Global burden of neurological disorders: challenges and opportunities with the available data

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The first Global Burden of Disease Study (GBD) in 1990 quantified the health effects of more than 100 diseases. Since then, the GBD project has published updates several times. Neurological disorders have been shown to be major contributors to disability and reduced life expectancy by the GDB analyses.[1] *The Lancet Neurology* has now reported 11 neurological disorder GBD 2016 studies over the past few months.

The GBD project focuses on key epidemiological measures, such as incidence, prevalence, and mortality, and their variation by age, gender, Socio-demographic Index, and location. A time-honoured rule of thumb in epidemiology is that the prevalence of a disease is a function of its incidence and duration.[2] The simple relationship between prevalence, incidence, and duration of disease underlies many key results in the GBD publications.

Incidence measures how quickly new cases of a disease arise in a population and thus the probability that a healthy individual will develop a particular disease. Population incidence is therefore an important predictor of individual risk and is widely used to examine the association between a disease and suspected risk factors, as well as the effectiveness of disease prevention measures such as vaccination to prevent meningitis[3] or treatment of hypertension and atrial fibrillation to decrease stroke.[4]

Prevalence depends both on how quickly new cases of a disease arise and how long affected people survive. For many neurological diseases, disease duration is equal to life expectancy after diagnosis. Important determinants of survival are access to health services and the quality of health care, in addition to diagnostic and therapeutic interventions. Prevalence is useful in estimating the need for facilities and personnel and is thus a measure of the burden of a particular disease to the health-care system. However, it is a poor predictor of risk because an increase in prevalence might be due to an increase in incidence or to improved survival.

Mortality in a population is simply the incidence of death—a function of disease incidence and case fatality. Disability-adjusted life-years (DALYs) is a composite measure of the overall disease burden expressed as the number of years lost to ill health, disability, and early death.[2] In 2016, neurological disorders were ranked as the leading cause of DALYs and the second-leading cause of deaths globally.[1]

The validity and thereby the usefulness of estimates in the GBD project depend on many factors.[5] Factors relevant for neurological diseases include completeness and validity of neurological case identification, which in turn depend on access to health care, diagnostic criteria, temporal changes in diagnostic criteria, and data quality of underlying data sources. For instance, geographic differences in incidence of motor neuron diseases might be explained in part by differences in validity of case ascertainment.[6] For several diseases, diagnoses are based on clinical information supplemented with neuroimaging techniques. Substantial improvements in imaging in past decades has enhanced identification of neurological conditions such as multiple sclerosis, the prevalence of which has increased in many world regions since 1990.[7] Another dimension of case identification is the slow development of symptoms of many neurological disorders. These disorders have a preclinical phase with no firm diagnosis and a clinical phase when the diagnosis is established. For example, patients with Alzheimer's disease or other dementias might have symptoms years before they receive a diagnosis.[8] The global numbers of people living with dementia and deaths due to dementia thus more than doubled from 1990 to 2016, undoubtedly due in part to improved case ascertainment and the ageing of the population.[8]

Changes in diagnostic criteria, the potential for length and lead-time bias, and diagnostic validity might affect estimates of incidence and survival time. Although temporal decreases in incidence generally reflect real change, increases in incidence can be more difficult to interpret. Such increases might only accrue from earlier diagnosis or technological improvements in diagnostic accuracy.

For stroke, a preventable neurological disorder, age-standardised rates have declined in all world regions, according to the GBD 2016 Stroke Collaborators.[4] However, the study also highlighted key challenges with interpretation of risk factor estimates in GBD. The population attributable fraction explained by the examined stroke risk factors added up to more

than 100%.[4] The calculations are based on important assumptions. And even removal of all the reported risk factors will not prevent all cases of stroke. However, huge potential still exists for prevention of this serious disorder.[9] Many neurological disorders often coexist with other serious chronic diseases such as atherosclerosis, diabetes, kidney disease, and cancer.

The prevalence of neurological disorders will increase in the coming decades, because of the growth and ageing of the world population. Because few neurological diseases can be cured, preventive efforts need to be improved.

The GBD project is an important resource for health-care planning and resource allocation. It also provides key information on worldwide variation in occurrence of neurological disorders. The huge global variation in these disorders reflects the methodological challenges, as well as variations in occurrence of underlying environmental, lifestyle, social, and genetic risk factors. In addition to prevalence studies on the burden of neurological disorders, more analytical studies of potential risk factors are urgently needed to create opportunities for preventing these devastating diseases.

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I declare no competing interests.

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Recovery from brain injury: a surprising new drug target

Although treatment for patients with acute stroke has been greatly advanced by interventions that restore blood flow through blocked arteries, no treatments exist to enhance the brain's recovery of lost function due to the injury. The same is true for individuals who survive traumatic brain injury. Now, however, surprising findings of a study published in February, 2019,[1] suggest that a therapy originally developed to treat HIV infection might also enhance recovery after brain injury.

Because the brain is the most plastic organ in a human being, it seems intuitive that molecular and cellular mechanisms involved in synaptic plasticity might be important for its repair. Indeed, spontaneous behavioural recovery occurs in parallel with reorganisation of neuronal circuits (or remapping), which can then support functions lost after brain injury. At the foundation of the investigators' approach was recognition that common molecular mechanisms are shared between brain repair and the processes of learning and memory. Driven by the observation that inhibition of C-C chemokine receptor type 5 (CCR5) signalling enhances learning, memory, and plasticity in hippocampal and cortical circuits,[2] the investigators tested the hypothesis that CCR5 signalling might have a role in the recovery of brain function following stroke or traumatic brain injury.

Under physiological conditions in humans, CCR5 is expressed in microglia but following stroke CCR5 expression is substantially upregulated in neurons. The investigators show that selectively reducing (or knocking down) gene expression of CCR5 in mouse neurons of the premotor cortex several days after an induced focal stroke in the motor cortex accelerated and enhanced behavioural recovery. These behavioural changes occurred in parallel with structural and physiological changes associated with synaptic plasticity, including the preservation of peri-infarct dendritic spines and the upregulation of a cascade of molecular messengers that are important in synaptogenesis.

Although these investigators used knockdown experiments to elucidate the role of CCR5 in mouse models of stroke, Joy and colleagues have turned to genetics to replicate these experiments in humans. Genetic variation,