoda Mojiri-forushani, Nagabhishek Moka, Ali H Mokdad, Sabrina Molinaro, Holger Möller, Lorenzo Monasta, Md Moniruzzaman, Fateme Montazeri, Maryam Moradi, Yousef Moradi, Maziar Moradi-Lakeh, Paula Moraga, Negar Morovatdar, Shane Douglas Morrison, Abbas Mosapour, Jonathan F Mosser, Elias Mossialos, Majid Motaghinejad, Parsa Mousavi, Seyed Ehsan Mousavi, Sumaira Mubarak, Lorenzo Muccioli, Faraz Mughal, George Duke Mukoro, Admir Mulita, Francesc Mulita, Fungai Musaigwa, Ahmad Mustafa, Ghulam Mustafa, Sathish Muthu, Ahamarshan Jayaraman Nagarajan, Pirouz Naghavi, Ganesh R Naik, Firzan Nainu, Tapas Sadasivan Nair, Hastyar Hama Rashid Najmuldeen, Nouredin Nakhostin Ansari, Gopal Nambi, Hossein Namdar Areshtanab, Shumaila Nargus, Bruno Ramos Nascimento, Abdullah Y Naser, Abdulqadir J J Nashwan, Hadis Nasoori, Ahmed Nasreldein, Zuhair S Natto, Javaid Nauman, Biswa Prakash Nayak, Athare Nazri-Panjaki, Mohammad Negaresh, Hadush Negash, Ionut Negoii, Ruxandra Irina Negoii, Serban Mircea Negru, Seyed Aria Nejadghaderi, Mohammad Hadi Nematollahi, Olivia D Nesbit, Charles Richard James Newton, Dang H Nguyen, Hau Thi Hien Nguyen, Hien Quang Nguyen, Ngoc-Trinh Thi Nguyen, Phat Tuan Nguyen, Van Thanh Nguyen, Robina Khan Niazi, Taxiarchis Konstantinos Nikolouzakis, Vikram Nirranjan, Lawrence Achilles Nnyanzi, Efaq Ali Noman, Nafise Noroozi, Bo Norrving, Jean Jacques Noubiap, Chisom Adaobi Nri-Ezedi, George Ntaios, Virginia Nuñez-Samudio, Dieta Nurrika, Bogdan Oancea, Ismail A Odetokun, Martin James O'Donnell, Ropo Ebenezer Ogunsakin, James Odhiambo Oguta, In-Hwan Oh, Hassan Okati-Aliabad, Sylvester Reuben Okeke, Akinkunmi Paul Okekunle, Osaretin Christabel Okonji, Patrick Godwin Okwute, Andrew T Olagunju, Muideen Tunbosun Olaiya, Matifan Dereje Olana, Matthew Idowu Olatubi, Gláucia Maria Moraes Oliveira, Isaac Iyinoluwa Olufadewa, Bolajoko Olubukunola Olusanya, Ahmed Omar Bali, Sokking Ong, Obinna E Onwujekwe, Michal Ordak, Aislyn U Orji, Doris V Ortega-Altamirano, Uchechukwu Levi Osuagwu, Nikita Ostavnov, Stanislav S Ostavnov, Amel Ouyahia, Mayowa O Owolabi, Mahesh Padukudru P A, Kevin Pacheco-Barrios, Jagadish Rao Padubidri, Pramod Kumar Pal, Padmavali Nanaji Palange, Claudia Palladino, Raffaele Palladino, Raul Felipe Palma-Alvarez, Feng Pan, Demosthenes Panagiotakos, Songhomitra Panda-Jonas, Anamika Pandey, Ashok Pandey, Jeyaraj Durai Pandian, Helena Ulylartha Pangaribuan, Ioannis Pantazopoulos, Shahina Pardhan, Pragyan Paramita Parija, Romil R Parikh, Seoyeon Park, Ashwaghosha Parthasarathi, Ava Pashaei, Jay Patel, Shankargouda Patil, Dimitrios Patoulias, Shrikant Pawar, Paolo Pedersini, Umberto Pensato, David M Pereira, Jeevan Pereira, Maria Odete Pereira, Mario F P Peres, Norberto Perico, Simone Perna, Ionela-Roxana Petcu, Fanny Emily Petermann-Rocha, Hoang Tran Pham, Michael R Phillips, Gabriel D Pinilla-Monsalve, Michael A Piradov, Evgenii Plotnikov, Dimitri Poddighe, Burcu Polat, Ramesh Poluru, Constance Dimity Pond, Govinda Raj Poudel, Alireza Pouramini, Ali Mohammad Pourbagher-Shahri, Mohammad Pourfridoni, Naeimeh Pourtaheri, Peralam Yegneswaran Prakash, Sanjay Prakash, V Prakash, Elton Junio Sady Prates, Natalie Pritchett, Hery Purnobasuki, Nameer Hashim Qasim, Ibrahim Qattea, Gangzhen Qian, Venkatraman Radhakrishnan, Pौर्या Raae, Hadi Raeisi Shahraki, Ibrar Rafique, Alberto Raggi, Pankaja Raghav Raghav, Meghdad M Rahati, Fakher Rahim, Zahra Rahimi, Mahban Rahimifard, Md Obaidur Rahman, Mohammad Hifz Ur Rahman, Mosiur Rahman, Muhammad Aziz Rahman, Amir Masoud Rahmani, Shayan Rahmani, Hamed Rahmani Youshanlouei, Masoud Rahmati, Sheetal Raj Moolambally, Ali Rajabpour-Sanati, Hazem Ramadan, Shakthi Kumaran Ramasamy, Premkumar Ramasabramani, Sheena Ramazanu, Nemanja Rancic, Indu Ramachandra Rao, Sowmya J Rao, Deepthi Rapaka, Vahid Rashedi, Ahmed Mustafa Rashid, Mohammad-Mahdi Rashidi, Mehran Rashidi Alavijeh, Ashkan Rasouli-Saravani, Salman Rawaf, Christian Razo, Elrashdy Moustafa Mohamed Redwan, Atefe Rekabi Bana, Giuseppe Remuzzi, Nazila Rezaei, Negar Rezaei, Nima Rezaei, Mohsen Rezaeian, Taeho Gregory Rhee, Abanoub Riad, Stephen R Robinson, Mónica Rodrigues, Jefferson Antonio Buendia Rodriguez, Leonardo Roever, Emma L B Rogowski, Michele Romoli, Luca Ronfani, Priyanka Roy, Koushik Roy Pramanik, Enrico Rubagotti, Milagros A Ruiz, Tom C Russ, Katharina S Sunnerhagen, Aly M A Saad, Zahra Saadatian, Korosh Saber, Morteza SaberiKamarposhti, Simona Sacco, Basema Saddik, Erfan Sadeghi, Saeid Sadeghian, Umar Saeed, Usman Saeed, Mahdi Safdarian, Sher Zaman Safi, Rajesh Sagar, Dominic Sagoe, Fatemeh Saheb Sharif-Askari, Narjes Saheb Sharif-Askari, Amirhossein Sahebkar, Soumya Swaroop Sahoo, Mohammad Ali Sahaian, Seyed Aidin Sajedi, Joseph W Sakshaug, Mohamed A Saleh, Hossein Salehi Omran, Marwa Rashad Salem, Sohrab Salimi, Hossein Samadi Kafli, Sara Samadzadeh, Saad Samargandy, Yoseph Leonardo Samodra, Vijaya Paul Samuel, Abdallah M Samy, Nima Sanadgol, Rama Krishna Sanjeev, Francesco Sanmarchi, Damian Francesco Santomauro, Ichitarini Nurullita Santri, Milena M Santric-Milicevic, Aswini Saravanan, Arash Sarveezad, Maheswar Satpathy, Mete Saylan, Mehdi Sayyah, Nikolaos Scarmeas, Markus P Schlaich, Art Schuermans, Michaël Schwarzingler, David C Schwebel, Siddharthan Selvaraj, Ashenafi Kibret Sendekie, Pallav Sengupta, Subramanian Senthilkumar, Dragos Serban, Mihretu Tagesse Sergindo, Yashendra Sethi, SeyedAhmad SeyedAlinaghi, Allen Seylani, Mohammad Shabani, Maryam Shabany, Mahan Shafie, Saeed Shahabi, Ataollah Shahbandi, Samiah Shahid, Fariba Shahraki-Sanavi, Hamid R Shahsavari, Moyad Jamal Shahwan, Masood Ali Shaikh, KS Shaji, Sunder Sham, Adisu Tafari T Shama, Muhammad Aaqib Shamim, Mehran Shams-Beyranvand, Mohammad Anas Shamsi, Mohd Shanawaz, Medha Sharath, Sadaf Sharfaei, Amin Sharifan, Manoj Sharma, Rajesh Sharma, Bereket Beyene Shashamo, Maryam Shayan, Rahim Ali Sheikhi, Shashank Shekhar, Jiabin Shen, Suchitra M Shenoy, Pavanchand H Shetty, Desalegn Shiferaw Shiferaw, Mika Shigematsu, Rahman Shiri, Aminu Shittu, K M Shivakumar, Fereshthek Shokri, Sina Shool, Seyed Afshin Shorofi, Sunil Shrestha, Akhenaten Benjamin Siankam Tankwanchi, Emmanuel Edwar Siddiq, Inga Dora Sigfusdottir, João Pedro Silva, Luís Manuel Lopes Rodrigues Silva, Ehsan Sinaei, Balbir Bagicha Singh, Garima Singh, Paramdeep Singh, Surjit Singh, Sarah Brooke Sirota, Shrawan Sivakumar, Abdullah Al Mamun Sohag, Ranjan Solanki, Hamidreza Soleimani, Solikhah Solikhah, Yerukneh Solomon, Yonatan Solomon, Suhang Song, Yimeng Song, Houman Sotoudeh, Michael Spartalis, Benjamin A Stark, Joseph R Starnes, Antonina V Starodubova, Dan J Stein, Timothy J Steiner, Lars Jacob Stovner, Muhammad Suleman, Rizwan Suliankatchi Abdulkader, Abida Sultana, Jing Sun, David Sunkersing, Angel Sunny, Hani Susianti, Chandan Kumar Swain, Mindy D Szeto, Rafael Tabarés-Seisdedos, Seyed Mohammad Tabatabaei, Shima Tabatabai, Mohammad Tabish, Majid Taheri, Azin Tahvildari, Ardeshir Tajbaksh, Mircea Tampa, Jacques JL Lukenze Tamuzi, Ker-Kan Tan, Haosu Tang, Minale Tareke, Ingan Ukur Tarigan, Nathan Y Tat, Vivian Y Tat, Razieh Tavakoli Oliaee, Seyed Mohammad Tavangar, Arian Tavasol, Yibekal Manaye Tefera, Arash Tehrani-Banihashemi, Worku Animaw Temesgen, Mohamad-Hani Temsah, Masayuki Teramoto, Amensisa Hailu Tesfaye, Edosa Geta Tesfaye, Riki Tesler, Ocean Thakali, Pugazhenthnan Thangaraju, Rajshree Thapa, Rekha Thapar, Nikhil Kenny Thomas, Amanda G Thrift, Jansje Henny Vera Ticoalu, Tala Tillawi, Razie Toghrol, Marcello Tonelli, Marcos Roberto Tovani-Palone, Eugenio Traini, Nghia Minh Tran, Ngoc-Ha Tran, Phu Van Tran, Samuel Joseph Tromans, Thomas Clement Truelsen, Thien Tan Tri Tai Truyen, Aristidis Tsatsakis, Guesh Mebrahtom Tsegay, Evangelia Eirini Tsermpini, Abdul Rohim Tualeka, Derara Girma Tufa, Chukwudi S Ubah, Aniefiok John Udoakang, Inam Ulhaq, Muhammad Umair, Srikanth Umakanthan, Krishna Kishore Umaphathi, Brigid Unim,

Bhaskaran Unnikrishnan, Asokan Govindaraj Vaithinathan, Alireza Vakilian, Sahel Valadan Tahbaz, Rohollah Valizadeh, Jef Van den Eynde, Priya Vart, Shoban Babu Varthya, Tommi Juhani Vasankari, Siavash Vaziri, Balachandrar Vellingiri, Narayanaswamy Venkatasubramanian, Georgios-Ioannis Verras, Dominique Vervoort, Jorge Hugo Villafaña, Leonardo Villani, Andres Fernando Vinueza Veloz, Maria Viskadourou, Sergey Konstantinovich Vladimirov, Vasily Vlassov, Simona Ruxandra Volovat, Loc Tri Vu, Isidora S Vujcic, Birhanu Wagaye, Yasir Waheed, Waseem Wahood, Mandaras Tariku Walde, Fang Wang, Shu Wang, Yanzhong Wang, Yuan-Pang Wang, Muhammad Waqas, Abdul Waris, Kosala Gayan Weerakoon, Robert G Weintraub, Abrha Hailay Weldemariam, Ronny Westerman, Joanna L Whisnant, Dakshitha Praneeth Wickramasinghe, Nuwan Darshana Wickramasinghe, Barbara Willekens, Lauren B Wilner, Andrea Sylvia Winkler, Charles D A Wolfe, Ai-Min Wu, Sarah Wulf Hanson, Suowen Xu, Xiaoyue Xu, Ali Yadollahpour, Sajad Yaghoubi, Galal Yahya, Kazumasa Yamagishi, Lin Yang, Yuichiro Yano, Yao Yao, Sisay Shewasinad Yehualashet, Alex Yeshaneh, Metin Yesiltepe, Siyan Yi, Arzu Yiğit, Vahit Yiğit, Dong Keon Yon, Naohiro Yonemoto, Yuyi You, Mustafa Z Younis, Chuanhua Yu, Hadiza Yusuf, Siddhesh Zadey, Mohammad Zahedi, Fathiah Zakhani, Nazar Zaki, Alireza Zali, Giulia Zamagni, Ramin Zand, Ghazal G Z Zandieh, Moein Zangiabadian, Amin Zarghami, Mikhail Sergeevich Zastrozhin, Mohammed G M Zeariya, Zelalem Banjaw Zegeye, Francis Zeukeng, Chunxia Zhai, Chen Zhang, Haijun Zhang, Yunquan Zhang, Zhi-Jiang Zhang, Hanqing Zhao, Yang Zhao, Peng Zheng, Hengxing Zhou, Bin Zhu, Abzal Zhumagaliuly, Magdalena Zielińska, Yossef Teshome Zikarg, Mohammad Zoladl, Christopher J L Murray, Kanyin Liane Ong†, Valery L Feigin†, Theo Vos†, and Tarun Dua†

*Joint first authors

†Joint senior authors

Affiliations

Institute for Health Metrics and Evaluation (J D Steinmetz PhD, E Cousin PhD, H Hagins MSPH, M E Moberg MS, M L Mehlman PhD, A Y Aravkin PhD, R G Bender BS, B Berice MPH, K Bhangdia MS, K Burkart PhD, K Coberly BS, X Dai PhD, Prof L Dandona MD, Prof R Dandona PhD, F E Dean BA, Prof S D Dharmaratne MD, M A Dirac MD, A J Ferrari PhD, L M Force MD, W M Gardner MPH, H Han MSc, M Hassen BSc, Prof S I Hay FMedSci, C O Johnson PhD, N J Kassebaum MD, C Keller MPH, H H Kyu PhD, K M Lau BS, Prof S S Lim PhD, T Mestrovic PhD, A H Mokdad PhD, J F Mosser MD, O D Nesbit MA, A U Orji BA, N Pritchett DrPH, C Razo PhD, E L B Rogowski BA, D F Santomauro PhD, S B Sirota MA, B A Stark MA, J L Whisnant MPH, L B Wilner MPH, S Wulf Hanson PhD, P Zheng PhD, Prof C J L Murray DPhil, K L Ong PhD, Prof V L Feigin PhD, Prof T Vos PhD), Department of Health Metrics Sciences, School of Medicine (E Cousin PhD, A Y Aravkin PhD, K Burkart PhD, X Dai PhD, Prof R Dandona PhD, Prof S D Dharmaratne MD, M A Dirac MD, L M Force MD, Prof S I Hay FMedSci, N J Kassebaum MD, H H Kyu PhD, Prof S S Lim PhD, A Misganaw PhD, A H Mokdad PhD, P Zheng PhD, Prof C J L Murray DPhil, Prof T Vos PhD), Department of Applied Mathematics (A Y Aravkin PhD), Department of Family Medicine (M A Dirac MD), Department of Neurological Surgery (R G Ellenbogen MD), Division of Pediatric Hematology-Oncology (L M Force MD), Department of Epidemiology (H Guo MPH), Department of Neurology (R Kalani MD), Department of Anesthesiology and Pain Medicine (N J Kassebaum MD, V Krishnamoorthy MD), Department of Global Health (S Kochhar MD), Division of Plastic and Reconstructive Surgery (S D Morrison MD), and Health Systems and Population Health (A B Siankam Tankwanchi PhD), University of Washington, Seattle, WA, USA; Department of Mental Health and Substance Use (K M Seeher PhD, N Schiess MD, C Servili MD, V Cavallera MD, T Dua MD) and Department of Data and Analytics (B Cao PhD), WHO, Geneva, Switzerland; Center for Economic and Social Research (E Nichols PhD), Department of Neurosurgery (A Abedi MD), Keck School of Medicine (A Abedi MD), and Department of Radiology (A Gholamrezaezhad MD), University of Southern California, Los Angeles, CA, USA; Department of Clinical Governance

and Quality Improvement (Y H Abate MSc), Aleta Wondo Hospital, Aleta Wondo, Ethiopia; Antai College of Economics (J Abbas PhD) and Shanghai Mental Health Center (Prof M R Phillips MD), Shanghai Jiao Tong University, Shanghai, China; Infectious and Tropical Research Center (M A Abbasi PhD), Department of Radiology (M Dashti MD), School of Nursing and Midwifery (H Hassankhani PhD), Department of Immunology (F Jadidi-Niaragh PhD), Department of Community Medicine (S Mousavi MD), Department of Mental Health and Psychiatric Nursing (H Namdar Areshtanab PhD), and Drug Applied Research Center (H Samadi Kafil PhD), Tabriz University of Medical Sciences, Tabriz, Iran; Department of Orthopedic Surgery (M Abbasian MD), Department of Pediatrics (S Aly MD), TH Chan School of Public Health (Prof T W Bärnighausen MD), Center for Primary Care (S Basu PhD), Harvard Business School (F Caetano dos Santos PhD), Division of Cardiovascular Medicine (G Chi MD), Division of Cardiology (I Y Elgendy MD), Department of Health Policy and Oral Epidemiology (Z S Natto DrPH), and Department of Physical Medicine and Rehabilitation (K Pacheco-Barrios MD), Harvard University, Boston, MA, USA; Department of Orthopaedic Surgery (M Abbasian MD), Department of Biotechnology (S Aghamiri PhD), National Nutrition and Food Technology Research Institute (M Ajami PhD), Department of Hematology and Blood Banking (D Bashash PhD), Neurology Department (M Fathi MD), Psychiatric Nursing and Management Department (F Ghadirian PhD), Department of Medical Genetics (M Ghasemi PhD), Center for Comprehensive Genetic Services (M Ghasemi PhD), Obstetrics and Gynecology Department (E Ghotbi MD), Obesity Research Center (A Haj-Mirzaian MD), Urology and Nephrology Research Center (H Hesami MD, H Salehi Omran MD), Ophthalmic Research Center (H Hesami MD), Department of Immunology (K Jahankhani MSc), Virtual School of Medical Education and Management (N Jahanmehr PhD), Prevention of Cardiovascular Disease Research Center (N Jahanmehr PhD), Department of Neurosurgery (H Khayat Kashani MD), Social Determinants of Health Research Center (A Kolahi MD, M Rashidi MD), Department of Genetics (R Mirfakhraie PhD), School of Medicine (F Montazeri MD, S Nejadghaderi MD, S Rahmani MD, M Zangiabadian MD), Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases (M Motaghinejad PhD), Department of Biology and Anatomical Sciences (P Raei PhD), Immunology Department (A Rasouli-Saravani PhD), Department of Anesthesiology (S Salimi MD, A Tajbakhsh MD, A Tajbakhsh MD), Ophthalmic Research Center (M Shayan MD), Emergency Department (S Shool MD), Department of Medical Education (S Tabatabai PhD), Medical Ethics and Law Research Center (M Taheri PhD), Skin Research Center (A Tahvildari MD), Medicine Faculty (A Tavasol MD), and Functional Neurosurgery Research Center (Prof A Zali MD), Shahid Beheshti University of Medical Sciences, Tehran, Iran; Advanced Diagnostic and Interventional Radiology Research Center (H Abbastabar PhD), The Institute of Pharmaceutical Sciences (Prof M Abdollahi PhD), School of Pharmacy (Prof M Abdollahi PhD), Research Center for Immunodeficiencies (H Abolhassani PhD, Prof N Rezaei PhD), Hematology, Oncology and Stem Cell Transplantation Research Center (H Alemi MD), Universal Scientific Education and Research Network (M Amirzade-Iranaq DDS), Department of Health Information Management (S Ayyoubzadeh PhD), Non-communicable Diseases Research Center (S Azadnajafabad MD, Prof F Farzadfar DSc, M Keykhaei MD, S Maroufi MS, F Montazeri MD, S Rahmani MD, M Rashidi MD, N Rezaei MD, N Rezaei PhD), Neuroscience Institute (M Babaei MD), School of Medicine (A Behnoush BS, H Karimi MD, A Khalaji BS, S Khanmohammadi MD, M Mayeli MD, M Merati MD, S Mohammadi MD), Department of Pediatric Neurology (M Bemanalizadeh MD), Department of Scientific Research (F Chichagi MD), Department of Neurosurgery (M Dabbagh Ohadi MD), Multiple Sclerosis Research Center (S Eskandarieh PhD, Prof M Sahraian MD), Neurology Department of Shariati Hospital (B Ghaderi Yazdi MD), Department of Health in Emergencies and Disasters (M Hadei PhD), Urology Research Center (F Kafi MD, A Pouramini MD), Immunology Department (J Karami PhD), Students' Scientific Research Center (M Keykhaei MD, M Khadembashiri MD), Center for Research and Training in Skin

Diseases and Leprosy (F Khamesipour PhD), Sina Trauma and Surgery Research Center (M Khormali MD, S Shool MD), Children's Medical Center (F Kompani MD), Department of Physical Medicine and Rehabilitation (N Maghbouli MD), Department of Pediatric Cardiology (Prof E Malakan Rad MD), Digestive Diseases Research Institute (V Mansouri MD, A Mohamadkhani PhD), Department of Epidemiology and Biostatistics (M Mansournia PhD), Faculty of Medicine (E Mohammadi MD), National Institute for Health Research (M Mohammadshahi PhD), Non-communicable Disease Research Center (P Mousavi MD), Department of Physiotherapy (Prof N Nakhostin Ansari PhD), Department of Pharmacology (N Noroozi DVM), Pharmaceutical Sciences Research Center (M Rahimifard PhD), Endocrinology and Metabolism Research Institute (N Rezaei PhD), Iranian Research Center for HIV/AIDS (S SeyedAlinaghi PhD), Sina Trauma Research Center (M Shabany PhD), Department of Neurology (M Shafie MD), Department of Medicine (A Shahbandi MD), Department of Pharmaceutical Care (A Sharifan PharmD), Research Center for Rational Use of Drugs (A Sharifan PharmD), and Department of Pathology (Prof S Tavangar MD), Tehran University of Medical Sciences, Tehran, Iran (R Heidari-Soureshjani MSc, E Mohammadi MD); Department of Surgery (M Abdelmassih MD), Marshall University, Huntington, WV, USA; School of Medicine (M Abdollahi MD, M Farjoud Kouhanjani MD), Health Policy Research Center (R Amani DVM), Epilepsy Research Center (Prof A A Asadi-Pooya MD, M Farjoud Kouhanjani MD), Student Research Committee (A Faramarzi MD), Department of Otolaryngology (A Faramarzi MD), Department of Neurosurgery (F Ghaffaripasand MD), Shiraz Neuroscience Research Center (F Iranvanpour PhD, M Jafarinia PhD, R Tavakoli Olliaee PhD), Center for Nanotechnology in Drug Delivery (M Jafari PhD), Trauma Research Center (M Karajizadeh PhD), Neuromodulation and Pain Center (A Karimi MD), Health Policy Research Center (H Kasraei MD, S Shahabi PhD), Research Consultation Center (E Sadeghi PhD), and Department of Physical Therapy (E Sinaei MSc), Shiraz University of Medical Sciences, Shiraz, Iran; Department of Small Animal Clinical Sciences (M Abdollahifar PhD), University of Saskatchewan, Saskatoon, SK, Canada; Evidence-Based Practice Center (R Abd-Rabu MD, F Alahdab MSc) and Department of Radiology (S Ghozy MD), Mayo Clinic Foundation for Medical Education and Research, Rochester, MN, USA; Community and Maternity Nursing Unit (D M Abdulah MPH) and Department of Pathology and Microbiology (J Q Ahmed MSc), University of Duhok, Duhok, Iraq; Department of Physiotherapy (A Abdullahi PhD), Community Medicine Department (Prof M A Gadanya FMCPH), and Department of Nursing Science (M Ladan PhD), Bayero University, Kano, Nigeria; Department of Rehabilitation Sciences (A Abdullahi PhD, M U Ali MSc), Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China; Department of Public Health Sciences (V Abedi PhD), Pennsylvania State University, Hershey, PA, USA; Biocomplexity Institute (V Abedi PhD), Virginia Tech, Blacksburg, VA, USA; Postgraduate Department (Prof R A Abeldaño Zuñiga PhD), University of Sierra Sur, Miahuatlan de Porfirio Diaz, Mexico; National Research Council of Mexico, Mexico City, Mexico (Prof R A Abeldaño Zuñiga PhD); Laboratory Technology Sciences Department (H Abidi PhD) and Department of Nursing (M Zoladl PhD), Yasuj University of Medical Sciences, Yasuj, Iran; Department of Community Medicine (O Abiodun MPH), Babcock University, Ilishan-Remo, Nigeria; Department of Family and Community Health (R G Aboagye MPH), Institute of Health Research (R K Alhassan PhD, M Immurana PhD), Department of Population and Behavioural Sciences (H Amu PhD), University of Health and Allied Sciences, Ho, Ghana; Department of Biosciences and Nutrition (H Abolhassani PhD), Karolinska University Hospital, Huddinge, Sweden; Department of Cardiology (Prof V Abovans MD), Dupuytren University Hospital, Limoges, France; University of Limoges, Limoges, France (Prof V Abovans MD); Department of Adult Health Nursing (W A Abrha MSc, A H Weldemariam MSc), Department of Public Health (T W Angesom MSc), and Department of Nursing (G G Gebremeskel MSc, T G Haile MSc, G M Tsegay MSc), Aksum University, Aksum, Ethiopia; Department of Neurology (A Abualhasan MD, A Hassan MD, M I Hegazy PhD) and Neurophysiology Department (Prof H R Elhabashy MD), Cairo University, Cairo, Egypt; Clinical Sciences Department (E Abu-Gharbieh PhD, N R Dash MD, Prof R Halwani PhD, N Saheb Sharif-Askari PhD), Pharmacy Practice and Pharmacotherapeutics (Prof K H Alzoubi PhD), Department of Clinical Sciences (M Bilalaga MBBS), Sharjah Institute for Medical Research (N M Elemam PhD, B Saddik PhD), College of Medicine (Prof R Halwani PhD, M A Saleh PhD), Clinical Sciences (Prof A A Maghazachi PhD), and Sharjah Institute of Medical Sciences (F Saheb Sharif-Askari PhD), University of Sharjah, Sharjah, United Arab Emirates (K A Altirkawi MD); Department of Therapeutics (Prof S Aburuz PhD), Institute of Public Health (L A Ahmed PhD, I Elbarazi DrPH), College of Medicine and Health Sciences (Prof M Grivna PhD, J Nauman PhD), Family Medicine Department (M A Khan MSc), and Big Data Analytics Center (Prof N Zaki PhD), United Arab Emirates University, Al Ain, United Arab Emirates; College of Pharmacy (Prof S Aburuz PhD), University of Jordan, Amman, Jordan; Department of Human Anatomy (L H Adamu PhD), Federal University Dutse, Dutse, Nigeria; Centre for Social Research in Health (I Y Addo PhD, S R Okeke PhD), St George and Sutherland Clinical School (H Akbarialiabad MD), School of Population Health (Z Dai PhD, X Xu PhD), and School of Medicine (P K Maulik PhD), University of New South Wales, Sydney, NSW, Australia; Quality and Systems Performance Unit (I Y Addo PhD), Cancer Institute NSW, Sydney, NSW, Australia; College of Medicine (O M Adebayo MD), Psychiatry Department (O O Ayinde MSc), Department of Community Medicine (O S Ilesanmi PhD), and Department of Medicine (Prof M O Owolabi DrM), University College Hospital, Ibadan, Ibadan, Nigeria; Department of Obstetrics and Gynecology (V Adekanmbi PhD), Department of Internal Medicine (W Lee PhD), and Department of Pathology (V Y Tat BS), University of Texas, Galveston, TX, USA; Department of Pharmaceutical Sciences (T A Adekiya PhD), Howard University, Washington, DC, USA; Department of Pharmacy (W Adikusuma PhD), University of Muhammadiyah Mataram, Mataram, Indonesia; Faculty of Medicine (Q E S Adnani PhD), Universitas Padjadjaran, Bandung, Indonesia; Clinical Sciences Department (S Adra MD), University of Sharjah, Sharjah, United Arab Emirates; Department of Public Health (T Afework MPH), Department of Microbiology, Immunology and Parasitology (M D Olana PhD), and Department of Anatomy (Y T Zikarg MSc), Addis Ababa University, Addis Ababa, Ethiopia; Department of Sociology (T Afework MPH) and School of Cardiovascular and Metabolic Health (F E Petermann-Rocha PhD), University of Glasgow, Glasgow, UK; Department of Community Medicine (A A Afolabi MPH, O S Ilesanmi PhD), Institute for Advanced Medical Research and Training (R O Akinyemi PhD), Department of Epidemiology and Medical Statistics (M Ekholuenetale MSc, A F Fagbamigbe PhD), Faculty of Public Health (M Ekholuenetale MSc, I I Olufadewa MHS), Department of Health Promotion and Education (S E Ebitoye MPH), College of Medicine (A P Okekunle PhD), and Department of Medicine (Prof M O Owolabi DrM), University of Ibadan, Ibadan, Nigeria; Department of Medical Information Sciences (A Afraz MSc), Department of Physiology and Pharmacology (H Bashiri PhD), Institute of Neuropharmacology (H Bashiri PhD), Neurology Research Center (M Ilaghi MD), Kerman Neuroscience Research Center (M Ilaghi MD), Department of Immunology (Prof A Jafarzadeh PhD), Department of Clinical Biochemistry (M Nematollahi PhD), and Department of Neuroscience (Prof M Shabani PhD), Kerman University of Medical Sciences, Kerman, Iran; Department of Community Medicine (Prof S Afzal PhD), King Edward Memorial Hospital, Lahore, Pakistan; Department of Public Health (Prof S Afzal PhD), Public Health Institute, Lahore, Pakistan; Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia" (Prof A Agodi PhD, M Barchitta PhD), Department of Medical and Surgical Sciences and Advanced Technologies (E D'Amico MD), Department of General Surgery and Surgical-Medical Specialties (Prof G Isola PhD), Clinical and Experimental Medicine (C Ledda PhD), and Department GF Ingrassia (A Maugeri PhD), University of Catania, Catania, Italy; Department of Geography and Planning (W Agyemang-Duah MSc), Queen's University, Kingston, ON, Canada; School of Public Health (B O Ahinkorah MPhil, D Demant PhD) and

School of Computing Sciences (Prof J Sun PhD), University of Technology Sydney, Sydney, NSW, Australia; Department of Medical Biochemistry (A Ahmad PhD), Department of Pediatrics (Prof G Mustafa MD), and Department of Pharmacology (M Tabish MPharm), Shaqra University, Shaqra, Saudi Arabia; Health Research Institute (D Ahmad PhD), University of Canberra, Canberra, ACT, Australia; Public Health Foundation of India, Gandhinagar, India (D Ahmad PhD); Department of Health and Biological Sciences (S Ahmad PhD), Abasyn University, Peshawar, Pakistan; Department of Natural Sciences (S Ahmad PhD), Labanese American University, Beirut, Lebanon; Department of Neuroscience (A Ahmadzade MD), Department of Public Health (A Avan MD), Department of Medical Informatics (N Firouraghi PhD, S Tabatabaei PhD), Clinical Research Development Unit (N Morovatdar MD), Neuroscience Department (A Pourbagher-Shahri MD), Applied Biomedical Research Center (A Sahebkar PhD), Biotechnology Research Center (A Sahebkar PhD), and Clinical Research Development Unit (S Tabatabaei PhD), Mashhad University of Medical Sciences, Mashhad, Iran; School of Pharmacy (A Ahmed MPhil), Monash University, Bandar Sunway, Malaysia; Department of Pharmacy (A Ahmed MPhil), Quaid I Azam University Islamabad, Islamabad, Pakistan; Institute of Endemic Diseases (A Ahmed MSc) and Unit of Basic Medical Sciences (E E Siddig MD), University of Khartoum, Khartoum, Sudan; Swiss Tropical and Public Health Institute (A Ahmed MSc), University of Basel, Basel, Switzerland; Department of Biosciences (H Ahmed PhD), COMSATS Institute of Information Technology, Islamabad, Pakistan; Department of Epidemiology (M B Ahmed MPH, D S Shiferaw MPH), Department of Midwifery (B A Mizana MSc), and Department of Biomedical Science (Z B Zegeye MSc), Jimma University, Jimma, Ethiopia; Australian Center for Precision Health (M B Ahmed MPH), University Department of Rural Health (Prof R J Gray PhD), and Department of Clinical and Health Sciences (N B Kumsa MSc), University of South Australia, Adelaide, SA, Australia; Brody School of Medicine (S Ahmed PhD), Department of Computer Science (A O Bodunrin MSc), and Department of Public Health (C S Ubah MPH), East Carolina University, Greenville, NC, USA (R T Aruleba PhD); Department of Food and Nutrition Policy and Planning Research (M Ajami PhD), National Institute of Nutrition, Tehran, Iran; Faculty of Medicine and Public Health (B Aji DrPH), Jenderal Soedirman University, Purwokerto, Indonesia; School of Community Health Sciences (O Ajumobi MPH), University of Nevada Reno, Reno, NV, USA; National Malaria Elimination Program (O Ajumobi MPH), Federal Ministry of Health, Abuja, Nigeria; Department of Medical Virology (S Akade MSc), Department of Biostatistics and Epidemiology (Prof S Bitaraf PhD, Z Rahimi PhD), Department of Public Health (M A Khafaie PhD), and Education Development Center (M Sayyah MD), Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Department of Medical Entomology (M Akbari PhD), Ilam University of Medical Sciences, Ilam, Iran; Department of Biomolecular Science (S Akhlaghi PhD), University of Mississippi, Oxford, MS, USA; Department of Internal Medicine (K Akinosoglou PhD), University of Patras, Patras, Greece; Internal Medicine and Infectious Diseases (K Akinosoglou PhD), University General Hospital of Patras, Patras, Greece; Institute of Neuroscience (R O Akinyemi PhD), Newcastle University, Newcastle upon Tyne, UK; Department of Epidemiology and Biostatistics (M Akonde MLS) and Department of Health Promotion, Education, and Behavior (T Mi PhD), University of South Carolina, Columbia, SC, USA; Clinical Research Support Center (S Al Hasan PhD), Kagawa University Hospital, Miki-cho, Japan; Institute of Global Health (T M A AL-Ahdal MPH) and Heidelberg Institute of Global Health (Prof T W Bärnighausen MD), Heidelberg University, Heidelberg, Germany; Faculty of Nursing (R M Al-amer PhD), Isra University- Jordan, Amman, Jordan; School of Nursing and Midwifery (R M Al-amer PhD), Translational Health Research Institute (R Chimoriya PhD, M Huda PhD), and Department of Engineering (G R Naik PhD), Western Sydney University, Sydney, NSW, Australia; Community and Mental Health Department (Prof M Albashtawy PhD), Al al-Bayt University, Mafraq, Jordan; Department of Molecular Biology and Genetics (Prof M T AlBataineh PhD) and Department of Epidemiology and Population Health (B Al-Omari PhD), Khalifa University, Abu Dhabi, United Arab Emirates; Department of Pediatrics (K A Aldawsari MD), Nicklaus Children's Hospital, Miami, FL, USA; Heart Center (K A Aldawsari MD), King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; Global Health Entrepreneurship (S Alemi PhD), Tokyo Medical and Dental University, Tokyo, Japan; Department of Bacteriology, Immunology, and Mycology (Prof A M Algammal PhD) and Department of Veterinary Microbiology (M Mabrok PhD), Suez Canal University, Ismailia, Egypt; Global Centre for Environmental Remediation (A A S Al-Gheethi PhD) and School of Medicine and Public Health (P Atorkey MPhil), University of Newcastle, Newcastle, NSW, Australia; Cooperative Research Centre for Contamination Assessment and Remediation of the Environment, Newcastle, NSW, Australia (A A S Al-Gheethi PhD); College of Nursing (Prof F A N Alhalaiqa PhD), Qatar University, Doha, Qatar; Psychological Sciences Association, Amman, Jordan (Prof F A N Alhalaiqa PhD); Department of Zoology (A Ali PhD), Abdul Wali Khan University Mardan, Mardan, Pakistan; Department of Public Health and Primary Care (E Ali MSc), Katholieke Universiteit Leuven, Belgium; Department of Biological Sciences (L Ali PhD), National University of Medical Sciences, Rawalpindi, Pakistan; Department of Medical Rehabilitation (Physiotherapy) (M U Ali MSc) and Department of Clinical Pharmacy and Pharmacy Administration (H Yusuf PhD), University of Maiduguri, Maiduguri, Nigeria; School of Medical Laboratory, Module of Microbiology and Parasitology (M M Ali PhD), Hawassa University, Hawassa, Ethiopia; Department of Biosciences (R Ali Pursuing PhD) and CIRBSc (M A Shamsi PhD), Jamia Millia Islamia, New Delhi, India; Centre for Biotechnology and Microbiology (S Ali PhD, S S Ali PhD), University of Swat, Charbagh, Swat, Pakistan; Department of Pharmacy (Z Ali PharmD), University of Peshawar, Peshawar, Pakistan; School of Public Health and Preventive Medicine (S M Alif PhD, Prof M Asghari-Jafarabadi PhD), Department of Epidemiology and Preventative Medicine (E K Chowdhury PhD), Department of Medicine (Prof A G Thrift PhD), Monash University, Melbourne, VIC, Australia; Pars Advanced and Minimally Invasive Medical Manners Research Center (Y Alimohamadi PhD), Health Management and Economics Research Center (H Ayatollahi PhD), Department of Health Information Management (H Ayatollahi PhD), School of Medicine (M Dodangeh MD, N Eissazade MD), Minimally Invasive Surgery Research Center (A Kabir MD), Endocrine Research Center (A Karimi Behnagh MD), Eye Research Center (H Kasraei MD), Neuro Musculoskeletal Research Center (M Khadembashiri MD), Bone and Joint Reconstruction Research Center (M Khonji MD), Department of Neuroscience (M Kourosh Arami PhD), Department of Anesthesiology (K Latifinaibin MD), Faculty of Medicine (S Maroufi MS), Preventive Medicine and Public Health Research Center (M Moradi-Lakeh MD, A Tehrani-Banihashemi PhD), Department of Epidemiology (Z Rahimi PhD), Colorectal Research Center (A Sarveazad PhD), Trauma and Injury Research Center (M Taheri PhD), and Department of Community and Family Medicine (A Tehrani-Banihashemi PhD), Iran University of Medical Sciences, Tehran, Iran (M Moradi MD); Department of Public Health (A A Aliyi MPH), Madda Walabu University, Goba, Ethiopia; Department of Biomedical Sciences (M Aljofan PhD) and Department of Medicine (J U Almazan PhD, Prof D Poddighe PhD), Nazarbayev University, Astana, Kazakhstan; Department of Health Policy and Management (Prof S M Aljunid PhD), Kuwait University, Kuwait, Kuwait; International Centre for Casemix and Clinical Coding (Prof S M Aljunid PhD), National University of Malaysia, Bandar Tun Razak, Malaysia; Department of Neurology (Prof S Alladi MD), National Institute of Mental Health and Neurosciences, Bangalore, India; College of Medicine (S Almustanyir MD), Alfaisal University, Riyadh, Saudi Arabia; Ministry of Health, Riyadh, Saudi Arabia (S Almustanyir MD); Department of Respiratory Care (J S Alqahtani PhD), Prince Sultan Military College of Health Sciences, Dammam, Saudi Arabia; Department of Public Health (I Alqasmi PhD), Saudi Electronic University, Riyadh, Saudi Arabia; Department of Prosthodontics and Implant Dentistry (A Alqutaibi PhD), Taibah University, Medina, Saudi Arabia; Department of Prosthodontics (A Alqutaibi PhD), Ibb University, Ibb, Yemen; Centre for Clinical Brain Sciences (Prof R Al-Shahi Salman PhD), Department of Neurosurgery (A K Demetriades MD), Global Health Governance Programme (J Patel BSc), and College of Medicine and Veterinary Medicine (G Verras MD), University of Edinburgh, Edinburgh, UK

(T C Russ PhD); Department of Basic Sciences (Z Altaany PhD), Yarmouk Univeristy, Irbid, Jordan; Department of Specialty Internal Medicine (Prof J A Al-Tawfiq MD), Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia; Medicine Department (Prof J A Al-Tawfiq MD), Indiana University School of Medicine, Indianapolis, IN, USA; Research Group in Hospital Management and Health Policies (Prof N Alvis-Guzman PhD), Universidad de la Costa, Barranquilla, Colombia; Research Group in Health Economics (Prof N Alvis-Guzman PhD), University of Cartagena, Cartagena, Colombia; Department of Medical Sciences (Prof Y M Al-Worafi PhD), Azal University for Human Development, Sana'a, Yemen; Department of Clinical Sciences (Prof Y M Al-Worafi PhD), University of Science and Technology of Fujairah, Fujairah, United Arab Emirates; Department of Pediatrics (Prof H Aly MD) and Department of Cardiovascular Medicine (S Shekhar MD), Cleveland Clinic, Cleveland, OH, USA; Department of Pediatric Cardiology (S Aly MD), Boston Children's Hospital, Boston, MA, USA; Department of Clinical Pharmacy, Faculty of Pharmacy (Prof K H Alzoubi PhD) and Department of Public Health (Prof Y S Khader PhD), Jordan University of Science and Technology, Irbid, Jordan; Department of Veterinary Pathology (R Amani DVM), Islamic Azad University, Babol, Iran; Department of Radiology (A Amindarolzarbi MD), Department of Biostatistics (A Columbus MS), Department of Neurosurgery (F Kazemi MD), Department of Health Policy and Management (D Vervoort MD), Division of Cardiology (M Viskadourou MD), and Department of International Health (H Zhang MS), Johns Hopkins University, Baltimore, MD, USA; Medicine, Quran and Hadith Research Center (S Amiri PhD), Baqiyatallah University of Medical Sciences, Tehran, Iran; Department of Maternal and Child Wellbeing (D A Amugsi PhD), African Population and Health Research Center, Nairobi, Kenya; Department of Medicine (G A Amusa MD), University of Jos, Jos, Nigeria; Department of Internal Medicine (G A Amusa MD), Jos University Teaching Hospital, Jos, Nigeria; Department of Sociology (Prof J Amzat PhD) and Department of Theriogenology and Animal Production (A Shittu MSc), Usmanu Danfodiyo University, Sokoto, Sokoto, Nigeria; Department of Sociology (Prof J Amzat PhD), University of Johannesburg, Johannesburg, South Africa; Faculty of Pharmacy (Prof R Ancuceanu PhD), Cardiology Department (C Andrei PhD), Ophthalmology Department (A Dascalu PhD), Department of Legal Medicine and Bioethics (S Hostici PhD), Department of General Surgery (I Negoii PhD, D Serban PhD), Department of Anatomy and Embryology (R I Negoii PhD), and Department of Dermatology (M Tampa PhD), Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Centre for Sensorimotor Performance (D Anderlini MD), Centre of Research Excellence in Stillbirth (T Begum MPH), Department of Urology (Prof E Chung MD), School of Public Health (A J Ferrari PhD, D F Santomauro PhD), Queensland Brain Institute (Prof J J McGrath MD), and Faculty of Medicine (M Moniruzzaman PhD), The University of Queensland, Brisbane, QLD, Australia; Neurology Department (D Anderlini MD), Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; Faculty of Medicine (D B Anderson PhD), Faculty of Medicine and Health (J Comachio PhD), Sydney Medical School (S Islam PhD), Save Sight Institute (H Kandel PhD, Y You PhD), and School of Veterinary Science (B B Singh PhD), University of Sydney, Sydney, NSW, Australia; Department of Medicine (S Androudi PhD), University of Thessaly, Volos, Greece; Department of Child Neurology (D Angappan MD), Oregon Health and Science University, Portland, OR, USA; Department of Pharmacology (A Anil MD, J Charan MD, M Shamim MBBS, S Singh MD, S B Varthya MD), Department of Anatomy (Prof N Bhardwaj MD), Department of Community Medicine and Family Medicine (P Bhardwaj MD, Prof P R Raghav MD), School of Public Health (P Bhardwaj MD), Department of Forensic Medicine and Toxicology (T Kanchan MD), Department of Surgical Oncology (Prof S Misra MCh), Department of Pharmacology and Research (A Saravanan MD), and Department of Community Medicine (G Singh MD), All India Institute of Medical Sciences, Jodhpur, India; All India Institute of Medical Sciences, Bhubaneswar, India (A Anil MD); Department of Epidemiology and Biostatistics (Prof A Ansari-Moghaddam PhD), Health Promotion Research Center (M Khammarnia PhD, H Okati-Aliabad PhD, F Shahraki-Sanavi PhD), and Department of Health Promotion (A Nazri-Panjaki MSc), Zahedan University of Medical Sciences, Zahedan, Iran; Department of Pathology (R Anwer PhD), Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia; College of Pharmacy (M Arafat PhD), Al Ain University, Abu Dhabi, United Arab Emirates; College of Art and Science (D Areda PhD), Ottawa University, Surprise, AZ, USA; College of Liberal Arts and Sciences (D Areda PhD), Arizona State University, Tempe, AZ, USA; Department of Paediatrics (Prof H Ariffin MD) and University of Malaya Medical Centre (Prof H Ariffin MD), University of Malaya, Kuala Lumpur, Malaysia; Department of Advanced Nursing Care (H Arifin MSc), Taipei Medical University, Surabaya, Indonesia; Department of Medical Laboratory Sciences (M Arkek MSc) and Department of Psychiatry (M T Walde MSc), Haramaya University, Harar, Ethiopia; Department of Neurobiology, Care Sciences and Society (Prof J Årnlöv PhD, S Fereshtehnejad PhD) and Department of Molecular Medicine and Surgery (Prof J H Kauppila MD), Karolinska Institute, Stockholm, Sweden; School of Health and Social Studies (Prof J Årnlöv PhD), Dalarna University, Falun, Sweden; University College of Medicine and Dentistry (Prof M Arooj PhD), University Institute of Radiological Sciences and Medical Imaging Technology (T Ashraf MS), University Institute of Public Health (A A Baig PhD, S Hameed MPH, A A Malik PhD, S Nargus PhD, S Nargus PhD), Department of Oral Biology (A Fahim PhD), Institute of Molecular Biology and Biotechnology (S Shahid PhD), and Research Centre for Health Sciences (S Shahid PhD), The University of Lahore, Lahore, Pakistan (Prof M Ashraf PhD); Department of Biophysics (A A Artamonov PhD), Russian Academy of Sciences, Moscow, Russia; Department of Epidemiology (K D Artanti MSc, A Hargono DMD) and Faculty of Public Health (S Martini PhD), Universitas Airlangga, Surabaya, Indonesia; Neurology Department (Prof A A Asadi-Pooya MD), Thomas Jefferson University, Philadelphia, PA, USA; External Quality Assessment (T F Asena PhD), Ethiopian Health and Nutrition Research Institute, Addis Ababa, Ethiopia; Department of Statistics (T F Asena PhD), Department of Medical Anatomy (A Bekele MSc), Department of Anatomy (S Demissie MSc), and Department of Nursing (A M Mersha MSc, B B Shashamo MSc), Arba Minch University, Arba Minch, Ethiopia; Cabrini Research (Prof M Asghari-Jafarabadi PhD), Cabrini Health, Malvern, VIC, Australia; Department of Pediatrics and Child Health Nursing (K A Atalell MSc), Department of Clinical Pharmacy (G S Chanie MSc, A K Sendekie MSc), Department of Human Physiology (M Diress MSc), Department of Environmental and Occupational Health (G G Kabito MPH), and Department of Environmental and Occupational Health and Safety (A H Tesfaye MPH), University of Gondar, Gondar, Ethiopia; Department of Immunology (S Athari PhD) and Critical Care and Emergency Nursing (N Hanifi PhD), Zanjan University of Medical Sciences, Zanjan, Iran; School of Nursing and Midwifery (B T Atinifu MSc), Department of Public Health (L Getacher MPH), Department of Biomedical Sciences (Y Solomon MSc), and Department of Pediatrics and Child Health Nursing (S S Yehualashet MSc), Debre Berhan University, Debre Berhan, Ethiopia; Hunter New England Population Health, Wallsend, NSW, Australia (P Atorkey MPhil); Faculty of Nursing (M M W Atout PhD, Prof A M Batiha PhD), Philadelphia University, Amman, Jordan; Department of Forensic Medicine (A Atreya MD), Lumbini Medical College, Palpa, Nepal; Northumbria HealthCare NHS Foundation Trust, Newcastle upon Tyne, UK (A Aujayeb MBBS); The Judith Lumley Centre (B Ayala Quintanilla PhD), Department of Public Health (H Jiang PhD, Prof C Liu PhD), and School of Nursing and Midwifery (M Rahman PhD), La Trobe University, Melbourne, VIC, Australia; San Martin de Porres University, Lima, Peru (B Ayala Quintanilla PhD); Department of Medicine (Z Azizi MD, M Babaei MD) and Blood and Marrow Transplantation and Cellular Therapy Program (A Goyal MD), Stanford University, Palo Alto, CA, USA; Department of Microbiology (K Azizian PhD), School of Medicine (S Khateri MD), Environmental Health Research Center (S Mohammadi PhD), and Department of Epidemiology and Biostatistics (Y Moradi PhD), Kurdistan University of Medical Sciences, Sanandaj, Iran; Department of Neurovascular Research (A Y Azzam MD), Nested Knowledge, Saint Paul, MN, USA; Faculty of Medicine (A Y Azzam MD), October 6 University, 6th of October City, Egypt; Gomal Center of Biochemistry and Biotechnology (M Badar PhD),

Gomal University, Dera Ismail Khan, Pakistan; Department of Forensic Science (A D Badiye PhD), Government Institute of Forensic Science, Nagpur, India; Division of Orthopaedics (S Baghdadi MD), Children's Hospital of Philadelphia, Philadelphia, PA, USA; School of Medicine (S Bagherieh BSc, A Dehghan MD), Department of Pediatrics (M Bemanalizadeh MD, N Javadi MD), Department of Environmental Health Engineering (A Fatehizadeh PhD), Student Research Committee (N Javadi MD, M Rashidi Alavijeh MD), Hypertension Research Center (F Kafi MD), Department of Bariatric Surgery and Cardiovascular Disease (A Pouramini MD), Isfahan Gastroenterology and Hepatology Research Center (M Rashidi Alavijeh MD), and Department of Medical Physics (K Saber PhD), Isfahan University of Medical Sciences, Isfahan, Iran; School of Public Affairs (R Bai MD), Nanjing University of Science and Technology, Nanjing, China; Division of Biological Sciences (S Balakrishnan PhD), Tamil Nadu State Council for Science and Technology, Tamil Nadu, India; Department of Psychology and Neurosciences (S Balalla PhD) and National Institute for Stroke and Applied Neurosciences (A Merkin PhD, Prof V L Feigin PhD), Auckland University of Technology, Auckland, New Zealand; Center of Innovation, Technology and Education (Prof O C Baltatu PhD), Anhembi Morumbi University, Sao Jose dos Campos, Brazil; Department of Hypertension (Prof M Banach PhD), Medical University of Lodz, Lodz, Poland; Polish Mothers' Memorial Hospital Research Institute, Lodz, Poland (Prof M Banach PhD); Nuffield Department of Surgical Sciences (S Bandyopadhyay BA) and Nuffield Department of Primary Care Health Sciences (T Tillawi MD), Oxford University, Oxford, UK; Department of Neurosurgery (S Bandyopadhyay BA), University of Southampton, Southampton, UK; Department of Pharmacology (I Banerjee MD), Sir Seewoosagur Ramgoolam Medical College, Belle Rive, Mauritius; Vocational School of Technical Sciences (M Baran PhD), Batman University, Batman, Türkiye; Department of Neurosciences (Prof M A Barboza MD), Costa Rican Department of Social Security, San Jose, Costa Rica; School of Medicine (Prof M A Barboza MD), University of Costa Rica, San Pedro, Costa Rica; Miami Cancer Institute (M Bardhan MD), Baptist Health South Florida, Miami, FL, USA; School of Psychology (Prof S L Barker-Collo PhD), University of Auckland, Auckland, New Zealand; Department of Public and Environmental Health (A Barrow MPH), University of The Gambia, Brikama, The Gambia; Epidemiology and Disease Control Unit (A Barrow MPH), Ministry of Health, Kotu, The Gambia; Department of Animal Sciences (H A Bashiru MSc), Obafemi Awolowo University, Ile-Ife, Nigeria; Department of Veterinary Physiology and Biochemistry (A Basiru PhD) and Department of Veterinary Public Health and Preventive Medicine (I A Odetokun PhD), University of Ilorin, Ilorin, Nigeria; Faculty of Pharmacy (J D Basso PharmD), Coimbra Chemistry Centre (J D Basso PharmD), and Department of Geography and Demography (M Rodrigues PhD), University of Coimbra, Coimbra, Portugal; School of Public Health (S Basu PhD, A Begde MSc), Department of Primary Care and Public Health (Prof A Majeed MD, R Palladino MD, Prof S Rawaf MD), Department of Surgery and Cancer (Prof E Mossialos PhD), and Division of Brain Sciences (Prof T J Steiner PhD), Imperial College London, London, UK; Department of Medical Education (K Batra PhD) and Department of Social and Behavioral Health (Prof M Sharma PhD), University of Nevada, Las Vegas, Las Vegas, NV, USA; Department of Psychiatry (Prof B T Baune PhD) and Institute for Epidemiology and Social Medicine (A Karch MD), University of Münster, Münster, Germany; Department of Psychiatry (Prof B T Baune PhD), Melbourne Medical School, Melbourne, VIC, Australia; School of Public Health (Prof N Bedi MD), Dr D Y Patil University, Mumbai, India; Epidemiology Department (M Khan MD), Substance Abuse and Toxicology Research Center (S Mohan PhD), and Department of Health Education and Promotion (M Shanawaz MD), Jazan University, Jazan, Saudi Arabia (Prof N Bedi MD); School of Sport, Exercise and Health Sciences (A Begde MSc), Loughborough University, Loughborough, UK; Health System and Population Studies Division (T Begum MPH, K N Koly MSc), International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; Department of Regulatory Affairs (B Behnam MD), NSF International, Ann Arbor, GA, USA; Department of Regulatory Affairs (B Behnam MD), Amarex Clinical Research, Germantown, MD, USA; Department of Epidemiology (S Khanmohammadi MD, S Nejadghaderi MD, H Soleimani MD) and Non-Communicable Diseases Research Center, Tehran, Iran (A Behnouch BS, A Khalaji BS); Division of Pulmonary, Critical Care, and Sleep (M Beiranvand PhD), University of Florida, Jacksonville, FL, USA; Department of Neurology (Prof Y Béjot PhD), University Hospital of Dijon, Dijon, France; Dijon Stroke Registry (Prof Y Béjot PhD), University of Burgundy, Dijon, France; Department of Medical Laboratory Science (M A Belete MSc), Department of Environmental Health (M Gebrehiwot DSc), and Department of Public Health Nutrition (B Wagaye MPH), Wollo University, Dessie, Ethiopia; Department of Oral Pathology and Microbiology (U I Belgaumi MD), Krishna Vishwa Vidyapeeth deemed to be University, Karad, India; Debakay Heart and Vascular Center (B Benfor MD), Houston Methodist Academic Institute, Houston, FL, USA; Department of Cardiovascular Surgery (B Benfor MD), Houston Methodist Hospital, Houston, TX, USA; Nuffield Department of Population Health (D A Bennett PhD), Nuffield Department of Medicine (Prof R J Maude PhD), Department of Psychiatry (Prof C R J Newton MD), and Health Economics Research Centre (Prof J A B Rodriguez PhD), University of Oxford, Oxford, UK; Department of Internal Medicine (I M Bensenor PhD, A C Goulart PhD), Center for Clinical and Epidemiological Research (A C Goulart PhD), and Department of Psychiatry (Prof M F P Peres MD, Y Wang PhD), University of São Paulo, São Paulo, Brazil; Faculty of Medicine (P J G Bettencourt PhD), Catholic University of Portugal, Rio de Mouro, Portugal; School of Pharmacy (K A Beyene PhD), University of Auckland, Auckland, New Zealand; Department of Pharmaceutical and Administrative Sciences (K A Beyene PhD), University of Health Sciences and Pharmacy in St Louis, St Louis, MO, USA; Department of Pharmacology (A Bhadra MPH), Popular Medical College, Dhaka, Bangladesh; Department of Forensic Chemistry (D S Bhagat PhD), Government Institute of Forensic Science, Aurangabad, Aurangabad, India; Department of Internal Medicine (A Bhargava MD), Wayne State University, Detroit, MI, USA; Global Health Neurology Lab (S Bhaskar PhD), NSW Brain Clot Bank, Sydney, NSW, Australia; Department of Neurology and Neurophysiology (S Bhaskar PhD), South West Sydney Local Health District and Liverpool Hospital, Sydney, NSW, Australia; Department of General Medicine (A N Bhat MD), Department of Internal Medicine (A Bloor MD), Forensic Medicine and Toxicology Department (H L Dsouza MD), Department of Community Medicine (N Joseph MD, N Kumar MD, P Mithra MD, R Thapar MD), Department of Medicine (S Raj Moolambally MD), Department of Forensic Medicine (P H Shetty MD), and Kasturba Medical College (Prof B Unnikrishnan MD), Manipal Academy of Higher Education, Mangalore, India; Department of Internal Medicine (V Bhat MBBS), St John's National Academy of Health Sciences, Bangalore, India; Medical Lab Technology (G K Bhatti PhD), Chandigarh University, Mohali, India; Human Genetics and Molecular Medicine (Prof J S Bhatti PhD) and Department of Zoology (B Vellingiri PhD), Central University of Punjab, Bathinda, India; Department of Pharmaceutical Sciences (R Bhatti PhD), Guru Nanak Dev University, Amritsar, India; Social Determinants of Health Research Center (A Bijani PhD), Cellular and Molecular Biology Research Center (Prof S Mahjoub PhD), Department of Clinical Biochemistry (Prof S Mahjoub PhD), and Department of Biochemistry (A Mospour PhD), Babol University of Medical Sciences, Babol, Iran; Scientific-Tools, Bergamo, Italy (B Bikbov MD); Department of Neurology (Prof A Biswas DM), Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital, Kolkata, India; Faculty of Health Sciences (V R Bitra PhD), University of Botswana, Gaborone, Botswana; Department of Global Public Health and Primary Care (Prof T Bjørge PhD, O Dadras DrPH), Center for International Health (S Hassan MPhil), Bergen Center for Ethics and Priority Setting (S Hassan MPhil), and Department of Psychosocial Science (D Sagoe PhD), University of Bergen, Bergen, Norway; Cancer Registry of Norway, Oslo, Norway (Prof T Bjørge PhD); School of Business Administration (Prof V Bodolica PhD), American University of Sharjah, Sharjah, United Arab Emirates; Department of Epidemiology (D Braithwaite PhD), UF Health Cancer Center (S D Karanth PhD), and Computer and Information Science and Engineering (P Naghavi MSc), University of Florida, Gainesville, FL, USA; Cancer Population Sciences

Program (D Braithwaite PhD), University of Florida Health Cancer Center, Gainesville, FL, USA; Department of Public Health and Primary Care (Prof C Brayne MD), University of Cambridge, Cambridge, UK; Division of Clinical Epidemiology and Aging Research (Prof H Brenner MD), German Cancer Research Center, Heidelberg, Germany; Department of IT Technologies in Biomedical Engineering for Research (A Briko PhD) and Department of Medical and Technical Information Technology (A Hammoud MSc), Bauman Moscow State Technical University, Moscow, Russia; Joint China-Cuba Lab for Neurotechnology (Prof M L Bringas Vega PhD), University of Electronic Sciences and Technology of China UESTC, Chengdu, China; Neuroinformatics Department (Prof M L Bringas Vega PhD), Cuban Neuroscience Center, Havana, Cuba; Department of Injury (J Brown PhD) and Injury Division (H Möller PhD), The George Institute for Global Health, Newtown, NSW, Australia; Faculty of Medicine (J Brown PhD), School of Population Health (H Möller PhD), University of New South Wales, Kensington, NSW, Australia; Department of Veterinary Integrative Biosciences (C M Budke PhD) and Department of Health Promotion and Community Health Sciences (M Hossain MPH), Texas A&M University, College Station, TX, USA; Department of Woman and Child Health and Public Health (D Buonsenso MD), Fondazione Policlinico Universitario A Gemelli IRCCS, Roma, Italy; Global Health Research Institute (D Buonsenso MD), Università Cattolica del Sacro Cuore, Roma, Italy; Research School of Population Health (R A Burns PhD), Australian National University, Canberra, ACT, Australia; Department of Biopharmaceutics and Clinical Pharmacy (Y Bustanji PhD), The University of Jordan, Amman, Jordan; Department of Basic Biomedical Sciences, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates (Y Bustanji PhD); Faculty of Pharmacy (M Butt MS), University of Central Punjab, Lahore, Pakistan; Department of Family and Community Medicine (N S Butt PhD), Pediatric Dentistry Department (Prof O A A Elmeligy PhD), Rabigh Faculty of Medicine (A A Malik PhD), Department of Dental Public Health (Z S Natto DrPH), and Department of Community Medicine (S Samargandy PhD), King Abdulaziz University, Jeddah, Saudi Arabia; School of Public Health and Health Systems (Z A Butt PhD), University of Waterloo, Waterloo, ON, Canada; Al Shifa School of Public Health (Z A Butt PhD), Al Shifa Trust Eye Hospital, Rawalpindi, Pakistan; Department of Neurology (L S Cabral MD), Porto Alegre Clinical Hospital, Porto Alegre, Brazil; Department of Interventional Neuroradiology (L S Cabral MD), Hospital Moinhos de Vento, Porto Alegre, Brazil; Department of Clinical Pharmacy (Prof D Calina PhD), University of Medicine and Pharmacy of Craiova, Craiova, Romania; Health and Nutrition Research Center (I R Campos-Nonato PhD), Health Systems Research Center (D V Ortega-Altamirano DrPH), National Institute of Public Health, Cuernavaca, Mexico; Dana-Farber Cancer Institute, Boston, MA, USA (C Cao MPH); Department of Pathology and Microbiology (Prof H Carabin PhD), University of Montreal, St-Hyacinthe, QB, Canada; Department of Health Care (Prof R Cárdenas DSc), Metropolitan Autonomous University, Mexico City, Mexico; Institute for Cancer Research, Prevention and Clinical Network, Florence, Italy (G Carreras PhD); Institute for Mental and Physical Health and Clinical Translation Strategic Research Center (A F Carvalho MD), School of Medicine (V Gupta PhD), Deakin University, Geelong, VIC, Australia; Colombian National Health Observatory (C A Castañeda-Orjuela MD) and Department of Public Health Research (J N Malagón-Rojas MSc), National Institute of Health, Bogota, Colombia; Epidemiology and Public Health Evaluation Group (C A Castañeda-Orjuela MD) and Department of Public Health (Prof F P De la Hoz PhD), National University of Colombia, Bogota, Colombia; Department of Infectious Diseases (A Casulli PhD) and Department of Cardiovascular, Endocrine-metabolic Diseases and Aging (B Unim PhD), National Institute of Health, Rome, Italy; National School of Public Health (F Catalá-López PhD), Institute of Health Carlos III, Madrid, Spain; Clinical Epidemiology Program (F Catalá-López PhD), Ottawa Hospital Research Institute, Ottawa, ON, Canada; Department of Pharmacological and Biomolecular Sciences (Prof A L Catapano PhD) and Department of Clinical Sciences and Community Health (Prof C La Vecchia MD), University of Milan, Milan, Italy; MultiMedica (Prof A L Catapano PhD), IRCCS, Sesto S Giovanni, Italy; Department of Psychiatry (A Caye PhD), Federal University of Rio Grande do Sul, Porto Alegre, Brazil; Department of Medical, Surgical and Health Sciences (L Cegolon PhD), University of Trieste, Trieste, Italy; Public Health Unit (L Cegolon PhD), University Health Agency Giuliano-Isontina, Trieste, Italy; College of Public Health, Medical and Veterinary Sciences (M Cenderadewi MPHTM) and Department of Public Health and Tropical Medicine (T I Emeto PhD), James Cook University, Townsville, QLD, Australia; Public Health Department (M Cenderadewi MPHTM), University of Mataram, Mataram, Indonesia; Mary MacKillop Institute for Health Research (Prof E Cerin PhD), Faculty of Health Sciences (G R Poudel PhD), Australian Catholic University, Melbourne, VIC, Australia; School of Public Health (Prof E Cerin PhD), University of Hong Kong, Hong Kong Special Administrative Region, China; Emerging Diseases and Climate Change Research Unit (P R U Chacón-Uscamaita DDS), Cayetano Heredia University, Lima, Peru; Heart Failure and Structural Heart Disease Unit (J Chan MBChB), Cardiovascular Analytics Group, Hong Kong Special Administrative Region, China; Temerty Faculty of Medicine (V Chattu MD) and Institute of Medical Science (U Saeed MSc), University of Toronto, Toronto, ON, Canada; Saveetha Dental College, SIMATS (V Chattu MD) and Centre of Molecular Medicine and Diagnostics (Prof S Patil PhD), Saveetha University, Chennai, India; Department of Medical Biochemistry (E Chekol Abebe MSc), Debre Tabor University, Debre Tabor, Ethiopia; School of Public Health (H Chen Beng), Zhejiang University, Hangzhou, China; Department of State Key Laboratory of Ophthalmology (J Chen BS), Sun Yat-sen University, Guangzhou, China; Department of Pharmacology (Prof S Chidambaram PhD) and Centre for Experimental Pharmacology and Toxicology (Prof S Chidambaram PhD), JSS Academy of Higher Education and Research, Mysuru, India; Westmead Clinical School (R Chimoriya PhD) and School of Pharmacy and Charles Perkins Centre (Z Dai PhD), University of Sydney, Sydney, NSW, Australia; Division of Infectious Diseases (P R Ching MD), Virginia Commonwealth University, Richmond, VA, USA; Iraq Field Epidemiology Training Program (A Chitheer MD), Ministry of Health, Baghdad, Iraq; The Nethersole School of Nursing (Y Chong PhD) and Jockey Club School of Public Health and Primary Care (J Huang MD), The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China; Chitkara College of Pharmacy (H Chopra PhD), Chitkara University, Punjab, India; Department of Community Medicine (Prof S G Choudhari MD, Prof A M Gaidhane MD), Datta Meghe Institute of Medical Sciences, Wardha, India; School of Public Health (E K Chowdhury PhD), Curtin University, Perth, WA, Australia; Florida International University (Prof R Chowdhury PhD), Florida International University, Miami, FL, USA; Department of Epidemiology (Prof R Chowdhury PhD) and Department of Emergency Medicine (I Pantazopoulos PhD), University of Bern, Bern, Switzerland; Bispebjerg Hospital (Prof H Christensen DMSc) and Rigshospitalet (T C Truelsen PhD), University of Copenhagen, Copenhagen, Denmark; Center for Biomedicine and Community Health (D Chu PhD), VNU-International School, Hanoi, Viet Nam; Department of Paediatric Surgery (I S Chukwu BmedSc), Federal Medical Centre, Umuahia, Nigeria; Department of AndroUrology (Prof E Chung MD), AndroUrology Centre, Brisbane, QLD, Australia; Nova Medical School (J Conde PhD), Nova University of Lisbon, Lisbon, Portugal; School of Medicine and Surgery (P A Cortesi PhD), University of Milan Bicocca, Monza, Italy; Research Unit on Applied Molecular Biosciences (V M Costa PhD, Prof D Dias da Silva PhD, J P Silva PhD), Department of Chemical Sciences (R A S Couto MD), Institute for Research and Innovation in Health (Prof N Cruz-Martins PhD), Laboratory for Process Engineering, Environment, Biotechnology and Energy (J Loureiro PhD), Department of Clinical Neurosciences and Mental Health (J Massano MD), and Associated Laboratory for Green Chemistry (Prof D M Pereira PhD), University of Porto, Porto, Portugal; Department of Family Medicine and Public Health (Prof M H Criqui MD), University of California San Diego, La Jolla, CA, USA; Therapeutic and Diagnostic Technologies (Prof N Cruz-Martins PhD), Cooperativa de Ensino Superior Politécnico e Universitário, Gandra, Portugal; Department of Internal Medicine (S Dadana MD), Cheyenne Regional Medical Center, Cheyenne, WY, USA; Department of Addiction Medicine (O Dadras DrPH), Haukland

University Hospital, Bergen, Norway; Walden University, Minneapolis, MN, USA (H A Danawi PhD); Public Health Foundation of India, Gurugram, India (Prof L Dandona MD, Prof R Dandona PhD, G Kumar PhD, D K Lal MD, A Pandey PhD); Department of Health Research (T Khanna PhD), Indian Council of Medical Research, New Delhi, India (Prof L Dandona MD); Department of Pediatrics (A H Darwish MD), Tanta University, Tanta, Egypt; Department of Biochemistry (S Das MD), Ministry of Health and Welfare, New Delhi, India; Ingram School of Engineering (S Das PhD), Texas State University, San Marcos, TX, USA; Ophthalmology Department (A Dascalu PhD), Fourth Department of General Surgery (D Serban PhD), Emergency University Hospital Bucharest, Bucuresti, Romania; Department of Legal Medicine, Psychiatry and Pathology (A de la Torre-Luque PhD), Universidad Complutense de Madrid, Madrid, Spain; Australian Institute for Suicide Research and Prevention (Prof D De Leo DSc), Griffith University, Mount Gravatt, QLD, Australia; Department of Mathematics (F E Dean BA), University of California Berkeley, Berkeley, CA, USA; Department of Epidemiology and Community Medicine (A Dehghan PhD), Fasa University of Medical Sciences, Fasa, Iran; Public Health Department (H Dejene MPH), Salale University, Fitcha, Ethiopia; School of Public Health and Social Work (D Demant PhD), Queensland University of Technology, Brisbane, QLD, Australia; Department of Neurosurgery (A K Demetriades MD), National Health Service Scotland, Edinburgh, UK; Epidemiology Branch (X Deng PhD), National Institute of Health, Durham, NC, USA; Graduate Medical Education (H D Desai MD), Gujarat Adani Institute of Medical Sciences, Bhuj, India; Department of Community Medicine (V G C Devanbu MD), Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Chennai, India; Division of Pathology (K Dhama PhD), ICAR-Indian Veterinary Research Institute, Bareilly, India; Department of Community Medicine (Prof S D Dharmaratne MD), University of Peradeniya, Peradeniya, Sri Lanka; Health Research Section (M Dhimol PhD) and Research Department (S Ghimire MPH, B P Marasini PhD, A Pandey MPH), Nepal Health Research Council, Kathmandu, Nepal; Toxicology Research Unit (Prof D Dias da Silva PhD), Cooperativa de Ensino Superior Politécnico e Universitário, Gandra, Portugal; Center of Complexity Sciences (Prof D Diaz PhD), National Autonomous University of Mexico, Mexico City, Mexico; Faculty of Veterinary Medicine and Zootechnics (Prof D Diaz PhD), Autonomous University of Sinaloa, Culiacán Rosales, Mexico; Research Unit (M Dibas MD), Sulaiman Al Rajhi University, Qassim, Saudi Arabia; Department of Epidemiology (D D Ding BS), University of Florida, Gainesville, FL, USA; Department of Experimental and Clinical Medicine (M Dinu PhD), University of Florence, Florence, Italy; Department of Medicine (T C Do MD) and School of Medicine (H Pham MD), Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Viet Nam; Department of Medicine (T H Do MD), Can Tho University of Medicine and Pharmacy, Can Tho, Viet Nam; Department of Pathology (K K Doan MD), Temple University Hospital, Philadelphia, PA, USA; Neurology Department (M Doheim MD), Biomedical Informatics and Medical Statistics Department (I El Sayed PhD), Pediatric Dentistry and Dental Public Health Department (Prof O A A Elmeligy PhD), and Tropical Health Department (R M Ghazy PhD), Alexandria University, Alexandria, Egypt; Department of Social Medicine and Health Care Organisation (K G Dokova PhD), Medical University "Prof Dr Paraskev Stoyanov", Varna, Bulgaria; Health Science Center (D Dongarwar MS), University of Texas, Houston, TX, USA; Forensic Medicine and Toxicology Department (H L Dsouza MD), Kasturba Medical College Mangalore, Mangalore, India; Office of Institutional Analysis (J Dube MA), University of Windsor, Windsor, ON, Canada; Department of Biotechnology (S Duraisamy PhD), SRM Institute of Science and Technology, Chennai, India; Department of Infection and Tropical Medicine (O C Durojaiye MPH), School of Health and Related Research (J O Oguta MSc), and Psychology Department (A Yadollahpour PhD), University of Sheffield, Sheffield, UK; Department of Oral Biology and Biomedical Sciences (S Dutta PhD), Faculty of Medicine, Bioscience and Nursing (P Sengupta PhD), MAHSA University, Jenjarom, Malaysia; Department of Medical Sciences (S Dutta PhD), Bharath Institute of Higher Education and Research, Chennai, India; Department of Conservative Dentistry with Endodontics (A M Dzedzic DSc), Medical

University of Silesia, Katowice, Poland; School of Health Sciences (H A Edinur PhD), Universiti Sains Malaysia, Kubang Kerian, Malaysia; Department of Biological Sciences (T C Ekundayo PhD) and Department of Biosciences and Biotechnology (A J Udoakang PhD), University of Medical Sciences, Ondo, Ondo, Nigeria; Neurology Department (Prof N El Nahas MD), Department of Entomology (A M Samy PhD), and Medical Ain Shams Research Institute (A M Samy PhD), Ain Shams University, Cairo, Egypt; Department of Pathology and Laboratory Medicine (M Elahi Najafi MD) and School of Medicine (Prof S Xu PhD), University of Rochester, Rochester, NY, USA; School of Population and Global Health (Prof F J Elgar PhD), McGill University, Montreal, QC, Canada; Division of Cardiology (I Y Elgendy MD, D H Nguyen BS) and Department of Radiology (A Haj-Mirzaian MD), Massachusetts General Hospital, Boston, MA, USA; Faculty of Medicine (M Elhadi MD), University of Tripoli, Tripoli, Libya; Department of Public Health (L T Elilo MPH, M T Sergindo MSc), Wachemo University, Hossana, Ethiopia; Egypt Center for Research and Regenerative Medicine, Cairo, Egypt (M A Elmonem PhD); Clinical Pathology Department (M Elshaer MD), Hygiene and Zoonoses Department (H Ramadan PhD), and Faculty of Pharmacy (M A Saleh PhD), Mansoura University, Mansoura, Egypt; Department of Infectious Diseases and Public Health (I Elshohaby PhD) and Department of Biomedical Sciences (A Waris MS), City University of Hong Kong, Hong Kong Special Administrative Region, China; Department of Animal Medicine (I Elshohaby PhD), Cardiovascular Department (Prof A M A Saad MD), and Department of Microbiology and Immunology (G Yahya PhD), Zagazig University, Zagazig, Egypt; Department of Ophthalmology (M Emamverdi MD), University of California Los Angeles, Los Angeles, CA, USA; Department of Neurology (Prof M Endres MD, S Samadzadeh MD), Institute of Public Health (F Fischer PhD), and Department of Surgery (N Haep MD), Charité-Universitätsmedizin Berlin, Berlin, Germany; Department of Paediatrics (C I Esezobor MB), Department of Medical Physiology (P G Okwute MSc), and Department of Psychiatry (A T Olagunju MD), University of Lagos, Lagos, Nigeria; Department of Paediatrics (C I Esezobor MB), Lagos University Teaching Hospital, Lagos, Nigeria; Environmental Health Engineering (Prof A Fadaei PhD), Community-Oriented Nursing Midwifery Research Center (M Heidari PhD), and Department of Health in Disasters and Emergencies (R Sheikh BHLthSci), Shahrekord University of Medical Sciences, Shahrekord, Iran; Research Centre for Healthcare and Community (A F Fagbamigbe PhD), Coventry University, Coventry, UK; Department of Neurological Surgery (J Fares MD), Northwestern University, Chicago, IL, USA; Department of Psychology (Prof A Faro PhD), Federal University of Sergipe, São Cristóvão, Brazil; Department of Parasite Vaccine Research and Production (S Fathi PhD), Razi Vaccine and Serum Research Institute, Karaj, Iran; Department of Community Medicine and Global Health (S A F Fatima MPhil) and Institute of Health and Society (Prof A S Winkler PhD), University of Oslo, Oslo, Norway; Department of Bacteriology (S A F Fatima MPhil), Norwegian Institute of Public Health, Oslo, Norway; Department of Social Medicine and Epidemiology (A Feizkhal MD), Gastrointestinal and Liver Diseases Research Center (S Hassanipour PhD), and Caspian Digestive Disease Research Center (S Hassanipour PhD), Guilan University of Medical Sciences, Rasht, Iran; Division of Neurology (S Fereshtehnejad PhD) and Department of Civil Engineering (O Thakali PhD), University of Ottawa, Ottawa, ON, Canada; Department of Social Sciences (Prof N Ferreira PhD), University of Nicosia, Nicosia, Cyprus; Department of Nursing (G Fetensa MSc) and Department of Public Health (E G Tesfaye MSc), Wollega University, Nekemte, Ethiopia; Department of Neurology (Prof A Fonseca PhD), University of Lisbon, Lisbon, Portugal; Department of Neurology (Prof A Fonseca PhD), Hospital de Santa Maria, Lisbon, Portugal; UO Neurologia, Salute Pubblica e Disabilità (A Fornari PhD, M Leonardi MD, A Raggi PhD), Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Department of Pharmacology (Prof B Foroutan PhD), Department of Clinical Microbiology (S Yaghoubi PhD), Iranshahr University of Medical Sciences, Iranshahr, Iran; Department of Dermatology (T Fukumoto PhD), Kobe University, Kobe, Japan; Department of Community Medicine (Prof M A Gadanya FMCPh), Aminu Kano Teaching Hospital, Kano, Nigeria; Food Technology Department

(Y Galali ResM), Salahaddin University-Erbil, Erbil, Iraq; Department of Nutrition and Dietetics (Y Galali ResM), Cihan University-Erbil, Erbil, Iraq; Faculty of Paramedical (N Galehdar PhD), Lorestan University of Medical Sciences, Khorramabad, Iran; Nutrition and Metabolism Branch (Q Gan MPH), International Agency for Research on Cancer, Lyon, France; Department of Community Medicine (A P Gandhi MD), ESIC Medical College and Hospital, Hyderabad, India; Institute of Health and Wellbeing (B Ganesan PhD), Federation University, Churchill, VIC, Australia; University School of Management and Entrepreneurship (N Garg PhD, R Sharma PhD), Delhi Technological University, Delhi, India; School of Medicine (S-Y Gau MD), Chung Shan Medical University, Taichung, Taiwan; Department of Pharmacology (Prof R K Gautam PhD), Indore Institute of Pharmacy, Indore, India; International Trachoma Initiative (T Gebre PhD), Task Force for Global Health, Decatur, GA, USA; Department of Nursing (G G Gebremeskel MSc), Mekelle University, Mekelle, Ethiopia; School of Public Health (H G Gebreslassie MPH) and Department of Medical Laboratory Sciences (H Negash MSc), Adigrat University, Adigrat, Ethiopia; Department of Environmental Health Engineering (R Ghanbari PhD), Qazvin University of Medical Sciences, Qazvin, Iran; Department of Epidemiology and Biostatistics (A Gholami PhD, F Khorashadizadeh PhD) and Non-Communicable Diseases Research Center (A Gholami PhD), Neyshabur University of Medical Sciences, Neyshabur, Iran; Department of Epidemiology and Prevention (A Gialluisi PhD), IRCCS Neuromed, Pozzilli, Italy; Warwick Medical School (Prof P S Gill DM), University of Warwick, Coventry, UK; National Human Genome Research Institute (L M Glasstetter BS), National Institute on Deafness and Other Communication Disorders (H J Hoffman MA), and National Institute of Neurological Disorders and Stroke (W J Koroshetz MD), National Institute of Health, Bethesda, MD, USA; Third Department of Neurology (E V Gnedovskaya PhD), Research Center of Neurology, Moscow, Russia (M A Kravchenko PhD, Prof M A Piradov DSc, Prof V L Feigin PhD); Clinical Biochemistry and Applied Cell Sciences (A Golchin PhD) and Cellular and Molecular Medicine Institute (A Golchin PhD), Urmia University of Medical Sciences, Urmia, Iran (R Valizadeh PhD); Health Systems and Policy Research Department (M Golechha PhD), Indian Institute of Public Health, Gandhinagar, India; Department of Genetics (P Goleij MSc), Sana Institute of Higher Education, Sari, Iran; Universal Scientific Education and Research Network (P Goleij MSc), Sleep Disorders Research Center (H Mohammadi PhD), and Department of Infectious Disease (Prof S Vaziri MD), Kermanshah University of Medical Sciences, Kermanshah, Iran; Department of Biomedical and Neuromotor Sciences (D Golinelli MD, S Guicciardi MD, L Muccioli MD, F Sanmarchi MD), University of Bologna, Bologna, Italy; Department of Physiotherapy (Prof M Gomes-Neto PhD), Federal University of Bahia, Salvador, Brazil; School of Nursing and Midwifery (Prof R J Gray PhD), La Trobe University, Bundoora, VIC, Australia; Department of Public Health and Preventive Medicine (Prof M Grivna PhD), Charles University, Prague, Czech Republic; Department of Health Informatics (H A Guadie MPH), Department of Psychiatry (M Tareke MSc), and Department of Nursing (W A Temesgen PhD), Bahir Dar University, Bahir Dar, Ethiopia; Cheeloo College of Medicine (B Guan MB) and Department of Orthopaedics (H Zhou MD), Shandong University, Jinan, China; Post Graduate School of Public Health (G Guarducci MD), University of Siena, Siena, Italy; Health Directorate (S Guicciardi MD), Local Health Authority of Bologna, Bologna, Italy; Department of Community Medicine (D A Gunawardane MD), University of Peradeniya, Kandy, Sri Lanka; Department of Public Health (B Gupta PhD), Torrens University Australia, Melbourne, VIC, Australia; Department of Preventive Cardiology (Prof R Gupta MD), Eternal Heart Care Centre and Research Institute, Jaipur, India; Department of Medicine (Prof R Gupta MD), Mahatma Gandhi University Medical Sciences, Jaipur, India; Toxicology Department (S Gupta MSc), Shriram Institute for Industrial Research, Delhi, India; Faculty of Medicine Health and Human Sciences (Prof V K Gupta PhD) and Macquarie Medical School (M Mirzaei PhD, Y You PhD), Macquarie University, Sydney, NSW, Australia; Department of Epidemiology and Psychosocial Research (R A Gutiérrez PhD), Ramón de la Fuente Muñiz National Institute of Psychiatry, Mexico City, Mexico; Global Virus Network, Middle East Region (F Habibzadeh MD), Shiraz, Iran; Clinical Neurological Sciences (V Hachinski DSc), The University of Western Ontario, London, ON, Canada; Lawson Health Research Institute, London, ON, Canada (V Hachinski DSc); Department of Pharmacology and Toxicology (R Haddadi PhD), Hamadan University of Medical Sciences, Hamadan, Iran; Department of Clinical Pharmacology and Medicine (Prof N R Hadi PhD), University of Kufa, Najaf, Iraq; Clinician Scientist Program (N Haep MD), Berlin Institute of Health, Berlin, Germany; NYU Shanghai, Shanghai, China (B J Hall PhD); Faculty of Health (M Hamiduzzaman PhD), Southern Cross University, Bilinga, QLD, Australia; Centre for Neuromuscular and Neurological Disorders (Prof G J Hankey MD) and Dobney Hypertension Centre (Prof M P Schlaich MD), University of Western Australia, Perth, WA, Australia; Perron Institute for Neurological and Translational Science, Perth, WA, Australia (Prof G J Hankey MD); Department of Biochemistry and Molecular Biology (Prof M Hannan PhD), Bangladesh Agricultural University, Mymensingh, Bangladesh; Department of Anatomy (Prof M Hannan PhD), Dongguk University, Gyeongju, South Korea; Department of Neurology, Xuanwu Hospital (Prof J Hao PhD, C Zhang MD), National Center for Neurological Disorders (Prof J Hao PhD), and National Center for Neurological Diseases, Xuanwu Hospital (C Zhang MD), Capital Medical University, Beijing, China; Medical Research Unit (H Harapan PhD), Universitas Syiah Kuala (Syiah Kuala University), Banda Aceh, Indonesia; School of Public Health (H Hareru MSc, T L Lerango MPH), Dilla University, Dilla, Ethiopia; Faculty of Medicine (N I Harlianto BSc), Julius Centre for Health Sciences and Primary Care (G A Kayode PhD), and Institute for Risk Assessment Sciences (E Traini MSc), Utrecht University, Utrecht, Netherlands; Department of Radiology (N I Harlianto BSc), University Medical Center Utrecht, Utrecht, Netherlands; Research Unit (J M Haro MD), University of Barcelona, Barcelona, Spain; Biomedical Research Networking Center for Mental Health Network, Barcelona, Spain (J M Haro MD); University of Tulsa College of Law (N N Hartman BS), University of Tulsa, Tulsa, OK, USA; Department of Economics and Statistics (N N Hartman BS), Department of Anesthesiology (V Krishnamoorthy MD), Center for the Study of Aging and Human Development (Y Yao MD), and Duke Global Health Institute (S Zadey MS), Duke University, Durham, NC, USA; Department of Zoology and Entomology (A I Hasaballah PhD), Al Azhar University, Cairo, Egypt; Department of Nursing (F Hasan MSc), Nursing School (M Kurniasari PhD), Department of Global Health and Health Security (K Latief MSCE), International PhD Program in Medicine (L Minh MD), Research Center for Artificial Intelligence in Medicine (L Minh MD), and School of Public Health (Y L Samodra MPH, Y L Samodra MPH), Taipei Medical University, Taipei, Taiwan; Department of Ophthalmology (H Hasani MD), Iran University of Medical Sciences, Karaj, Iran; Department of Radiology (M Hasanian MD), Arak University of Medical Sciences, Arak, Iran; Tabriz, Iran (H Hassankhani PhD); National Data Management Center for Health (M Hassen BSc), National Data Management Center for Health (A Misganaw PhD), and Water, Sanitation and Hygiene Unit (B Wagaye MPH), Ethiopian Public Health Institute, Addis Ababa, Ethiopia; Department of Diagnostic and Interventional Radiology and Neuroradiology (J Haubold MD) and Institute of Artificial Intelligence in Medicine (J Haubold MD), University Hospital Essen, Essen, Germany; Institute of Pharmaceutical Sciences (K Hayat MS), University of Veterinary and Animal Sciences, Lahore, Pakistan; Department of Pharmacy Administration and Clinical Pharmacy (K Hayat MS), Xian Jiaotong University, Xian, China; Santa Clara, CA, USA (G Heidari MD); Department of Microbiology (K Hezam PhD), Taiz University, Taiz, Yemen; School of Medicine (K Hezam PhD), Nankai University, Tianjin, China; Division for Health Service Promotion (Y Hiraike PhD), University of Tokyo, Tokyo, Japan; Division of Scientific Programs (H J Hoffman MA) and National Human Genome Research Institute (N Horita PhD), National Institutes of Health, Bethesda, MD, USA; Kasturba Medical College, Mangalore (R Holla MD, A Kamath MD), Manipal Institute of Management (S Kamath MHA), Department of Pharmacy Management (V S Ligade PhD), Department of Microbiology (P Y Prakash PhD), Manipal TATA Medical College (M Rahman PhD), and Department of Nephrology (I Rao DM), Manipal Academy of Higher Education, Manipal, India; Virginia Beach, VA, USA (K P Hopf MPH); Department of Pulmonology (N Horita PhD),

Yokohama City University, Yokohama, Japan; Social and Environmental Health Research (M Hossain MPH), Nature Study Society of Bangladesh, Khulna, Bangladesh; School of Population and Public Health (M Hossain MSc) and School of Nursing (A Pashaei MSc), University of British Columbia, Vancouver, BC, Canada; James P Grant School of Public Health (M Hossain MSc), BRAC University, Dhaka, Bangladesh; Department of Behavioural Science and Health (S Hossain MS), Department of Epidemiology and Public Health (Prof M Kivimäki PhD), Division of Psychology and Language Sciences (M Kumar PhD), Research Department of Epidemiology and Public Health (M A Ruiz PhD), and Department of Population Health Sciences (D Sunkersing PhD), University College London, London, UK; Department of Public Health and Informatics (S Hossain MS), Jahangirnagar University, Dhaka, Bangladesh; School of Health and Society (H Hosseinzadeh PhD), University of Wollongong, Wollongong, NSW, Australia; Institute of Research and Development (Prof M Hosseinzadeh PhD), Faculty of Medicine (H T H Nguyen MD) and Institute for Research and Training in Medicine, Biology and Pharmacy (H T H Nguyen MD), Duy Tan University, Da Nang, Viet Nam; Department of Computer Science (Prof M Hosseinzadeh PhD) and Diplomacy and Public Relations Department (A Omar Bali PhD), University of Human Development, Sulaymaniyah, Iraq; Clinical Legal Medicine Department (S Hostiuic PhD), National Institute of Legal Medicine Mina Minovici, Bucharest, Romania; Department of Psychology (C Hu PhD), Tsinghua University, Beijing, China; Research Division (M Huda PhD), ARCED Foundation, Dhaka, Bangladesh; Department of Biological Sciences and Chemistry (Prof J Hussain PhD) and Natural and Medical Sciences Research Center (M Waqas PhD), University of Nizwa, Nizwa, Oman; Department of Biomolecular Sciences (N R Hussein PhD), University of Zakho, Zakho, Iraq; School of Biotechnology (H Huynh BS) and School of Medicine (L T Vu MD), Tan Tao University, Long An, Viet Nam; Department of Occupational Safety and Health (Prof B Hwang PhD), China Medical University, Taichung, Taiwan; Department of Occupational Therapy (Prof B Hwang PhD), Asia University, Taichung, Taiwan; Faculty of Medicine (I M Ilic PhD, Prof M M Santric-Milicevic PhD), School of Public Health and Health Management (Prof M M Santric-Milicevic PhD), and Faculty of Medicine Institute of Epidemiology (I S Vujcic PhD), University of Belgrade, Belgrade, Serbia; Department of Epidemiology (Prof M D Ilic PhD), University of Kragujevac, Kragujevac, Serbia; Institute for Physical Activity and Nutrition (S Islam PhD), Deakin University, Burwood, VIC, Australia; Clinical Laboratory (F Ismail PhD), Tobruk University, Tobruk, Libya; Blood Transmitted Diseases (F Ismail PhD), National Center for Disease Control, Tobruk, Libya; Public Health Department of Social Medicine (Prof H Iso MD) and Graduate School of Medicine (Prof K Yamagishi MD), Osaka University, Suita, Japan; Department of Health Services Research (M Iwagami PhD) and Research and Development Center for Health Services (Prof K Yamagishi MD), University of Tsukuba, Tsukuba, Japan; Department of Non-Communicable Disease Epidemiology (M Iwagami PhD) and Centre for Global Mental Health (K N Koly MSc), London School of Hygiene & Tropical Medicine, London, UK; School of Health Systems and Public Health (C C D Iwu MPH), University of Pretoria, Pretoria, South Africa; Department of Biotechnology (M Iyer PhD), Karpagam Academy of Higher Education (Deemed to be University), Coimbatore, India; Department of Internal Medicine (A Jaan MD), Rochester General Hospital, Rochester, NY, USA; Research and Development Unit (L Jacob MD), Biomedical Research Networking Center for Mental Health Network, Sant Boi de Llobregat, Spain; Faculty of Medicine (L Jacob MD), University of Versailles Saint-Quentin-en-Yvelines, Montigny-Le Bretonneux, France; Department of Immunology (Prof A Jafarzadeh PhD), Department of Epidemiology and Biostatistics (Prof M Rezaei PhD), Department of Neurology (A Vakilian MD), and Non-communicable Diseases Research Center (A Vakilian MD), Rafsanjan University of Medical Sciences, Rafsanjan, Iran; College of Medicine and Medical Sciences (H Jahrami PhD), Arabian Gulf University, Manama, Bahrain; Ministry of Health (H Jahrami PhD), Manama, Bahrain; Centre for Community Medicine (A Jaiswal MD), Department of Preventive Oncology (J K Meena MD), and Department of Psychiatry (Prof R Sagar MD), All India Institute of Medical Sciences, New Delhi, India; Institute of Advanced Manufacturing Technologies (Prof M Jakovljevic PhD), Peter the Great St Petersburg Polytechnic University, St Petersburg, Russia; Institute of Comparative Economic Studies (Prof M Jakovljevic PhD), Hosei University, Tokyo, Japan; Department of Neurosciences (Prof R G Jamora PhD), University of the Philippines Manila, Manila, Philippines; Institute for Neurosciences (Prof R G Jamora PhD), St Luke's Medical Center, Bonifacio Global City, Philippines; Department of Data Analytics and Survey Research (S Jana MSc) and Department of Biostatistics and Epidemiology (K Roy Pramanik MSc), International Institute for Population Sciences, Mumbai, India; Department of Neurosurgery (S Javed MS), Research Institute at Nationwide Children's Hospital, Rawalpindi, Pakistan; Department of Neurosurgery (S Javed MD), Washington University in St Louis, St Louis, MO, USA; Centre of Studies and Research (S Jayapal PhD), Ministry of Health, Muscat, Oman; Department of Biochemistry (Prof S Jayaram MD), Government Medical College, Mysuru, India; Melbourne School of Population and Global Health (H Jiang PhD) and School of Health Sciences (A Meretoja MD), University of Melbourne, Melbourne, VIC, Australia; Center for Global Surgery (Prof W D Johnson MD), Loma Linda University, Loma Linda, CA, USA; Zoonoses Research Center (M Jokar DVM), Islamic Azad University, Karaj, Iran; Department of Clinical Sciences (M Jokar DVM), Jahrom University of Medical Sciences, Jahrom, Iran; Institute of Molecular and Clinical Ophthalmology Basel, Basel, Switzerland (Prof J B Jonas MD); Department of Ophthalmology (Prof J B Jonas MD) and Medical Clinic V (Prof W März MD), Heidelberg University, Mannheim, Germany; Department of Gastroenterology and Hepatology (A Joseph MD), Stanford University, Stanford, CA, USA; Department of Economics (C E Joshua BSc), National Open University, Benin City, Nigeria; Institute of Family Medicine and Public Health (M Jürisson PhD), University of Tartu, Tartu, Estonia; School of Public Health (Z Kabir PhD), University College Cork, Cork, Ireland; Department of Oral and Maxillofacial Pathology (V Kadasheiti MDS), Krishna Institute of Medical Sciences Deemed to be University, Karad, India; Department of Pharmaceutical Sciences (F Kalantar BPharm), Faran Shimi Pharmaceutical Company, Tehran, Iran; Dermatology Department (F Kaliyadan MD), King Faisal University, Hofuf, Saudi Arabia; Department of Neurology (A Kandel MD), University at Buffalo, Buffalo, NY, USA; Sydney Eye Hospital (H Kandel PhD), South Eastern Sydney Local Health District, Sydney, NSW, Australia; Faculty of Dentistry (K K Kanmodi MPH), University of Puthisastra, Phnom Penh, Cambodia; Office of the Executive Director (K K Kanmodi MPH), Cephas Health Research Initiative, Ibadan, Nigeria; Laboratory Science Department (J Karami PhD), Khomein University of Medical Sciences, Khomein, Iran; School of Health Professions and Human Services (I M Karaye MD), Hofstra University, Hempstead, NY, USA; Surgery Research Unit (Prof J H Kauppila MD), University of Oulu, Oulu, Finland; Public Health Foundation of India, New Delhi, India (H Kaur MPH); Department of ENT (N Kaur MS), Dr B R Ambedkar State Institute of Medical Sciences, Mohali, India; International Research Center of Excellence (G A Kayode PhD), Institute of Human Virology Nigeria, Abuja, Nigeria; Department of Healthcare Services Management (L Keikavoosi-Arani PhD) and School of Medicine (M Shams-Beyranvand MSc), Alborz University of Medical Sciences, Karaj, Iran; Amity Institute of Forensic Sciences (H Khajuria PhD, B P Nayak PhD), Amity University, Noida, India; Faculty of Veterinary Medicine, Shahrekord Branch (F Khamesipour PhD), Islamic Azad University, Shahrekord, Iran; Primary Care Department (M A Khan MSc), NHS North West London, London, UK; Department of Clinical Pharmacy (Y H Khan PhD, T Mallhi PhD), Jouf University, Sakaka, Saudi Arabia; Department of Critical Care Medicine (M Z Khan Suheb MD), St Luke's Aurora Medical Center, Milwaukee, WI, USA; Centre for Ethics (T Khanna PhD), Jawahar Lal Nehru University, New Delhi, India; College of Health, Wellbeing and Life Sciences (Prof K Khatab PhD), Sheffield Hallam University, Sheffield, UK; College of Arts and Sciences (Prof K Khatab PhD), Ohio University, Zanesville, OH, USA; Faculty of Nursing (H Khatatbeh PhD), Jerash University, Jerash, Jordan; Department of Basic Medical Sciences (M M Khatatbeh PhD), Yarmouk University, Irbid, Jordan; Global Consortium for Public Health Research (Prof M Khatib PhD), Datta Meghe Institute of Higher Education and Research, Wardha, India; Department of Public Health (Prof J Khubchandani PhD), New Mexico State University, Las Cruces, NM, USA; Department of Cognition and

Neuroscience (S Kian MD), University of Texas, Dallas, TX, USA; Department of Pediatrics (G Kim MD), Case Western Reserve University School of Medicine, Cleveland, OH, USA; Division of Pediatric Hospital Medicine (G Kim MD), UH Rainbow Babies and Children's Hospital, Cleveland, OH, USA; Department of Preventive Medicine (J Kim MSc, Prof Y Lee PhD), Korea University, Seoul, South Korea; Cardiovascular Disease Initiative (M Kim MD), Broad Institute of MIT and Harvard, Cambridge, MA, USA; School of Traditional Chinese Medicine (Y Kim PhD), Xiamen University Malaysia, Sepang, Malaysia; Department of Nutrition (R W Kimokoti MD), Simmons University, Boston, MA, USA; School of Health Sciences (Prof A Kisa PhD), Kristiania University College, Oslo, Norway; Department of International Health and Sustainable Development (Prof A Kisa PhD), Tulane University, New Orleans, LA, USA; Department of Nursing and Health Promotion (S Kisa PhD), Oslo Metropolitan University, Oslo, Norway; Department of Public Health (Prof M Kivimäki PhD, Prof T Lallukka PhD) and Department of Virology (F Zakham PhD), University of Helsinki, Helsinki, Finland; Global Healthcare Consulting, New Delhi, India (S Kochhar MD); Independent Consultant, Jakarta, Indonesia (S Kosen MD); San Juan de Dios Sanitary Park, Barcelona, Spain (A Koyanagi MD); Department of Anthropology (Prof K Krishan PhD), Panjab University, Chandigarh, India; Department of Demography (Prof B Kuate Defo PhD) and Department of Social and Preventive Medicine (Prof B Kuate Defo PhD), University of Montreal, Montreal, QC, Canada; Department of Mathematics (M Kuddus PhD) and Department of Population Science and Human Resource Development (M Rahman DrPH), University of Rajshahi, Rajshahi, Bangladesh; Department of Internal Medicine (A Kumar MD), Cabrini Institute, Akron, OH, USA; Department of Psychiatry (M Kumar PhD), University of Nairobi, Nairobi, Kenya; Global Health Institute (S Kundu MPH), North South University, Dhaka, Bangladesh; Department of Nutrition and Food Science (S Kundu MPH), Patuakhali Science and Technology University, Patuakhali, Bangladesh; Faculty of Medicine and Health Science (M Kurniasari PhD), Universitas Kristen Satya Wacana, Salatiga, Indonesia; Department of Health Services Research and Management (D Kusuma DSc), City University of London, London, UK; Faculty of Public Health (D Kusuma DSc) and Centre for Family Welfare (K Latief MSCE), University of Indonesia, Depok, Indonesia; Department of Nephrology (A Kuttikkattu MD), Pushpagiri Institute of Medical Sciences and Research Centre, Thiruvalla, India; Department of Health Policy and Strategy (Prof C Lahariya MD), Foundation for People-centric Health Systems, New Delhi, India; SD Gupta School of Public Health (Prof C Lahariya MD), Indian Institute of Health Management Research University, Jaipur, India; Department of Physiotherapy (T Laksono MS), Universitas Aisyiyah Yogyakarta, Yogyakarta, Indonesia; Institute of Allied Health Sciences (T Laksono MS), National Cheng Kung University, Tainan, Taiwan; Health Services Management Training Centre (J Lám PhD), Semmelweis University, Budapest, Hungary; NEVES Society for Patient Safety (J Lám PhD), Budapest, Hungary; Department of Community and Family Medicine (F H Lami PhD), University of Baghdad, Baghdad, Iraq; Unit of Genetics and Public Health (Prof I Landires MD) and Unit of Microbiology and Public Health (V Nuñez-Samudio PhD), Institute of Medical Sciences, Las Tablas, Panama; Department of Public Health (V Nuñez-Samudio PhD), Ministry of Health, Herrera, Panama (Prof I Landires MD); Department of Psychiatry and Psychotherapy (B Langguth PhD), University of Regensburg, Regensburg, Germany; Department of Otorhinolaryngology (S Lasrado MS), Father Muller Medical College, Mangalore, India; School of Medicine (M B Laurens MD), University of Maryland, Baltimore, MD, USA; Clinical Pharmacy and Pharmacy Management (B K Lawal PhD), Kaduna State University, Kaduna, Nigeria; Health Economics Division (L K D Le PhD), Monash University, Burwood, VIC, Australia; University of Medicine and Pharmacy at Ho Chi Minh City (T T Le MD), Department of General Medicine (V T Nguyen MD), and Department of Otolaryngology (N Tran MSc), University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Viet Nam; Department of Medical Humanities and Social Medicine (M Lee PhD), Ajou University School of Medicine, Suwon, South Korea; Medial Research Collaborating Center (M Lee PhD), Ajou University Medical Center, Suwon, South Korea; Pattern Recognition and Machine Learning Lab (Prof S Lee PhD), Gachon University, Seongnam, South Korea; Department of Precision Medicine (Prof S W Lee MD), Sungkyunkwan University, Suwon-si, South Korea; Department of Health Promotion and Health Education (M Li PhD), National Taiwan Normal University, Taipei, Taiwan; Department of Psychiatry (W Li PhD, T G Rhee PhD), Department of Genetics (S Pawar PhD), and School of the Environment (Y Song PhD), Yale University, New Haven, CT, USA; UCD Centre for Disability Studies (C Linehan PhD), University College Dublin, Dublin, Ireland; Department of Epidemiology and Biostatistics (Prof J Liu PhD), China Center for Health Development Studies (Y Yao MD), and School of Public Health (H Zhang MS), Peking University, Beijing, China; Institute for Health and Environment (W Liu PhD), Chongqing University of Science and Technology, Chongqing, China; Department of Internal Medicine (C Lo MD), Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV, USA; Department of Pediatrics (W D Lo MD), Ohio State University, Columbus, OH, USA; Department of Pediatric Neurology (W D Lo MD), Nationwide Children's Hospital, Columbus, OH, USA; Liberty University School of Osteopathic Medicine, Lynchburg, VA, USA (S W Lobo PhD); Department of Biomedical Sciences (S W Lobo PhD), Mercer University, Macon, GA, USA; Department of Basic Medical Sciences, Neuroscience and Sense Organs (Prof G Logroscino PhD), University of Bari Aldo Moro, Bari, Italy; Fondazione of Clinical Research in Neurology (Prof G Logroscino PhD), Fondazione Cardinale Giovanni Panico Hospital, Tricase, Italy; Interdisciplinary Centre of Marine and Environmental Research (G Lopes PhD), University of Porto, Matosinhos, Portugal; Department of Epidemiology and Evidence-Based Medicine (P D Lopukhov PhD) and Department of Information and Internet Technologies (S K Vladimirov PhD), IM Sechenov First Moscow State Medical University, Moscow, Russia; Department of Health Economics (L Lorenzovici MSc), Syreon Research Romania, Targu Mures, Romania; Department of Doctoral Studies (L Lorenzovici MSc), George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania; Institute of Nutritional Sciences (Prof S Lorkowski PhD), Friedrich Schiller University Jena, Jena, Germany; Competence Cluster for Nutrition and Cardiovascular Health, Jena, Germany (Prof S Lorkowski PhD); School of Health (J Loureiro PhD), Polytechnic Institute of Porto, Portugal; Geospatial Health and Development (J Lubinda PhD), Telethon Kids Institute, Perth, WA, Australia; School of Medicine (Prof G Lucchetti PhD), Federal University of Juiz de Fora, Juiz de Fora, Brazil; Department of Neurosciences and Behavioral Sciences (R Lutzy Saute MD), University of São Paulo, Ribeirão Preto, Brazil; Centre for Public Health and Wellbeing (Z Ma PhD), University of the West of England, Bristol, UK; Periodontal Department, Faculty of Medicine and Dentistry (Prof M Machoy PhD) and Department of Propeudeutics of Internal Diseases and Arterial Hypertension (Prof T Miazgowski MD), Pomeranian Medical University, Szczecin, Poland; Department of Biostatistics and Epidemiology (F Madadzadeh PhD), Yazd University of Medical Sciences, Yazd, Iran; Ophthalmology Department (M Magdy Abd El Razek MSc), Ministry of Health and Population, Aswan, Egypt; Radiology and Precision Health Program (M Mahmoudi PhD), Michigan State University, East Lansing, MI, USA; Faculty of Medicine (J N Malagón-Rojas MSc), El Bosque University, Bogota, Colombia; Department of Internal Medicine (K Malhotra MBBS), Dayanand Medical College and Hospital, Ludhiana, India; Material Science Programme (I Malik PhD), Indian Institute of Technology Kanpur, Kanpur, India; Department of Maternal and Child Nursing and Public Health (Prof D C Malta PhD, E J S Prates BS), Department of Clinical Medicine (Prof B R Nascimento PhD), Clinical Hospital (Prof B R Nascimento PhD), and Department of Applied Nursing (Prof M O Pereira PhD), Federal University of Minas Gerais, Belo Horizonte, Brazil; Department of Medical Laboratory Sciences (A Manuil PhD), Arba Minch University, ARBA MINCH, Ethiopia; Department of Biotechnology (B P Marasini PhD), Tribhuvan University, Kathmandu, Nepal; Biomedical Engineering Research Center (H Marateb PhD), Universitat Politècnica de Catalunya–Barcelona Tech, Barcelona, Spain; Biomedical Engineering (H Marateb PhD), University of Isfahan, Isfahan, Iran; Psychiatry Department (J Martínez-Raga PhD), Hospital Universitario Doctor Peset, Valencia, Spain; Department of Medicine (J Martínez-Raga PhD, Prof R Tabarés-Seisdedos PhD), University of Valencia, Valencia, Spain; Indonesian Public Health Association, Surabaya, Indonesia (S Martini PhD); Campus Caucaia

(F R Martins-Melo PhD), Federal Institute of Education, Science and Technology of Ceará, Caucaia, Brazil; Department of Nutrition and Dietetics (M Martorell PhD), University of Concepcion, Concepción, Chile; Centre for Healthy Living (M Martorell PhD), University of Concepción, Concepción, Chile; Clinical Institute of Medical and Chemical Laboratory Diagnostics (Prof W März MD), Medical University of Graz, Graz, Austria; Department of Public Health (Prof R R Marzo MD), Management and Science University, Shah Alam, Malaysia; Jeffrey Cheah School of Medicine and Health Sciences (Prof R R Marzo MD), Monash University, Subang Jaya, Malaysia; Department of Neurology (J Massano MD), University Hospital Center de Sao Joao, Porto, Portugal; Department of Anatomy, Genetics and Biomedical Informatics (Y Mathangasinghe MD) and Department of Surgery (D P Wickramasinghe MD), University of Colombo, Colombo, Sri Lanka; Australian Regenerative Medicine Institute (Y Mathangasinghe MD) and Department of Medicine (M T Olaiya PhD), Monash University, Clayton, VIC, Australia; Department of Public Health and Community Medicine (E Mathews PhD), Central University of Kerala, Kasaragod, India; Epidemiology Department (Prof R J Maude PhD), Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand; Research Division (P K Maulik PhD), The George Institute for Global Health, New Delhi, India; Department of Social Medicine and Family (M Mazaheri PhD), Dezfoul University of Medical Sciences, Dezfoul, Iran; Department of Ophthalmology (C McAlinden PhD), Singleton Hospital, Swansea, UK; National Centre for Register-based Research (Prof J J McGrath MD), Aarhus University, Aarhus, Denmark; Neurology Department (Prof M Mehndiratta MD), Janakpuri Super Specialty Hospital Society, New Delhi, India; Department of Neurology (Prof M Mehndiratta MD), Govind Ballabh Institute of Medical Education and Research, New Delhi, India; Department of Medical Oncology and Hematology (M A M Mendez-Lopez PhD), Kantonsspital St Gallen, St Gallen, Switzerland; Peru Country Office (W Mendoza MD), United Nations Population Fund, Lima, Peru; Faculty of Civil Engineering (Prof O Mendoza-Cano PhD), University of Colima, Colima, Mexico; Forensic Medicine Division (Prof R G Menezes MD), Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; Neurology Unit (A Meretoja MD), Helsinki University Hospital, Helsinki, Finland; University Centre Varazdin (T Mestrovic PhD), University North, Varazdin, Croatia; Department of Epidemiology (I Michalek PhD) and National Cancer Registry (I Michalek PhD), Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Department of Medical Physiology (E T Mihretie MSc), Madda Walabu University, Bale-Goba, Ethiopia; Department of Statistics and Econometrics (A Mirica PhD, I Petcu PhD), Bucharest University of Economic Studies, Bucharest, Romania; Internal Medicine Programme (Prof E M Mirrakhimov PhD), Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan; Department of Atherosclerosis and Coronary Heart Disease (Prof E M Mirrakhimov PhD), National Center of Cardiology and Internal Disease, Bishkek, Kyrgyzstan; Molecular Biology Unit (N S Mohamed MSc) and Bio-Statistical and Molecular Biology Department (N S Mohamed MSc), Sirius Training and Research Centre, Khartoum, Sudan; Research Institute for Health Development (S Mohammadi PhD), Kurdistan University of Medical Sciences, Sanandaj City, Iran; Department of Clinical Pharmacy and Pharmacy Practice (M Mohammed MSc) and Health Systems and Policy Research Unit (S Mohammed PhD), Ahmadu Bello University, Zaria, Nigeria; School of Pharmaceutical Sciences (M Mohammed MSc), Universiti Sains Malaysia (University of Science Malaysia), Penang, Malaysia; Department of Pharmaceutical Sciences (S Mohammed PhD), Notre Dame of Maryland University, Baltimore, MD, USA; Department of Pharmacy (S Mohammed PhD), Mizan-Tepi University, Mizan, Ethiopia; Department of Health Care Management (S Mohammed PhD), Technical University of Berlin, Berlin, Germany; Center for Transdisciplinary Research (S Mohan PhD), Saveetha Institute of Medical and Technical Science, Chennai, India; Department of Pharmacology (H Mojiri-Forushani PhD), Abadan School of Medical Sciences, Abadan, Iran; Oncology Department (N Moka MD), Appalachian Regional Healthcare, Hazard, KY, USA; Department of Internal Medicine (N Moka MD), University of Kentucky, Lexington, KY, USA; Institute of Clinical Physiology (S Molinaro PhD), National Research Council, Pisa, Italy; Clinical Epidemiology and Public Health Research Unit (L Monasta DSc, L Ronfani PhD, E Traini MSc) and Department of Epidemiology and Public Health (G Zamagni MSc), Burlo Garofolo Institute for Maternal and Child Health, Trieste, Italy; Computer, Electrical, and Mathematical Sciences and Engineering Division (P Moraga PhD), King Abdullah University of Science and Technology, Thuwal, Saudi Arabia; Department of Clinical Biochemistry (A Mospour PhD), Tarbiat Modares University, Tehran, Iran; Department of Health Policy (Prof E Mossialos PhD), London School of Economics and Political Science, London, UK; Epidemiology Department (S Mousavi MD), Aging Research Institute, Tabriz, Iran; Department of Epidemiology and Biostatistics (S Mubarik MS, Prof C Yu PhD) and School of Medicine (Z Zhang PhD), Wuhan University, Wuhan, China; School of Medicine (F Mughal FRCGP), Keele University, Keele, UK; Division of Psychology and Mental Health (F Mughal FRCGP), University of Manchester, Manchester, UK; Department of Surgery (G D Mukoro MD), Ahmadu Bello University Teaching Hospital, Zaria, Nigeria; Department of Medicine (A Mulita PhD), Democritus University of Thrace, Alexandroupolis, Greece; Department of Surgery (F Mulita PhD, G Verras MD), General University Hospital of Patras, Patras, Greece; Faculty of Medicine (F Mulita PhD), Department of Internal Medicine (G Ntaios PhD), and Department of Emergency Medicine (I Pantazopoulos PhD), University of Thessaly, Larissa, Greece; Department of Pathobiology, School of Veterinary Medicine (F Musaigwa PhD), University of Pennsylvania, Philadelphia, PA, USA; Department of Internal Medicine (A Mustafa MD), Staten Island University Hospital Northwell Health, Staten Island, NY, USA; Department of Pediatrics and Pediatric Pulmonology (Prof G Mustafa MD), Institute of Mother & Child Care, Multan, Pakistan; Department of Orthopaedics (S Muthu MS), Government Medical College, Dindigul, India; Quality Appraisal Committee (S Muthu MS), Orthopaedic Research Group, Coimbatore, India; Research and Analytics Department (A J Nagarajan MTech), Initiative for Financing Health and Human Development, Chennai, India; Department of Research and Analytics (A J Nagarajan MTech), Bioinsilico Technologies, Chennai, India; College of Medicine and Public Health (G R Naik PhD), Flinders University, Adelaide, Australia; Faculty of Pharmacy (F Nainu PhD), Hasanuddin University, Makassar, Indonesia; Health Workforce Department (T S Nair MD), World Health Organisation, Geneva, Switzerland; Medical Laboratory Analysis Department (H H Najmuldeen PhD), Cihan University-Sulaimaniya, Sulaimaniya, Iraq; Department of Health and Rehabilitation Sciences (Prof G Nambi PhD), Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia; Department of Applied Pharmaceutical Sciences and Clinical Pharmacy (A Y Naser PhD), Isra University, Amman, Jordan; Department of Nursing Education and Research (A J J Nashwan MSc), Hamad Medical Corporation, Doha, Qatar; Department of Pharmacology and Toxicology (H Nasoori PharmD), Department of Computer Engineering (M SaberiKamarposhti PhD), and Department of Microbiology (S Valadan Tahbaz PhD), Islamic Azad University, Tehran, Iran; Neurology Department (A Nasreldein PhD), Assuta Hospital, Assuit, Egypt; Department of Circulation and Medical Imaging (J Nauman PhD) and Department of Neuromedicine and Movement Science (Prof T J Steiner PhD, Prof L J Stovner PhD), Norwegian university of Science and Technology, Trondheim, Norway; Tehran, Iran (M Negaresh MD); Department of Internal Medicine (M Negaresh MD), Ardabil University of Medical Science, Ardabil, Iran; Department of General Surgery (I Negoï PhD), Emergency Hospital of Bucharest, Bucharest, Romania; Department of Cardiology (R I Negoï PhD), Cardio-Aid, Bucharest, Romania; Department of Oncology (S Negru MD), Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Department of Neurosciences (Prof C R J Newton MD), Kenya Medical Research Institute/Wellcome Trust Research Programme, Kilifi, Kenya; Department of Medical Engineering (D H Nguyen BS), University of South Florida, Tampa, FL, USA; Cardiovascular Research Department (H Q Nguyen MD), Methodist Hospital, Merrillville, IL, USA; Department of Epidemiology (N T Nguyen PhD), Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Viet Nam; Obstetrics and Gynecology Department (N T Nguyen PhD), Hung Vuong hospital, Ho Chi Minh City, Viet Nam; Department of Surgery (P T Nguyen MD), Danang Family Hospital, Danang, Viet Nam; International Islamic

University Islamabad, Islamabad, Pakistan (R K Niazi PhD); Department of General Surgery (T K Nikolouzakakis PhD), University Hospital of Heraklion, Heraklion, Greece; Laboratory of Toxicology (T K Nikolouzakakis PhD) and Department of Medicine (Prof A Tsatsakis DSc), University of Crete, Heraklion, Greece; Department of Public Health (V Niranjan PhD), HSE Ireland, Dublin, Ireland; Department of Public Health (V Niranjan PhD), UNICAF, Larnaca, Cyprus; Center for Public Health (L A Nnyanzi PhD), Teesside University, Middlesbrough, UK; Department of Applied Microbiology (E A Noman PhD), Oslo University Hospital, Taiz, Yemen; Faculty of Applied Sciences and Technology (E A Noman PhD), Universiti Tun Hussein Onn Malaysia, Johor, Malaysia; Department of Clinical Sciences (Prof B Norrving PhD), Lund University, Lund, Sweden; Centre for Heart Rhythm Disorders (J Noubiap MD), University of Adelaide, Adelaide, SA, Australia; Department of Paediatrics (C A Nri-Ezedi MD), Nnamdi Azikiwe University, Awka, Anambra State Nigeria, Awka, Nigeria; Public Health Department (D Nurrika PhD), Banten School of Health Science, South Tangerang, Indonesia; Ministry of Research, Technology and Higher Education, Higher Education Service Institutions (LL-DIKTI) Region IV, Bandung, Indonesia (D Nurrika PhD); Department of Applied Economics and Quantitative Analysis (Prof B Oancea PhD), University of Bucharest, Bucharest, Romania; Department of Medicine (M J O'Donnell PhD), National University of Ireland—Galway, Galway, Ireland; Discipline of Public Health Medicine (R E Ogunsakin PhD), University of KwaZulu-Natal, Durban, South Africa; Department of Preventive Medicine (I Oh PhD), Kyung Hee University, Dongdaemun-gu, South Korea; Sydney, NSW, Australia (S R Okeke PhD); Department of Food and Nutrition (A P Okeunle PhD), Seoul National University, Seoul, South Korea; School of Pharmacy (O C Okonji MSc), University of the Western Cape, Cape Town, South Africa; Department of Medical Physiology (P G Okwute MSc), Babcock University, Ilisan-Remo, Nigeria; Department of Psychiatry and Behavioural Neurosciences (A T Olagunju MD), McMaster University, Hamilton, ON, Canada; Medical Laboratory Sciences (M D Olana PhD), Ambo University, Ambo, Ethiopia; Department of Nursing Science (M I Olatubi PhD), Bowen University, Iwo, Nigeria; Cardiology Department (G M M Oliveira PhD), Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; Slum and Rural Health Initiative Research Academy (I I Olufadewa MHS), Slum and Rural Health Initiative, Ibadan, Nigeria; Centre for Healthy Start Initiative, Lagos, Nigeria (B O Olusanya PhD); Non-communicable Disease Prevention Unit (S Ong FAMS), Ministry of Health, Bandar Seri Begawan, Brunei; Early Detection and Cancer Prevention Services (S Ong FAMS), Pantai Jerudong Specialist Centre, Bandar Seri Begawan, Brunei; Department of Pharmacology and Therapeutics (Prof O E Onwujekwe PhD), University of Nigeria Nsukka, Enugu, Nigeria; Department of Pharmacotherapy and Pharmaceutical Care (M Ordak PhD) and Department of Biochemistry and Pharmacogenomics (M Zielińska MPharm), Medical University of Warsaw, Warsaw, Poland; School of Medicine (U L Osuagwu PhD), Western Sydney University, Campbelltown, NSW, Australia; Department of Optometry and Vision Science (U L Osuagwu PhD), University of KwaZulu-Natal, KwaZulu-Natal, South Africa; Laboratory of Public Health Indicators Analysis and Health Digitalization (N Ostavnov BA, S S Ostavnov PhD) and Department of Information Technologies and Management (S K Vladimirov PhD), Moscow Institute of Physics and Technology, Dolgoprudny, Russia; Department of Project Management (S S Ostavnov PhD) and Department of Health Care Administration and Economics (Prof V Vlassov MD), National Research University Higher School of Economics, Moscow, Russia; Faculty of Medicine (Prof A Ouyahia PhD), University Ferhat Abbas of Setif, Setif, Algeria; Division of Infectious Diseases (Prof A Ouyahia PhD), University Hospital of Setif, Setif, Algeria; Department of Respiratory Medicine (Prof M P P A DNB), Jagadguru Sri Shivarathreeswara University, Mysore, India; Vicerrectorado de Investigacion (K Pacheco-Barrios MD), Universidad San Ignacio de Loyola, Lima, Peru; Department of Forensic Medicine and Toxicology (J Padubidri MD) and Department of Microbiology (S M Shenoy MD), Kasturba Medical College, Mangalore, India; Department of Neurology (Prof P K Pal DM), National Institute of Mental Health and Neurosciences, Bangalore, India; Department of Microbiology (Prof P N Palange MD), Kaloji Narayana Rao University of Health Sciences, Adilabad, India; Research Institute for Medicines-FFUL (C Palladino PhD), Universidade de Lisboa, Lisbon, Portugal; Department of Public Health (R Palladino MD), University of Naples Federico II, Naples, Italy; Department of Mental Health (R F Palma-Alvarez PhD), Hospital Universitari Vall d'Hebron, Barcelona, Spain; Department of Psychiatry, Mental Health and Addictions (R F Palma-Alvarez PhD), Vall d'Hebron Institut de Recerca, Barcelona, Spain; Menzies Institute for Medical Research (F Pan PhD), University of Tasmania, Hobart, TS, Australia; Department of Nutrition and Dietetics (Prof D Panagiotakos PhD), Harokopio University, Athens, Greece; 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Research Center (A Parthasarathi MD), Allergy Asthma and Chest Center, Mysore, India; School of Dentistry (J Patel BSc), University of Leeds, Leeds, UK; College of Dental Medicine (Prof S Patil PhD), Roseman University of Health Sciences, South Jordan, UT, USA; Second Department of Internal Medicine (D Patoulias PhD), European Interbalkan Medical Center, Thessaloniki, Greece; Second Department of Cardiology (D Patoulias PhD), Aristotle University of Thessaloniki, Thessaloniki, Greece; Clinical Research Department (P Pedersini MSc, J H Villafañe PhD), IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy; Department of Neurology (U Pensato MD), IRCCS Humanitas Research Hospital, Milan, Italy; Department of Orthopedics (J Pereira MS), Yenepoya Medical College, Mangalore, India; International Institute for Educational Planning (Prof M F P Peres MD), Albert Einstein Hospital, São Paulo, Brazil; Mario Negri Institute for Pharmacological Research, Bergamo, Italy (N Perico MD, Prof G Remuzzi MD); Department of Biology (Prof S Perna PhD), University of Bahrain, Sakir, Bahrain; Facultad de Medicina (F E Petermann-Rocha PhD), Universidad Diego Portales, Santiago, Chile; Department of Psychiatry (Prof M R Phillips MD), Department of Neurology (Prof N Scarmeas PhD), and Department of Health and Behavior Studies (Prof I D Sigfusdottir PhD), Columbia University, New York, NY, USA; Department of Clinical Sciences (G D Pinilla-Monsalve MD), ICESI University, Cali, Colombia; Neuroscience Unit (G D Pinilla-Monsalve MD), Fundación Valle del Lili, Cali, Colombia; Research School of Chemistry and Applied Biomedical Sciences (E Plotnikov PhD), Tomsk Polytechnic University, Tomsk, Russia; Mental Health Research Institute (E Plotnikov PhD), Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia; Clinical Academic Department of Pediatrics (Prof D Poddighe PhD), University Medical Center, Astana, Kazakhstan; Department of Neurology (B Polat MD), Istanbul Medipol University, Istanbul, Türkiye; Department of Data Management and Analysis (R Poluru PhD), The INCLIN Trust International, New Delhi, India; Discipline of General Practice (Prof C D Pond PhD), University of Newcastle, Callaghan, NSW, Australia; Department of Medicine (A Pourbagher-Shahri MD) and Faculty of Medicine (A Rajabpour-Sanati MD), Birjand University of Medical Sciences, Birjand, Iran; Department of Medicine (M Pourfridoni Dipl), Jiroft University of Medical Sciences, Jiroft, Iran; Non-communicable Diseases Research Center (N Pourtaheri PhD), Bam University of Medical Sciences, Bam, Iran; Department of Neurology (Prof S Prakash DM), Smt BKS Medical Institute and Research Center, Vadodara, India; Askov and Rita Patel Institute of Physiotherapy (V Prakash PhD), Charotar University of Science and Technology, Anand, India; Department of Biology (Prof H Purnobasuki PhD), Airlangga University, Surabaya,

Indonesia; Department of Computer Science (N H Qasim PhD), Cihan University–Sulaymaniyah, Sulaymaniyah, Iraq; Department of Neonatology (I Qattea MD), Case Western Reserve University, Cleveland, OH, USA; Department of Cardiology (G Qian MS), Third Military Medical University, Chongqing, China; Department of Medical Oncology (Prof V Radhakrishnan MD), Cancer Institute (WIA), Chennai, India; Department of Epidemiology and Biostatistics (H Raeisi Shahraki PhD), Shiraz University of Medical Sciences, Shahrekord, Iran; Research and Development Coordination (I Rafique PhD), Health Research Institute, National Institutes of Health, Islamabad, Pakistan; Department of Basic Sciences (M M Rahati PhD), Khomein University of Medical Sciences, Khomein, Iran; Department of Health Sciences (Prof F Rahim PhD), Cihan University Sulaymaniyah, Sulaymaniyah, Iraq; Cihan University Sulaymaniyah Research Center, Sulaymaniyah, Iraq (Prof F Rahim PhD); National Institute of Infectious Diseases (M Rahman PhD), Center for Surveillance, Immunization, and Epidemiologic Research, Tokyo, Japan; Center for Evidence-Based Medicine and Clinical Research, Dhaka, Bangladesh (M Rahman PhD); Institute of Health and Wellbeing (M Rahman PhD), Federation University Australia, Berwick, VIC, Australia; Future Technology Research Center (A Rahmani PhD), National Yunlin University of Science and Technology, Yunlin, Taiwan; Department of Oncology and Hematology (H Rahmani Youshanlouei MD), University of Chicago, Chicago, IL, USA; Department of Physical Education and Sport Sciences (Prof M Rahmati PhD), Lorestan University, Khorramabad, Iran; Department of Radiology (S Ramasamy MD), Loyola University Medical Center, Maywood, IL, USA; Department of Community Medicine (P Ramasubramani MD), Mahatma Gandhi Medical College and Research Institute, Puducherry, India; Leadership Institute for Global Health Transformation (S Ramazanu PhD), National University of Singapore, Singapore; Centre for Clinical Pharmacology (N Rancic PhD), Medical Faculty of the Military Medical Academy, University of Defence in Belgrade, Belgrade, Serbia; Centre for Clinical Pharmacology (N Rancic PhD), Medical College of Georgia at Augusta University, Belgrade, Serbia; Department of Oral Pathology (S Rao MDS), Sharavathi Dental College and Hospital, Shimogga, India; College of Pharmaceutical Sciences (D Rapaka PhD), Andhra University, Visakhapatnam, India; University of Social Welfare and Rehabilitation Sciences, Tehran, Iran (V Rashedi PhD); Department of Medicine (A M Rashid MD), Jinnah Sindh Medical University, Karachi, Pakistan; Academic Public Health England (Prof S Rawaf MD), Public Health England, London, UK; Department Biological Sciences (Prof E M M Redwan PhD), King Abdulaziz University, Jeddah, Egypt; Department of Protein Research (Prof E M M Redwan PhD), Research and Academic Institution, Alexandria, Egypt; Department of Orthodontics (A Rekabi Bana MSc), Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Network of Immunity in Infection, Malignancy and Autoimmunity (Prof N Rezaei PhD), Universal Scientific Education and Research Network, Tehran, Iran; Department of Public Health Sciences (T G Rhee PhD), University of Connecticut, Farmington, CT, USA; Department of Public Health (A Riad DDS) and Czech National Centre for Evidence-based Healthcare and Knowledge Translation (A Riad DDS), Masaryk University, Brno, Czech Republic; Department of Psychology (Prof S R Robinson PhD), Royal Melbourne Institute of Technology University, Bundoora, VIC, Australia; Departamento de Farmacología y Toxicología (Prof J A B Rodriguez PhD), Universidad de Antioquia, Medellín, Colombia; Department of Clinical Research (L Roever PhD), Federal University of Uberlândia, Uberlândia, Brazil; Maurizio Bufalini Hospital, Cesena, Italy (M Romoli MD); Department of Labour (P Roy PhD), Directorate of Factories, Government of West Bengal, Kolkata, India; African Genome Center (E Rubagotti PhD), Mohammed VI Polytechnic University, Ben Guerir, Morocco; Center for Research in Congenital Anomalies and Rare Diseases (E Rubagotti PhD), Centro de Investigaciones en Anomalías Congénitas y Enfermedades Raras, Universidad Icesi, Cali, Colombia; School of Health and Social Care (M A Ruiz PhD), University of Essex, Colchester, UK; Institute of Neuroscience and Physiology (Prof K S Sunnerhagen PhD), University of Gothenburg, Gothenburg, Sweden; Department of Neurocare (Prof K S Sunnerhagen PhD), Sabzevar University of Medical Sciences, Gothenburg, Sweden; Faculty of Medicine (Z Saadatian PhD) and Infectious Diseases Research Center (Z Saadatian PhD), Gonabad University of Medical Sciences, Gonabad, Iran; Department of Neurology (Prof S Sacco MD), University of L'Aquila, L'Aquila, Italy; Department of Pediatric Neurology (S Sadeghian MD), Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Multidisciplinary Laboratory Foundation University School of Health Sciences (Prof U Saeed PhD), Foundation University, Islamabad, Pakistan; International Center of Medical Sciences Research, Islamabad, Pakistan (Prof U Saeed PhD); Hurvitz Brain Sciences Research Program (U Saeed MSc), Sunnybrook Research Institute, Toronto, ON, Canada; Department of Neurology (M Safdarian MD), Christian-Doppler University Hospital, Salzburg, Austria; Spinal Cord Injury and Tissue Regeneration Center Salzburg (M Safdarian MD), Paracelsus Medical University, Salzburg, Austria; Faculty of Medicine, Bioscience and Nursing (S Z Safi PhD), MAHSA University, Selangor, Malaysia; Interdisciplinary Research Centre in Biomedical Materials (S Z Safi PhD), COMSATS Institute of Information Technology, Lahore, Pakistan; Department of Community and Family Medicine (S S Sahoo MD) and Department of Radiodiagnosis (P Singh MD), All India Institute of Medical Sciences, Bathinda, India; Neurology Department (S Sajedi MD), Golestan University of Medical Sciences, Gorgan, Iran; Ludwig Maximilian University of Munich, Munich, Germany (J W Sakshaug PhD); Institute for Employment Research, Nuremberg, Germany (J W Sakshaug PhD); Public Health and Community Medicine Department (M R Salem MD), Cairo University, Giza, Egypt; Department of Neurology (S Samadzadeh MD), University of Southern Denmark, Odense, Denmark; Department of Anatomy (Prof V P Samuel PhD), Ras Al Khaimah Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates; Institute of Neuroanatomy (N Sanadgol PhD), Uniklinik Rhine-Westphalia Technical University of Aachen, Aachen, Germany; Department of Pediatrics (R K Sanjeev MD), Pravara Institute of Medical Sciences, Loni (BK), India; Policy and Epidemiology Group (D F Santomauro PhD), Queensland Centre for Mental Health Research, Wacol, QLD, Australia; College of Public Health (I N Santri PhD), University of Ahmad Dahlan, Yogyakarta, Indonesia; Indira Gandhi Medical College and Research Institute, Puducherry, India (A Saravanan MD); UGC Centre of Advanced Study in Psychology (M Satpathy PhD) and Analytical and Applied Economics Department (C K Swain MPhil), Utkal University, Bhubaneswar, India; Udyam-Global Association for Sustainable Development, Bhubaneswar, India (M Satpathy PhD); Market Access (M Saylan MD), Bayer, Istanbul, Türkiye; Department of Neurology (Prof N Scarmeas PhD), National and Kapodistrian University of Athens, Athens, Greece; Hypertension and Kidney Disease Laboratory (Prof M P Schlaich MD), Baker Heart and Diabetes Institute, Melbourne, VIC, Australia; Cardiovascular Research Center (A Schuermans BSc), Massachusetts General Hospital, Cambridge, MA, USA; Department of Cardiovascular Sciences (A Schuermans BSc, J Van den Eynde BSc), Katholieke Universiteit Leuven, Leuven, Belgium; Department of Methodology and Innovation in Prevention (M Schwarzwinger MD), University Hospital of Bordeaux, France, Bordeaux, France; University of Bordeaux (M Schwarzwinger MD), Inserm, Bordeaux, France; Department of Psychology (D C Schwebel PhD) and Department of Radiology (H Sotoudeh MD), University of Alabama at Birmingham, Birmingham, AL, USA; Faculty of Dentistry (S Selvaraj PhD), AIMST University, Bedong, Malaysia; Department of Medical Sciences (P Sengupta PhD), Bharath Institute of Higher Education and Learning, Chennai, India; Emergency Department (S Senthilkumaran MD), Manian Medical Centre, Erode, India; Department of Medicine and Surgery (Y Sethi MBBS), Government Doon Medical College, Dehradun, India; National Heart, Lung, and Blood Institute (A Seylani BS), National Institute of Health, Rockville, MD, USA; Department of Community Health (M Shabany PhD), Aja University of Medical Sciences, Tehran, Iran; Department of Chemistry (H Shahsavari PhD), Institute for Advanced Studies in Basic Sciences, Zanjan, Iran; Department of Clinical Sciences (Prof M J Shahwan PhD), Al-Quds University, Ajman, United Arab Emirates; Karachi, Pakistan (M A Shaikh MD); Medical College (Prof K Shaji MD), Kerala University of Health Sciences, Thrissur, India; Department of Pathology and Laboratory Medicine (S Sham MD), Northwell Health, New York City, NY, USA; Department of Public Health (A T T Shama MPH), Wollega University, Nekemt, Ethiopia;

Center for Medical and Bio-Allied Health Sciences Research (M A Shamsi PhD), Ajman University, Ajman, United Arab Emirates; Department of Medicine (M Sharath MD), Bangalore Medical College and Research Institute, Bangalore, India; Department of Clinical Review and Safety (S Sharfaei MD), Baim Institute for Clinical Research, Boston, MA, USA; Beth Israel Deaconess Medical Center (S Sharfaei MD), Harvard University, Boston, USA; Department of Ophthalmology (M Shayan MD), Harvard Medical School, Boston, MA, USA; Psychology Department (J Shen PhD), University of Massachusetts Lowell, Boston, MA, USA; Department of Public Health (D S Shiferaw MPH), Dambi Dollo University, Dembi Dollo, Ethiopia; National Institute of Infectious Diseases, Tokyo, Japan (M Shigematsu PhD); Finnish Institute of Occupational Health, Helsinki, Finland (R Shiri PhD); Department of Public Health Dentistry (Prof K M Shivakumar PhD), Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, India; Department of Epidemiology (F Shokri PharmD), Leiden University Medical Center, Leiden, Netherlands; Department of Medical-Surgical Nursing (S Shorofi PhD), Mazandaran University of Medical Sciences, Sari, Iran; Department of Nursing and Health Sciences (S Shorofi PhD), Flinders University, Adelaide, SA, Australia; School of Pharmacy (S Shrestha PharmD), Monash University, Selangor Darul Ehsan, Malaysia; Department of Medical Microbiology and Infectious Diseases (E E Siddig MD), Erasmus University, Rotterdam, Netherlands; Department of Psychology (Prof I D Sigfusdottir PhD), Reykjavik University, Reykjavik, Iceland; Center of Potential and Innovation of Natural Resources (Prof L M R Silva PhD), Polytechnic Institute of Guarda, Guarda, Portugal; Health Sciences Research Centre (Prof L M R Silva PhD), University of Beira Interior, Covilhã, Portugal; School of Public Health and Zoonoses (B B Singh PhD), Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, India; Department of Community Medicine (G Singh MD), Lady Hardinge Medical College, New Delhi, India; Department of Neurology (S Sivakumar MD), University of Massachusetts Medical School, Worcester, MA, USA; School of Health and Biomedical Science (A Sohag MSc), Royal Melbourne Institute of Technology University, Melbourne, VIC, Australia; Department of Pathology (R Solanki MD), Ross University School of Medicine, Bridgetown, Barbados; Department of Pathology (R Solanki MD), American University of the Caribbean School of Medicine, Cupecoy, Saint Martin; Faculty of Public Health (S Solikhah DrPH), Universitas Ahmad Dahlan, Yogyakarta, Indonesia; Department of Nursing (Y Solomon MSc), Dire Dawa University, Dire Dawa, Ethiopia; Department of Health Policy and Management (S Song PhD), University of Georgia College of Public Health, Athens, GA, USA; 3rd Department of Cardiology, National and Kapodistrian University of Athens (M Spartalis PhD), University of Athens, Athens, Greece; Department of Pediatric Cardiology (J R Starnes MD), Vanderbilt University Medical Center, Nashville, TN, USA; Department of Research and Learning (J R Starnes MD), Lwala Community Alliance, Rongo, Kenya; Nutrition and Dietetics Department (A V Starodubova DSc), Federal Research Institute of Nutrition, Biotechnology and Food Safety, Moscow, Russia; Department of Internal Disease (A V Starodubova DSc), Pirogov Russian National Research Medical University, Moscow, Russia; Risk and Resilience in Mental Disorders Unit (Prof D J Stein MD), South African Medical Research Council, Cape Town, South Africa; Department of Neurology and Clinical Neurophysiology (Prof L J Stovner PhD), St. Olavs Hospital, Trondheim, Norway; Center for Biotechnology and Microbiology (M Suleman PhD), University of Swat, Mingora, Pakistan; School of Life Sciences (M Suleman PhD), Xiamen University, China, Xiamen, China; National Institute of Epidemiology (R Suliakatchi Abdulkader MD), Indian Council of Medical Research, Chennai, India; Mental Health Research (A Sultana MD), Independent Consultant, Khulna, Bangladesh; Division of Global Mental Health (A Sultana MD), EviSyn Health, Khulna, Bangladesh; School of Medicine (Prof J Sun PhD), Griffith University, Gold Coast, QLD, Australia; Department of Pediatrics (A Sunny MD), Icahn School of Medicine at Mount Sinai, New York City, NY, USA; Department of Clinical Pathology (H Susianti PhD), Brawijaya University, Malang, Indonesia; Hospital Central Laboratory (H Susianti PhD), Dr Saiful Anwar General Hospital, Malang, Indonesia; Department of Dermatology (M D Szeto BS), University of Colorado, Aurora, CO, USA; Carlos III Health Institute (Prof R Tabarés-Seisdedos PhD), Biomedical Research Networking Center for Mental Health Network, Madrid, Spain; Department of Dermato-Venereology (M Tampa PhD), Dr Victor Babes Clinical Hospital of Infectious Diseases and Tropical Diseases, Bucharest, Romania; Department of Epidemiology (J J L Tamuzi MSc), Stellenbosch University, Cape Town, South Africa; Department of Medicine (J J L Tamuzi MSc), Northlands Medical Group, Omuthiya, Namibia; Department of Surgery (K Tan PhD), Yong Loo Lin School of Medicine (Prof N Venketasubramanian MBBS), Saw Swee Hock School of Public Health (S Yi PhD), National University of Singapore, Singapore, Singapore; State Key Laboratory of Numerical Modeling for Atmospheric Sciences and Geophysical Fluid Dynamics (H Tang PhD), Institute of Atmospheric Physics, Chinese Academy of Sciences, Beijing, China; Department of Economics (N Y Tat MS), Rice University, Houston, TX, USA; Department of Research and Innovation (N Y Tat MS), Enventure Medical Innovation, Houston, TX, USA; Department of Public Health (Y M Tefera MPH), Dire Dawa university, Dire Dawa, Ethiopia; Pediatric Intensive Care Unit (M Temsah MD), King Saud University, Riyadh, Saudi Arabia; Department of Epidemiology and Biostatistics (M Teramoto MD), Department of Bioengineering and Therapeutic Sciences (Prof M S Zastrozhin PhD), University of California San Francisco, San Francisco, CA, USA; Health Management Department (R Tesler PhD), Ariel University, Ariel, Israel; Department of Pharmacology (P Thangaraju MD), All India Institute of Medical Sciences, Raipur, India; Department of Medicine (R Thapa PhD), Monash Health, Melbourne, VIC, Australia; Department of Monitoring and Evaluation (R Thapa PhD), Nepal Development Society, Kathmandu, Nepal; Department of Gastroenterology (N K Thomas MD), PSG Institute of Medical Sciences and Research, Coimbatore, India; Faculty of Public Health (J H V Ticoalo MPH), Universitas Sam Ratulangi, Manado, Indonesia; Social Determinants of Health (R Toghroli PhD), Hormozgan University of Medical Sciences, Bandar Abbas, Iran; Department of Medicine (Prof M Tonelli MD), Department of Oncology (L Yang PhD), University of Calgary, Calgary, AB, Canada; Saveetha Dental College and Hospitals (M R Tovani-Palone PhD), Saveetha Institute of Medical and Technical Sciences, Chennai, India; SRM College of Pharmacy (M R Tovani-Palone PhD), SRM Institute of Science and Technology, Chennai, India; Department of Health (N M Tran MD), Children's Hospital 1, Ho Chi Minh City, Viet Nam; Department of Medicine (P V Tran BSc), Tra Vinh University, Tra Vinh City, Viet Nam; Department of Health Sciences (S J Tromans PhD), University of Leicester, Leicester, UK; Adult Learning Disability Service (S J Tromans PhD), Leicestershire Partnership National Health Service Trust, Leicester, UK; School of Medicine (T T Truyen MD), Nam Can Tho University, Can Tho, Viet Nam; Department of Psychiatry (E Tsermpini PhD), Dalhousie University, Halifax, NS, Canada; Department of Occupational Health and Safety (A R Tualeka PhD), Universitas Airlangga, Surabaya, Indonesia; Public Health Department (D G Tufa MPH), Salale University, Fiche, Ethiopia; College of Public Health (C S Ubah MPH), Temple University, Philadelphia, PA, USA; Health Department (I Ulhaq PhD), Ministry of Health, Peshawar, Pakistan; Health Department, Government of Khyber Pakhtunkhwa (I Ulhaq PhD), Directorate General of Health Services, Peshawar, Pakistan; Medical Genomics Research Department (M Umair PhD), King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; Department of Life Sciences (M Umair PhD), University of Management and Technology, Lahore, Pakistan; Department of Paraclinical Sciences (S Umakanthan MD), The University of the West Indies, St Augustine, Trinidad and Tobago; Department of Pediatric Cardiology (K Umapathi MD), Rush University, Chicago, IL, USA; College of Health and Sport Sciences (A G Vaithinathan MSc), University of Bahrain, Salmanya, Bahrain; Clinical Cancer Research Center (S Valadan Tahbaz PhD), Milad General Hospital, Tehran, Iran; Department of Internal Medicine (P Vart PhD), University of Groningen, Groningen, Netherlands; UKK Institute, Tampere, Finland (Prof T J Vasankari MD); Faculty of Medicine and Health Technology (Prof T J Vasankari MD), Tampere University, Tampere, Finland; Department of Human Genetics and Molecular Biology (B Vellingiri PhD), Bharathiar University, Coimbatore, India; Raffles Neuroscience Centre (Prof N Venketasubramanian MBBS), Raffles

Hospital, Singapore, Singapore; Department of Health Science and Public Health (L Villani DrPH), Università Cattolica del Sacro Cuore, Rome, Italy; Programa de doctorado IPK (A Vinueza Veloz MSc), Institute of Tropical Medicine, La Habana, Cuba; Department of Medical Oncology (S R Volovat PhD), University of Medicine and Pharmacy “Grigore T Popa” Iasi, Iași, Romania; Department of Medical Oncology (S R Volovat PhD), Regional Institute of Oncology, Iasi, Romania; Office of Research, Innovation, and Commercialization (Prof Y Waheed PhD), Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan; Gilbert and Rose-Marie Chagoury School of Medicine (Prof Y Waheed PhD), Lebanese American University, Byblos, Lebanon; Department of Interventional Radiology (W Wahood MS), University of Miami, Miami, FL, USA; School of Public Health (F Wang PhD), Xuzhou Medical University, Xuzhou, China; Department of Neurosurgery (S Wang MD), Beijing Tiantan Hospital, Beijing, China; School of Population Health and Environmental Sciences (Y Wang PhD, Prof C D A Wolfe MD), King's College London, London, UK; Department of Biotechnology and Genetic Engineering (M Waqas PhD), Hazara University Mansehra, Mansehra, Pakistan; Department of Parasitology (Prof K G Weerakoon PhD) and Department of Community Medicine (N D Wickramasinghe MD), Rajarata University of Sri Lanka, Anuradhapura, Sri Lanka; Cardiology Department (Prof R G Weintraub MB), Royal Children's Hospital, Melbourne, VIC, Australia; Department of Critical Care and Neurosciences (Prof R G Weintraub MB), Murdoch Childrens Research Institute, Melbourne, VIC, Australia; Competence Center of Mortality-Follow-Up of the German National Cohort (R Westerman DSc), Federal Institute for Population Research, Wiesbaden, Germany; Department of Neurology (B Willekens PhD), Antwerp University Hospital, Antwerp, Belgium; Faculty of Medicine and Health Sciences (B Willekens PhD), University of Antwerp, Antwerp, Belgium; Department of Neurology (Prof A S Winkler PhD), Technical University of Munich, Munich, Germany; NIHR Biomedical Research Centre (Prof C D A Wolfe MD), Guy's and St Thomas' Hospital and Kings College London, London, UK; Department of Orthopaedics (Prof A Wu MD), Wenzhou Medical University, Wenzhou, China; Department of Endocrinology, First Affiliated Hospital (Prof S Xu PhD), University of Science and Technology of China, Hefei, China; Cardiovascular Program (X Xu PhD), The George Institute for Global Health, Sydney, NSW, Australia; Department of Cells and Tissues (G Yahya PhD), Molecular Biology Institute of Barcelona, Spanish National Research Council, Barcelona, Spain; Cancer Epidemiology and Prevention Research (L Yang PhD), Alberta Health Services, Calgary, AB, Canada; Department of Family Medicine and Community Health (Y Yano MD), Duke University, Durham, IL, USA; Department of Midwifery (A Yeshaneh MSc), Wolkite University, Wolkite, Ethiopia; Department of Pharmacology, Physiology and Neuroscience (M Yesiltepe PhD), Rutgers University, Newark, Türkiye; Clinical Investigation Unit (M Yesiltepe PhD), Ankara City Hospital, Ankara, Türkiye; KHANA Center for Population Health Research, Phnom Penh, Cambodia (S Yi PhD); Department of Health Management (A Yiğit PhD, V Yiğit PhD), Süleyman Demirel Üniversitesi (Süleyman Demirel University), Isparta, Türkiye; Department of Pediatrics (Prof D Yon MD), Kyung Hee University, Seoul, South Korea; Department of Neuropsychopharmacology (N Yonemoto PhD), National Center of Neurology and Psychiatry, Kodaira, Japan; Department of Public Health (N Yonemoto PhD), Juntendo University, Tokyo, Japan; Department of Health Policy and Management (Prof M Z Younis PhD), Jackson State University, Jackson, MS, USA; School of Business and Economics (Prof M Z Younis PhD), Universiti Putra Malaysia, Kuala Lumpur, Malaysia; Department of Medical Biotechnology (M Zahedi MSc), Student Research Committee (M Zahedi MSc), Iran University of Medical Sciences, Tehran, Iran; Faculty of Medicine and Health Sciences (F Zakhham PhD), Hodeidah University, Hodeidah, Yemen; Department of Neuroscience (R Zand MD), Geisinger Health System, Danville, PA, USA; Department of Neurology (R Zand MD), University of Tennessee, Memphis, TN, USA; Department of Radiology (G G Z Zandieh MD), Johns Hopkins University, Baltimore, MD, USA; Menzies Institute for Medical Research (A Zarghami MD), Hobart, TAS, Australia; Addictology Department (Prof M S Zastrozhin PhD), Russian Medical Academy of Continuous Professional Education, Moscow, Russia; Department of Public Health

(M G M Zeariya PhD), University of Hail, Hail, Saudi Arabia; Department of Zoology and Entomology (M G M Zeariya PhD), Al-Azhar University, Cairo, Egypt; The Biotechnology Centre (F Zeukeng PhD), University of Yaoundé I, Yaounde, Cameroon; Department of Biochemistry and Molecular Biology (F Zeukeng PhD), University of Buea, Buea, Cameroon; Department of Epidemiology and Biostatistics (C Zhai MD), Ministry of Public Health, Hefei, China; Department of Oncology (C Zhai MD), The First Affiliated Hospital of Anhui Medical University, Hefei, China; School of Public Health (Y Zhang PhD), Hubei Province Key Laboratory of Occupational Hazard Identification and Control (Y Zhang PhD), Wuhan University of Science and Technology, Wuhan, China; College of Traditional Chinese Medicine (H Zhao MD), Hebei University, Baoding, China; The Department of Basic Medicine (Y Zhao BS), Army Medical University, Chongqing, China; School of Public Health and Emergency Management (B Zhu PhD), Southern University of Science and Technology, Shenzhen, China; Department of Public Health (A Zhumagaliuly MD), Kazakh National Medical University, Almaty, Kazakhstan

Contributors

Detailed information about individual author contributions to the research are available in the appendix (pp 81–93). Members of the core research team (J Steinmetz, L Ong, T Vos) for this topic area had full access to the underlying data used to generate estimates presented in this paper. All other authors had access to, and reviewed, estimates as part of the research evaluation process. J Steinmetz, L Ong, and T Vos accessed and verified the underlying data reported in this study.

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Data sharing

The findings of this study are supported by data available in public online repositories, data publicly available on request of the data provider, and data not publicly available due to restrictions by the data provider. Non-publicly available data were used under license for the current study but might be available from the authors of this study on reasonable request to the corresponding author and with permission of the data provider.

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