

- 1 GD 2016 Meningitis Collaborators. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; **17**: 1061–82.
- 2 GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol* 2017; **16**: 877–97.
- 3 Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1151–210.
- 4 Tartof S, Cohn A, Tarbangdo F, et al. Identifying optimal vaccination strategies for serogroup A *Neisseria meningitidis* conjugate vaccine in the African meningitis belt. *PLoS One* 2013; **8**: e63605.
- 5 Trotter CL, Lingani C, Fernandez K, et al. Impact of MenAfriVac in nine countries of the African meningitis belt, 2010–15: an analysis of surveillance data. *Lancet Infect Dis* 2017; **17**: 867–72.



Global burden of motor neuron diseases: mind the gaps



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According to the International Classification of Diseases ninth (ICD-9) and tenth (ICD-10) editions, the category of motor neuron diseases comprises amyotrophic lateral sclerosis, progressive muscular atrophy, primary lateral sclerosis, progressive bulbar palsy, spinal muscular atrophy, and hereditary spastic paraparesis. Spinal muscular atrophy and hereditary spastic paraparesis have a genetic basis, whereas amyotrophic lateral sclerosis, progressive bulbar disease, and primary lateral sclerosis, all of which are adult forms of motor neuron disease, have both familial and sporadic forms. Spinal muscular atrophy is a disease of infancy and childhood, hereditary spastic paraparesis often presents in childhood, and the remaining forms of motor neuron disease occur mostly in people aged older than 50 years. All motor neuron diseases are rare (rare diseases are defined by a prevalence of <1 per 2000 population in Europe),¹ and obtaining sufficient data to generate a global burden for all motor neuron diseases is challenging. By systematic analysis of all available data between 1990 and 2016, from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016 now reported in *The Lancet Neurology*, the GBD 2016 Motor Neuron Disease Collaborators have provided the first report of the burden of motor neuron diseases for 195 countries and territories.²

Calculating the burden of motor neuron disease for European populations is straightforward. European population-based registers report consistent incidence rates (2–3 per 100 000 person-years) of amyotrophic lateral sclerosis.³ Population-based data for individuals of non-European descent are sparse, but incidence rates might be lower in Asia (0.7–0.8 per 100 000 person-years) than European populations.⁴ The incidence of spinal muscular atrophy varies across populations. This variation is most probably a function of different carrier

rates of the disease-causing variants of the *SMN* gene across different ancestral populations,⁵ whereas the reasons for the geographic variations in incidence of amyotrophic lateral sclerosis are unclear.

Amyotrophic lateral sclerosis is a complex genetic disorder, and analysis of data from population-based registers suggests that disease pathogenesis is a six-step process.⁶ The number of steps is reduced for people carrying a known disease-causing variant, such as a hexanucleotide expansion in *C9orf72* or a pathogenic mutation in *SOD1*.⁷ The frequencies of these mutations vary across ancestral populations, but this variability does not fully account for the non-uniform geographical distribution, as known familial amyotrophic lateral sclerosis accounts for only 10–15% of all cases.⁸ Being of mixed ancestry might be protective in sporadic disease, as a population-based study of mortality in Cuba revealed rates that were lower in the mixed population (0.55 per 100 000 person-years) compared with those primarily of Spanish or African origin (about 0.9 per 100 000 person-years).⁹

Using all available data, the GBD team have now estimated the years of life lost (YLLs), years of life lived with disability (YLDs), and disability-adjusted life-years (DALYs) associated with motor neuron diseases. The number of people with motor neuron diseases is increasing, but this is mostly attributable to population ageing.¹ The burden of motor neuron diseases is mainly attributable to amyotrophic lateral sclerosis, and is highest in countries with high Socio-demographic Index (SDI; a composite measure of income per capita, education, and fertility), including countries in high-income North America, Australasia, and western Europe; this finding is unsurprising because health services are well developed and provide high standards of clinical care. Age-standardised incidence rates of motor neuron

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disease are lower in high-income Asia Pacific and because of this, the burden of motor neuron disease is lower in countries in this region than in others with high SDI levels. These findings suggest that causative factors other than sociodemographic development are likely to be responsible for geographic variation in incidence and burden of disease. The geographic variation in disease burden could not be explained by the risk factors available for quantification by the GBD methods, suggesting that additional factors, including ancestral origin and genetic background, might be important in determining risk.

By deconstructing the subscales of the amyotrophic lateral sclerosis functional rating scale using a large clinical dataset for amyotrophic lateral sclerosis, the GBD 2016 Motor Neuron Disease Collaborators provide a useful approach for establishing global disability burden and a baseline from which to measure the economic impact of progressive motor decline. However, because this system classifies motor neuron diseases purely on the basis of motor system degeneration, and because we do not yet have a way to capture the extra-motor domains associated with amyotrophic lateral sclerosis reliably, the study could not establish the additional global burden associated with the 50% of patients who develop cognitive and behavioural impairment, and the 13% of patients with amyotrophic lateral sclerosis who have concomitant behavioural variant frontotemporal dementia.¹⁰ Furthermore, the work relies on incomplete data that were generated between 1996 and 2016—a period that saw growth in our understanding of the wider phenotypes associated with motor neuron diseases, affecting patient ascertainment and disease characterisation.¹¹ This increased understanding is particularly true of the cognitive and behavioural aspects of amyotrophic lateral sclerosis, which are now more widely recognised than at the start of the study period.

Notwithstanding these limitations, this report of the global burden of motor neuron diseases is an important first step in defining the societal impact of these conditions. The study provides a useful framework within which the global impact of these diseases can be examined, and shows the substantial gaps in our knowledge, particularly relating to understudied populations of non-European or mixed ancestry.

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- 1 European Commission. Non-communicable diseases. https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en (accessed Oct 17, 2018).
- 2 GBD 2016 Motor Neuron Disease Collaborators. Global, regional, and national burden of motor neuron disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; published online Nov 5. [http://dx.doi.org/10.1016/S1474-4422\(18\)30404-6](http://dx.doi.org/10.1016/S1474-4422(18)30404-6).
- 3 Logroscino G, Traynor BJ, Hardiman O, et al. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry* 2010; **81**: 385–90.
- 4 Chiò A, Logroscino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology* 2013; **41**: 118–30.
- 5 Verhaart IEC, Robertson A, Wilson JJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy—a literature review. *Orphanet J Rare Dis* 2017; **12**: 124.
- 6 Al-Chalabi A, Calvo A, Chio A, et al. Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. *Lancet Neurol* 2014; **13**: 1108–13.
- 7 Chiò A, Mazzini L, D'Alfonso S, et al. The multistep hypothesis of ALS revisited: the role of genetic mutations. *Neurology* 2018; **91**: e635–42.
- 8 Ryan M, Heverin M, Doherty MA, et al. Determining the incidence of familiarity in ALS: a study of temporal trends in Ireland from 1994 to 2016. *Neurol Genet* 2018; **4**: e239.
- 9 Zaldivar T, Gutierrez J, Lara G, Carbonara M, Logroscino G, Hardiman O. Reduced frequency of ALS in an ethnically mixed population: a population-based mortality study. *Neurology* 2009; **72**: 1640–45.
- 10 Phukan J, Elamin M, Bede P, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry* 2012; **83**: 102–18.
- 11 Hardiman O, Al-Chalabi A, Brayne C, et al. The changing picture of amyotrophic lateral sclerosis: lessons from European registers. *J Neurol Neurosurg Psychiatry* 2017; **88**: 557–63.