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

GBD 2016 Motor Neuron Disease Collaborators*

Summary

Background Understanding how prevalence, incidence, and mortality of motor neuron diseases change over time and by location is crucial for understanding the causes of these disorders and for health-care planning. Our aim was to produce estimates of incidence, prevalence, and disability-adjusted life-years (DALYs) for motor neuron diseases for 195 countries and territories from 1990 to 2016 as part of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016.

Methods The motor neuron diseases included in this study were amyotrophic lateral sclerosis, spinal muscular atrophy, hereditary spastic paraplegia, primary lateral sclerosis, progressive muscular atrophy, and pseudobulbar palsy. Incidence, prevalence, and DALYs were estimated using a Bayesian meta-regression model. We analysed 14165 site-years of vital registration cause of death data using the GBD 2016 cause of death ensemble model. The 84 risk factors quantified in GBD 2016 were tested for an association with incidence or death from motor neuron diseases. We also explored the relationship between Socio-demographic Index (SDI; a compound measure of income per capita, education, and fertility) and age-standardised DALYs of motor neuron diseases.

Findings In 2016, globally, 330 918 (95% uncertainty interval [UI] 299 522–367 254) individuals had a motor neuron disease. Motor neuron diseases have caused 926 090 (881 566–961 758) DALYs and 34 325 (33 051–35 364) deaths in 2016. The worldwide all-age prevalence was 4·5 (4·1–5·0) per 100 000 people, with an increase in age-standardised prevalence of 4·5% (3·4–5·7) over the study period. The all-age incidence was 0·78 (95% UI 0·71–0·86) per 100 000 person-years. No risk factor analysed in GBD showed an association with motor neuron disease incidence. The largest age-standardised prevalence was in high SDI regions: high-income North America (16·8, 95% UI 15·8–16·9), Australasia (14·7, 13·5–16·1), and western Europe (12·9, 11·7–14·1). However, the prevalence and incidence were lower than expected based on SDI in high-income Asia Pacific.

Interpretation Motor neuron diseases have low prevalence and incidence, but cause severe disability with a high fatality rate. Incidence of motor neuron diseases has geographical heterogeneity, which is not explained by any risk factors quantified in GBD, suggesting other unmeasured risk factors might have a role. Between 1990 and 2016, the burden of motor neuron diseases has increased substantially. The estimates presented here, as well as future estimates based on data from a greater number of countries, will be important in the planning of services for people with motor neuron diseases worldwide.

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Introduction

Motor neuron diseases are a group of neurodegenerative disorders related to upper and lower motor neuron degeneration, including amyotrophic lateral sclerosis, spinal muscular atrophy, hereditary spastic paraplegia, primary lateral sclerosis, progressive muscular atrophy, and pseudobulbar palsy. Amyotrophic lateral sclerosis, the most common motor neuron disease, is clinically characterised by extensive paralysis leading to death generally by respiratory failure, with 50% of patients dying within 15–20 months after diagnosis.1,3

Although spinal muscular atrophy and hereditary spastic paraplegia are known to have a genetic basis, the causes of other motor neuron diseases remain unknown, but are postulated to combine environmental and genetic factors.1,4 Genetic variants have been associated with amyotrophic lateral sclerosis,1 whereas the contribution of environmental factors, with the possible exception of smoking,1,5 is still not clear because of the difficulties in assessment of potential risk factors retrospectively in case-control studies.

Previous reviews and meta-analyses using a worldwide approach to study amyotrophic lateral sclerosis reported a median prevalence of 4·48 per 100 000 (IQR 3·03–6·70)7 and a standardised incidence rate of 1·68 per 100 000 person-years (95% CI 1·50–1·85)8 that varied with geography, sex, and age.9 Amyotrophic lateral sclerosis is rare before age 50 years, with peak incidence...
Motor neuron diseases are a group of rare neurodegenerative disorders (amyotrophic lateral sclerosis, spinal muscular atrophy, hereditary spastic paraplegia, primary lateral sclerosis, progressive muscular atrophy, and pseudobulbar palsy) that are fatal in 50% of affected people within 15 to 20 months after diagnosis. Previous epidemiological studies of motor neuron diseases showed large geographical variations in incidence, but no data on motor neuron disease incidence existed for most countries. We did a systematic review of prevalence, incidence, and mortality risk in PubMed for articles published in English from Jan 1, 1990, to Dec 31, 2015; In the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), systematic reviews for motor neuron diseases are done every 3 years, with new sources suggested by GBD collaborators included in each round of estimates. The search terms were: ("motor neuron disease"[MeSH Terms] OR ("motor"[All Fields] AND "neuron"[All Fields] AND "disease"[All Fields]) OR "motor neuron disease"[All Fields] OR ("motor"[All Fields] AND "neuron"[All Fields] AND "diseases"[All Fields]) OR "motor neuron diseases"[All Fields] OR ("amyotrophic lateral sclerosis"[MeSH Terms] OR ("amyotrophic"[All Fields] AND "neuron"[All Fields] AND "disease"[All Fields]) OR "amyotrophic lateral sclerosis"[All Fields]) OR ALS[All Fields] OR ("motor neuron disease"[MeSH Terms] OR ("motor"[All Fields] AND "neuron"[All Fields] AND "disease"[All Fields]) OR "motor neuron disease"[All Fields] OR ("primary"[All Fields] AND "lateral"[All Fields] AND "disease"[All Fields]) OR ("primary lateral sclerosis"[All Fields]) OR ("PLS"[Journal] OR "pls"[All Fields]) OR ("muscular atrophy, spinal"[MeSH Terms] OR ("muscular"[All Fields] AND "atrophy"[All Fields] AND "spinal"[All Fields]) OR "spinal muscular atrophy"[All Fields] OR ("progressive"[All Fields] AND "muscular"[All Fields] AND "atrophy"[All Fields]) OR ("pseudobulbar"[MeSH Terms] OR ("pseudobulbar"[All Fields] AND “palsy”[All Fields] OR "pseudobulbar palsy"[All Fields]) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms] OR "population-based"[All Fields]).

Evidence before this study
Motor neuron diseases are a group of rare neurodegenerative disorders (amyotrophic lateral sclerosis, spinal muscular atrophy, hereditary spastic paraplegia, primary lateral sclerosis, progressive muscular atrophy, and pseudobulbar palsy) that are fatal in 50% of affected people within 15 to 20 months after diagnosis. Previous epidemiological studies of motor neuron diseases showed large geographical variations in incidence, but no data on motor neuron disease incidence existed for most countries. We did a systematic review of prevalence, incidence, and mortality risk in PubMed for articles published in English from Jan 1, 1990, to Dec 31, 2015; In the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), systematic reviews for motor neuron diseases are done every 3 years, with new sources suggested by GBD collaborators included in each round of estimates. The search terms were: ("motor neuron disease"[MeSH Terms] OR ("motor"[All Fields] AND "neuron"[All Fields] AND "disease"[All Fields]) OR "motor neuron disease"[All Fields] OR ("motor"[All Fields] AND "neuron"[All Fields] AND "diseases"[All Fields]) OR "motor neuron diseases"[All Fields] OR ("amyotrophic lateral sclerosis"[MeSH Terms] OR ("amyotrophic"[All Fields] AND "neuron"[All Fields] AND "disease"[All Fields]) OR "amyotrophic lateral sclerosis"[All Fields]) OR ALS[All Fields] OR ("motor neuron disease"[MeSH Terms] OR ("motor"[All Fields] AND "neuron"[All Fields] AND "disease"[All Fields]) OR "motor neuron disease"[All Fields] OR ("primary"[All Fields] AND "lateral"[All Fields] AND "disease"[All Fields]) OR ("primary lateral sclerosis"[All Fields]) OR ("PLS"[Journal] OR "pls"[All Fields]) OR ("muscular atrophy, spinal"[MeSH Terms] OR ("muscular"[All Fields] AND "atrophy"[All Fields] AND "spinal"[All Fields]) OR "spinal muscular atrophy"[All Fields] OR ("progressive"[All Fields] AND "muscular"[All Fields] AND "atrophy"[All Fields]) OR ("pseudobulbar"[MeSH Terms] OR ("pseudobulbar"[All Fields] AND “palsy”[All Fields] OR "pseudobulbar palsy"[All Fields]) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms] OR "population-based"[All Fields]).

Added value of this study
This is the first concerted effort to make the methods and results of GBD accessible to clinicians and researchers with an interest in motor neuron disease. We show that the burden of motor neuron disease is highest in countries with a high Socio-demographic Index (SDI), a measure of country social development based on education, income, and fertility), especially high-income North America, western Europe, and Australasia, but not in high-income Asia Pacific. We show that age-standardised incidence rates of motor neuron diseases vary within each SDI level, suggesting that causative factors other than sociodemographic development are responsible for the geographical variation in disease occurrence. We also show that the geographical heterogeneity of motor neuron disease burden is not explained by any of the 84 risk factors quantified in GBD, suggesting a role of unmeasured risk factors.

Implication of all the available evidence
The burden of motor neuron diseases is currently greatest in high-income countries and this burden is increasing because of population ageing. Small increases in age-standardised incidence and prevalence rates occurred between 1990 and 2016, but we report larger increases in counts because of population ageing and population growth. Despite the absence of a cure for motor neuron diseases, these findings are important to health service planning as the care of patients with motor neuron disease is intensive and expensive. Additional research into the causes of motor neuron disease is needed.

Methods
Overview
General methods used in GBD 2016 are reported in the appendix. Specific methods relevant to the estimation of motor neuron disease burden are described here. Motor neuron diseases included in this analysis were amyotrophic lateral sclerosis, spinal muscular atrophy, hereditary spastic paraplegia, primary lateral sclerosis, progressive muscular atrophy, and pseudobulbar palsy. We analysed

geographical location. Our study considers motor neuron diseases across the whole age spectrum including spinal muscular atrophy, a rare disorder in the first years of life affecting proximal limbs and respiratory muscles. The relationships between motor neuron disease burden and country development level, as measured by the Socio-demographic Index (SDI), a composite measure of income per capita, years of schooling, and total fertility rate, were also analysed.

Methods
Overview
General methods used in GBD 2016 are reported in the appendix. Specific methods relevant to the estimation of motor neuron disease burden are described here. Motor neuron diseases included in this analysis were amyotrophic lateral sclerosis, spinal muscular atrophy, hereditary spastic paraplegia, primary lateral sclerosis, progressive muscular atrophy, and pseudobulbar palsy. We analysed
motor neuron diseases across all ages, and included motor neuron disease with a strong genetic component with high prevalence in the early years of life.

Mortality
The International Classification of Diseases ninth edition (ICD-9) code for motor neuron diseases is 335 and the ICD-10 code is G12. Mortality from motor neuron diseases was modelled by use of CODEm, the cause of death ensemble model used throughout GBD. The model used 14165 site-years of data—ie, a combination of location and calendar year—as well as predictive covariates on asbestos production, mean serum cholesterol, fruit consumption, average latitude, proportion of the population with access to sanitation, proportion of the population with access to clean water, health-care access and quality, education, log-transformed lag-distributed income, and SDI. Predictive covariates in our cause of death analytical tool, CODEm, are based on literature review of factors that have been found to be associated with a disease of interest without necessarily having sufficient evidence for a causal relationship. CODEm is designed to choose the set of covariates that best predicts mortality rates given the available data from vital registrations and verbal autopsy studies.

Non-fatal disease modelling
The El Escorial Criteria were used as the reference diagnostic criteria for amyotrophic lateral sclerosis. Spinal muscular atrophy cases defined by ICD codes were also included. Data from administrative health records reporting by ICD codes were also included. We identified 55 sources through our systematic literature review, including 47 sources on incidence, covering seven of the 21 world regions, and eight sources on prevalence, covering five of the 21 world regions (appendix). We also added 3 years (2000, 2010, and 2012) of US medical claims data. There were no data for southeast Asia, Oceania, central Asia, eastern Europe, Australasia, the Caribbean, Andean Latin America, central Latin America, south Asia, central sub-Saharan Africa, southern sub-Saharan Africa, and western sub-Saharan Africa. Where data points spanned age ranges greater than 20 years, we split the data into 5-year age bands using the age pattern of the USA, where we had the most detailed motor neuron disease data by age.

We used DisMod-MR 2.1, the Bayesian meta-regression modelling tool developed for GBD, to generate results that were consistent with the available data on prevalence and incidence, as well as with our estimates for mortality due to motor neuron diseases. In the model, we included a setting of no remission (ie, no cure). We used DisMod-MR 2.1 to adjust for systematic bias in the first 2 years of US claims data, because the data for 2000 and 2010 were systematically lower than the data for 2012. Additionally, we included the absolute value of latitude, as a country-level predictor on prevalence, and included national income, with a built-in short lag, as a country-level predictor on excess mortality rate.

Motor neuron disease severity and YLDs
To identify the different health consequences of motor neuron diseases, we analysed data from the largest amyotrophic lateral sclerosis clinical database with a total of 8635 patient records: the Pooled Resource Open-access ALS Clinical Trials (PRO-ACT). These data were compiled by the PRO-ACT Consortium, which is a collaboration between Prize4Life and the Northeast ALS Consortium, with funding from the ALS Therapy Alliance. The data available in the PRO-ACT database have been volunteered by PRO-ACT Consortium members. We used records with complete information on the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R; n=4838) and selected only the observation at enrolment into a trial to eliminate potential bias from treatment effects.

We used the ALSFRS-R to establish the severity distribution of three symptom domains: motor impairment, respiratory problems, and speech impairment. Motor impairment of the legs was assessed by two questions, and we mapped a combined score of 8 to a state of no impairment, 5–7 to mild impairment, 2–4 to moderate impairment, and 0–1 to severe impairment. Three additional questions assessed fine motor impairment, and a combined score of 12 corresponded to no impairment, 9–11 to mild impairment, 3–8 to moderate impairment, and 0–2 to severe impairment. To summarise total motor impairment, we took the more severe of the two rankings. Respiratory problems were assessed by one question, and a score of 4 indicated no impairment, 3 indicated mild impairment, 2 indicated moderate impairment, and 0–1 indicated severe impairment. Finally, there was one question on speech impairment, and we mapped a score of 4 to no impairment, and any other score to an impaired state.

After establishing the severity status, we estimated the relative proportions of each of the 29 combinations of the different levels on the three domains. To derive combined disability weights for each impairment combination, which constitute the different potential health outcomes of motor neuron disease, we used a multiplicative aggregation formula.

DALYs
The proportions from the ALSFRS-R analysis were applied to the prevalence estimates derived from DisMod-MR 2.1, and the prevalence of each long-term outcome was multiplied by the combined disability weights to get uncorrected YLDs. The initial YLD estimates were adjusted for comorbidity by use of the comorbidity simulation across all causes included in GBD 2016. We calculated YLLs by multiplying the...
number of deaths in each age group by the remaining life expectancy derived from the GBD standard life table (appendix). DALYs were then calculated by summing YLLs and YLDs.

Uncertainty was propagated by sampling 1000 draws at each computational step, which allowed for the combination of uncertainty from different sources, including input data, data processing steps, and residual non-sampling error. Uncertainty intervals (UIs) were defined as the 25th and 975th values of the ordered draws and were used to define significant change over time. This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations (appendix).

Risk factors
In GBD 2016, the contribution of 84 risks and combinations of risks to disease burden was quantified. Criteria for inclusion of risks into GBD include: the size beyond the populations included in epidemiological studies; availability of sufficient data and methods to enable estimation of exposure levels by country; and the probable importance of a risk factor to disease burden or policy considerations.

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

Results
All results presented in this paper can be found in the GBD 2016 online results tool, with all estimates from 1990 to 2016 for all world regions. The same results can also be explored by use of the GBD 2016 data visualisation tool.

In 2016, 330,918 (95% UI 299,522–367,254) individuals worldwide had a motor neuron disease: 161,901 (48.9%) in high SDI, 50,286 (15.2%) in high-middle SDI, 70,924 (21.4%) in middle SDI, 38,873 (11.8%) in low-middle SDI, and 8,545 (2.6%) in low SDI countries (table). The all-age global prevalence was 4.5 (4.1–5.0) per 100,000 population. Globally, we estimated there to be 57,452 (52,522–63,242) incident cases of a motor neuron disease, and all-age global incidence of motor neuron disease to be 0.78 (0.71–0.86) per 100,000 person-years. We estimated there to be 34,325 (33,051–35,364) motor neuron disease-related deaths (table), with an all-age cause-specific mortality rate of 0.46 (0.45–0.48) per 100,000 person-years. Motor neuron diseases caused 926,090 (881,566–961,758) DALYs (table; age-standardised DALYs rate 13.2, 12.5–13.7), of which 70,165 (49,321–93,203) were YLDs (age-standardised rate 1.0, 0.7–1.3) and 855,924 (819,373–883,289) were YLLs (age-standardised rate 12.2, 11.6–12.6).

From 1990 to 2016, the worldwide age-standardised mortality rates of motor neuron disease increased by 8.0% (95% UI 0.1–1.2 to 12.2; table). A statistically significant increase in age-standardised mortality was present across all SDI quintiles, except for the low SDI group. Globally, the age-standardised prevalence of motor neuron disease increased by 4.5% (3.4–5.7; table) while the all-age prevalence increased by 18.8% (15.28 to 22.21). A map of age-standardised prevalence of motor neuron disease in each country for both sexes is shown in figure 1. Age-standardised prevalence increased in low SDI, low-middle SDI, middle SDI, high-middle SDI, and high SDI quintiles (table). The age-standardised incidence of motor neuron disease was stable in all SDI groups, except for the high SDI quintile where incidence increased by 13.0% (11.9 to 14.1) from 1.60 to 1.81 per 100,000 population (see the GBD 2016 online results tool). No statistically significant change was found in the global age-standardised DALY rate of motor neuron diseases (–1.5%, –9.3 to 2.9; table).

Considering 21 GBD regions, in 2016, the highest all-age prevalence was observed in high-income North America (20.2, 95% UI 19.0–21.5), followed by Australasia (17.7, 16.2–19.2) and western Europe (16.7, 15.3–18.1). The lowest all-age prevalence was in sub-Saharan Africa, especially in central sub-Saharan Africa (0.9, 0.8–1.1), followed by eastern sub-Saharan Africa (1.0, 0.8–1.1) and western sub-Saharan Africa (1.0, 0.9–1.2). Only a small proportion of these geographical differences in the prevalence can be explained by a different age structure of the countries: in 2016, age-standardised prevalence per 100,000 population ranged from a high of 22.6 (20.9–24.7) in Canada to a low of 1.1 (0.9–1.2) in the Central African Republic. Among regions with high SDI values, age-standardised prevalence per 100,000 population was lowest in high-income Asia Pacific, southern Latin America, eastern Europe and central Europe (figure 1). Age-standardised prevalence per 100,000 population was 16.8 (15.8–17.9) in high-income North America, 14.7 (13.5–16.1) in Australasia, 12.9 (11.7–14.1) in western Europe, 1.2 (1.1–1.4) in central sub-Saharan Africa, 1.3 (1.1–1.4) in eastern sub-Saharan Africa, and 1.3 (1.2–1.5) in western sub-Saharan Africa. Half of the world’s prevalent cases resided in countries in the highest SDI quintile, most of whom were living in high-income North America and western Europe (table).

The prevalence ranking was generally consistent with that of incidence (see the GBD 2016 online results tool). The highest age-standardised incidence per 100,000 person-years was in Australasia with 2.77 (2.63 to 2.91), followed by high-income North America with 2.30 (2.20 to 2.41) and western Europe with 2.00 (1.89 to 2.11). The lowest age-standardised incidence
| Country          | Death counts (95% CI) | Percentage change in age-standardised rates, 1990–2016 |
|------------------|-----------------------|------------------------------------------------------|
| Global           | 34,325 (33,051 to 35,364) | 8.0% (0.9 to 12.2) |
| High SDI         | 21,162 (20,081 to 22,480) | 14.1% (5.3 to 21.9) |
| High-middle SDI  | 472 (439 to 507) | 20.7% (9.9 to 31.8) |
| Middle SDI       | 518 (494 to 542) | 22.7% (9.7 to 36.0) |
| Low-middle SDI   | 281 (245 to 311) | 36.7% (11.7 to 57.3) |
| Low SDI          | 443 (382 to 620) | 20.2% (–1.8 to 41.9) |
| High-income North America | 18,952 (18,226 to 19,680) | 27.2% (19.7 to 32.8) |
| Canada           | 9,595 (8,73 to 10,545) | 20.8% (6.8 to 33.6) |
| Greenland        | 0 (0 to 0) | 3.3% (–2.4 to 6.4) |
| USA              | 7,632 (7,315 to 7,902) | 27.9% (20.9 to 34.0) |
| Australasia      | 850 (776 to 925) | 20.0% (6.0 to 32.9) |
| Australia        | 711 (643 to 779) | 21.9% (6.8 to 36.3) |
| New Zealand      | 139 (122 to 157) | 10.8% (5.0 to 26.5) |
| High-income Asia-Pacific | 19,195 (17,377 to 20,755) | –9.2% (–15.6 to –2.9) |
| Brunei           | 1 (0 to 1) | 7.3% (–2.4 to 41.3) |
| Japan            | 17,965 (16,560 to 19,372) | –2.5% (–10.2 to 4.5) |
| Singapore        | 23 (19 to 29) | 9.9% (–14.2 to 39.2) |
| South Korea      | 100 (72 to 130) | –33.9% (–55.6 to –8.1) |
| Western Europe   | 10,367 (9,723 to 10,988) | 15.2% (3.6 to 22.1) |
| Andorra          | 2 (2 to 3) | 13.2% (–15.4 to 52.2) |
| Austria          | 152 (136 to 168) | 36.8% (20.9 to 54.1) |
| Belgium          | 263 (232 to 293) | 24.8% (6.5 to 41.7) |
| Cyprus           | 13 (11 to 14) | –15.4% (–47.4 to 2.4) |
| Denmark          | 134 (114 to 156) | –15.4% (–29.5 to 0.4) |
| Finland          | 183 (159 to 204) | –23.8% (–38.3 to –9.3) |
| France           | 1557 (1408 to 1707) | 5.0% (–5.7 to 17.7) |
| Germany          | 19,111 (16,968 to 21,299) | 1.3% (–16.3 to 19.9) |
| Greece           | 111 (95 to 124) | 156.3% (104.4 to 202.3) |
| Iceland          | 8 (7 to 9) | 23.7% (5.9 to 41.6) |
| Ireland          | 120 (104 to 138) | 24.7% (4.4 to 47.8) |
| Israel           | 73 (59 to 89) | –23.2% (–43.1 to –0.9) |
| Italy            | 1,418 (1,270 to 1,570) | 35.8% (18.6 to 54.5) |
| Luxembourg       | 9 (8 to 10) | 4.4% (–11.4 to 20.3) |
| Malta            | 8 (7 to 10) | 14.5% (–5.9 to 40.8) |
| Netherlands      | 494 (444 to 554) | 7.8% (–7.9 to 22.8) |
| Norway           | 124 (107 to 141) | 1.9% (–13.2 to 18.0) |
| Portugal         | 185 (166 to 205) | 9.5% (7.0 to 12.4) |
| Spain            | 905 (891 to 919) | 41.1% (25.9 to 56.8) |
| Sweden           | 304 (266 to 344) | 35.9% (15.5 to 55.5) |
| Switzerland      | 184 (143 to 233) | –7.4% (–31.0 to 22.2) |
| United Kingdom   | 2,199 (2,075 to 2,281) | 23.8% (15.5 to 39.3) |
| Argentina        | 279 (247 to 309) | 29.2% (4.0 to 48.4) |
| Chile            | 152 (116 to 192) | 4.7% (–2.6 to 41.0) |
| Uruguay          | 47 (42 to 51) | –1.5% (–15.5 to 12.7) |

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| Region                  | Deaths 2016 counts | Percentage change in age-standardised rates, 1990–2016 | Prevalence 2016 counts | Percentage change in age-standardised rates, 1990–2016 | DALYs 2016 counts | Percentage change in age-standardised rates, 1990–2016 |
|-------------------------|---------------------|-------------------------------------------------------|------------------------|-------------------------------------------------------|------------------|-------------------------------------------------------|
| Eastern Europe          |                     |                                                       |                        |                                                       |                  |                                                       |
| Belarus                 | 270 (583 to 909)    | 36.1% (6.0 to 72.7)                                   | 6497 (5784 to 7141)    | 3.2% (0.3 to 6.0)                                     | 21,974 (17,757 to 27,107) | 24.3% (0.7 to 54.7)                                   |
| Bulgaria                | 17 (14 to 20)       | –28.5% (–42.5 to –13.1)                               | 245 (216 to 277)       | –4.5% (–9.1 to 0.1)                                   | 493 (414 to 580) | –40.9% (–51.5 to –28.6)                               |
| Malta                   | 6 (5 to 7)          | 22.5% (–14.0 to 23.0)                                 | 128 (114 to 145)       | 10.5% (5.1 to 16.8)                                   | 373 (317 to 439) | 16.6% (–9.6 to 46.4)                                  |
| Algeria                 | 11 (13 to 15)       | 30.9% (8.8 to 53.1)                                   | 115 (101 to 131)       | 9.1% (3.4 to 15.2)                                    | 240 (210 to 272) | 6.5% (–10.2 to 22.7)                                 |
| Andorra                 | 1 (1 to 2)          | 50.0% (0.0 to 100.0)                                  | 115 (101 to 131)       | 9.1% (3.4 to 15.2)                                    | 240 (210 to 272) | 6.5% (–10.2 to 22.7)                                 |
| (Table continues on next page)
| Country                        | Deaths 2016 counts | Prevalence | DALYs 2016 counts |
|-------------------------------|-------------------|-----------|-----------------|
|                              | (1990–2016)       | (1990–2016) | (1990–2016)     |
|                              | Percentage change | Percentage change | Percentage change |
|                              | in age-standardised rates | in age-standardised rates | in age-standardised rates |
|                              | (%)               | (%)       | (%)             |
| Caribbean                     |                   |           |                 |
|                               |                   |           |                 |
| Antigua and Barbuda           | 0 (0 to 0)        | 3 (1 to 3) | 7 (6 to 8)      |
| The Bahamas                   | 2 (2 to 2)        | 14 (13 to 16) | 59 (51 to 69) |
| Barbados                      | 4 (3 to 4)        | 14 (13 to 15) | 95 (84 to 107) |
| Belize                        | 1 (1 to 1)        | 10 (9 to 11) | 33 (25 to 43)  |
| Bermuda                       | 0 (0 to 0)        | 3 (1 to 4)  | 11 (8 to 13)   |
| Curaçao                       | 91 (81 to 101)    | 502 (449 to 559) | 2500 (2228 to 2769) |
| Dominica                      | 1 (1 to 0)        | 3 (2 to 3)  | 16 (14 to 19)  |
| Dominican Republic            | 16 (13 to 20)     | 303 (268 to 344) | 529 (428 to 631) |
| Grenada                       | 1 (1 to 0)        | 3 (3 to 4)  | 16 (13 to 19)  |
| Guyana                        | 2 (2 to 3)        | 18 (16 to 21) | 72 (59 to 86)  |
| Haiti                         | 23 (16 to 31)     | 225 (196 to 260) | 957 (633 to 1391) |
| Saint Lucia                   | 21 (20 to 22)     | 156 (141 to 174) | 636 (555 to 709) |
| Saint Vincent and the Grenadines | 1 (1 to 0)      | 4 (3 to 4)  | 19 (17 to 21)  |
| Suriname                      | 2 (2 to 2)        | 15 (13 to 17) | 65 (56 to 75)  |
| Trinidad and Tobago           | 7 (6 to 7)        | 46 (41 to 52) | 197 (173 to 221) |
| Virgin Islands                | 2 (1 to 2)        | 6 (6 to 7)  | 39 (32 to 46)  |
| Tropical Latin America        |                   |           |                 |
|                               |                   |           |                 |
| Brazil                        | 1132 (1051 to 1197) | 7919 (6994 to 9132) | 32909 (3085 to 34846) |
| Paraguay                      | 23 (19 to 26)     | 206 (184 to 233) | 723 (650 to 834) |
| East Asia                     | 3097 (2956 to 3234) | 56466 (48633 to 65987) | 111827 (104988 to 118511) |
|                               | -1.3% (1.2 to 16.3) | 18.2% (15.3 to 20.9) | -11.6% (-22.7 to 13.2) |
| China                         | 2988 (2839 to 3122) | 54405 (46781 to 61692) | 107731 (100956 to 114351) |
| North Korea                   | 60 (43 to 96)     | 955 (847 to 1088) | 2477 (1814 to 3998) |
| Taiwan (province of China)    | 49 (40 to 57)     | 1104 (982 to 1253) | 1619 (1342 to 1882) |
| Southeast Asia                | 903 (770 to 997)  | 16378 (14345 to 18910) | 33240 (28726 to 36864) |
|                               | 25.2% (0 to 37.0) | 10.4% (9.2 to 11.6) | 10.5% (-5.9 to 20.4) |
|                               |                   |           |                 |
| Cambodia                      | 15 (11 to 19)     | 316 (278 to 362) | 622 (452 to 783) |
| Indonesia                     | 325 (232 to 397)  | 6151 (5192 to 7307) | 12962 (10905 to 15281) |
| Laos                          | 7 (5 to 10)       | 142 (124 to 163) | 390 (242 to 562) |
| Malaysia                      | 43 (33 to 49)     | 814 (722 to 925) | 1541 (1236 to 1781) |
| Maldives                      | 0 (0 to 0)        | 8 (7 to 10)  | 13 (11 to 16)  |
| Mauritius                     | 3 (2 to 4)        | 41 (37 to 47) | 103 (89 to 121) |
| Myanmar                       | 110 (93 to 131)   | 1285 (1139 to 1466) | 3879 (3307 to 4615) |
| Sri Lanka                     | 40 (32 to 51)     | 593 (523 to 674) | 1360 (1074 to 1677) |
| Seychelles                    | 0 (0 to 0)        | 3 (2 to 3)  | 7 (5 to 8)  |
| Thailand                      | 123 (106 to 142)  | 2166 (1941 to 2458) | 4091 (3553 to 4724) |
| Vietnam                       | 123 (99 to 153)   | 2504 (2209 to 2846) | 4324 (3536 to 5319) |
| Oceania                       | 13 (10 to 18)     | 212 (187 to 244) | 467 (384 to 621) |
|                               | -5.7% (-21.2 to 12.4) | 4.0% (1.6 to 6.5) | -3.8% (-19.4 to 15.3) |

(Continued from previous page)

| Asia                              |                   |           |                 |
| Artic                             |                   |           |                 |
| American Samoa                    | 0 (0 to 0)        | 2 (2 to 2) | 5 (4 to 6)  |
| Federated States of Micrones      | 0 (0 to 0)        | 2 (2 to 2) | 8 (6 to 11) |
| Fiji                              | 2 (1 to 2)        | 22 (19 to 25) | 52 (40 to 66) |

(Continued on next page)
### Articles

**Deaths Prevalence DALYs**

| Country                  | Deaths | Prevalence | DALYs |
|--------------------------|--------|------------|-------|
|                           | 2016 counts | 1990–2016 age-standardised rates | 2016 counts | 1990–2016 age-standardised rates | 2016 counts | 1990–2016 age-standardised rates |
| **Sub-Saharan Africa**    |         |            |       |                                |         |                                |        |
| Zimbabwe                 | 1 (1 to 1) | -45.2% (-56.6 to -39.4) | 6 (6 to 7) | -16.3% (-20.2 to -12.5) | 30 (24 to 35) | -42.6% (-54.6 to -27.4) |
| Northern Mariana Islands | 0 (0 to 0) | 46.4% (10.2 to 95.3) | 2 (2 to 2) | 4.7% (1.4 to 8.4) | 9 (7 to 12) | 46.0% (10.7 to 96.7) |
| Marshall Islands         | 0 (0 to 0) | -0.9% (-27.8 to 29.8) | 1 (1 to 2) | 4.7% (0.9 to 8.2) | 4 (3 to 6) | 1.1% (-25.3 to 28.8) |
| **Lanka**                |         |            |       |                                |         |                                |        |
| **South Asia**           |         |            |       |                                |         |                                |        |
| Pakistan                 | 223 (220 to 330) | 16.6% (-8.0 to 36.8) | 4075 (3541 to 4754) | 4.5% (2.7 to 6.1) | 13 364 (8976 to 16 996) | 7.8% (-17.8 to 28.8) |
| Bangladesh               | 146 (104 to 240) | -25.6% (-46.6 to -1.4) | 2857 (2501 to 3272) | 8.6% (5.0 to 12.5) | 5726 (4307 to 8582) | -29.6% (-31.9 to 32.9) |
| Bhutan                   | 1 (1 to 2) | 30.2% (-8.1 to 75.0) | 15 (14 to 18) | 11.5% (7.7 to 15.7) | 40 (31 to 57) | 11.7% (-28.4 to 54.8) |
| India                    | 2309 (1894 to 2726) | 56.9% (21.4 to 86.5) | 255 (21450 to 30120) | 16.1% (14.0 to 17.6) | 756 (236,154 to 90,580) | 48.0% (15.8 to 65.0) |
| Nepal                    | 33 (23 to 57) | 45.8% (4.8 to 125.7) | 514 (449 to 592) | 8.1% (4.4 to 12.7) | 1177 (848 to 1929) | 25.4% (-9.3 to 104.3) |
| Pakistan                 | 223 (125 to 311) | 66.4% (18.0 to 133.3) | 3448 (3020 to 3988) | 7.0% (3.3 to 10.8) | 8950 (7142 to 12333) | 48.5% (11.2 to 95.9) |
| **Sub-Saharan Africa**    |         |            |       |                                |         |                                |        |
| Namibia                  | 2 (1 to 2) | 42.5% (-33.1 to 133.9) | 31 (27 to 36) | 6.6% (3.1 to 10.1) | 80 (37 to 119) | 41.8% (-32.9 to 129.7) |
| Lesotho                  | 2 (1 to 2) | 108.8% (0 to 214.2) | 26 (22 to 30) | 6.5% (2.7 to 10.2) | 61 (44 to 89) | 106.2% (2.0 to 206.7) |
| South Africa             | 55 (50 to 59) | 29.3% (1.9 to 49.7) | 841 (711 to 1003) | 5.9% (4.4 to 7.5) | 1937 (1769 to 2108) | 19.8% (-2.6 to 37.4) |
| Zambia                   | 1 (1 to 2) | 30.0% (0.0 to 104.8) | 16 (14 to 19) | 5.0% (1.5 to 8.8) | 31 (20 to 45) | 31.6% (-15.9 to 97.2) |
| Zimbabwe                 | 12 (9 to 15) | 38.2% (-4.2 to 153.8) | 168 (145 to 197) | -1.4% (-4.7 to 1.7) | 449 (356 to 574) | 33.2% (-2.8 to 126.9) |

(Table continues on next page)
### Deaths and Prevalence of Motor Neuron Disease

| Location                      | Deaths 1990–2016 | Prevalence 1990–2016 | DALYs 1990–2016 |
|-------------------------------|------------------|----------------------|-----------------|
| **Total**                     | 1091             | 5183                 | 17,241          |
| **Continental**               |                  |                      |                 |
| **Sub-Saharan Africa**        |                  |                      |                 |
| Burundi                       | 4 (3 to 7)       | -20.9% (-41.5 to 13.8)| 208 (140 to 342)| -23.5% (-43.3 to 14.4)|
| Comoros                       | 0 (0 to 0)       | -3.8% (-29.9 to 25.9)| 15 (11 to 22)  | -11.2% (-34.8 to 18.1)|
| Djibouti                      | 0 (0 to 0)       | 23.6% (-15.4 to 87.4)| 23 (16 to 33)  | 2.5% (30.9 to 45.0) |
| Eritrea                       | 2 (1 to 3)       | 17.2% (-18.3 to 66.2)| 93 (71 to 139) | 10.4% (20.4 to 19.0)|
| Ethiopia                      | 31 (22 to 61)    | -8.5% (-40.5 to 54.1)| 137 (102 to 236)| -18.5% (-48.2 to 44.2)|
| Kenya                         | 15 (12 to 21)    | 44.5% (3.2 to 85.8)  | 731 (593 to 925)| 25.0% (2-5 to 49.1)|
| Madagascar                    | 8 (5 to 14)      | -4.6% (-35 to 30.4)  | 455 (398 to 592)| -1.2% (-40 to 16.5)|
| Malawi                        | 6 (4 to 11)      | 15.2% (-23 to 73.4)  | 329 (226 to 515)| -9.8% (-41.6 to 49.5)|
| Mozambique                    | 10 (6 to 19)     | -0.4% (-29.7 to 32.4)| 501 (484 to 787)| -12.3% (-39.0 to 23.6)|
| Rwanda                        | 3 (2 to 8)       | 6.2% (-40 to 67.3)   | 174 (102 to 278)| -2.2% (-42.1 to 49.5)|
| Somalia                       | 3 (2 to 6)       | -5.6% (-28.9 to 25.6)| 157 (108 to 270)| -16.1% (-39.1 to 23.6)|
| South Sudan                   | 4 (2 to 7)       | -1.5% (-26.8 to 31.7)| 198 (127 to 322)| -16.5% (-39.1 to 18.7)|
| Tanzania                      | 23 (16 to 40)    | 11.4% (-12 to 43.6)  | 1170 (858 to 1765)| -3.4% (-28 to 28.0)|
| Uganda                        | 11 (8 to 21)     | 17.3% (-43 to 112.1) | 628 (443 to 1049)| 6.8% (4-8 to 78.1)|
| Zambia                        | 10 (7 to 14)     | 54.2% (3 to 123.4)   | 465 (318 to 666)| 15.0% (-23 to 70.1)|
| **Central sub-Saharan Africa**|                  |                      |                 |
| Angola                        | 9 (6 to 16)      | 18.6% (-22 to 81.6)  | 1083 (943 to 1273)| 0.8% (-1.3 to 2.9)|
| Central African Republic      | 2 (2 to 4)       | 5.3% (-20.6 to 36.6)| 103 (67 to 159) | -0.2% (-25.6 to 32.0)|
| Congo (Brazzaville)           | 3 (2 to 4)       | -9.9% (-37 to 20.3)  | 115 (80 to 161) | -11.6% (-38.5 to 16.6)|
| Democratic Republic of the Congo| 24 (16 to 43)  | -4.5% (-23 to 14.4)  | 1222 (826 to 1861)| -14.5% (-36.8 to 13.5)|
| Equatorial Guinea             | 0 (0 to 1)       | 0.3% (-43 to 75.5)   | 20 (13 to 31)  | -14.9% (-51.6 to 58.0)|
| Gabon                         | 1 (1 to 2)       | 10.1% (-2.4 to 51.3) | 50 (37 to 66)  | 3.4% (-27.8 to 41.2)|
| **Eastern sub-Saharan Africa**|                  |                      |                 |
| Burundi                       | 12 (9 to 14)     | 16.8% (-6.2 to 46.3) | 485 (398 to 592)| 8.4% (-14.4 to 36.4)|
| Sierra Leone                  | 5 (3 to 6)       | 13.6% (-1.8 to 49.5) | 223 (133 to 317)| -2.0% (-27 to 29.1)|
| Togo                          | 6 (4 to 8)       | 19.7% (-21 to 60.8)  | 245 (154 to 337)| 13.2% (-26.2 to 47.8)|

95% uncertainty intervals are in parentheses. DALYs = disability-adjusted life-years. SDI = socio-demographic index.
was in western sub-Saharan Africa (0·36, 0·31 to 0·41), followed by southern sub-Saharan Africa (0·37; 0·32 to 0·43), central Asia (0·39; 0·34 to 0·44), central sub-Saharan Africa (0·39; 0·33 to 0·44), and eastern sub-Saharan Africa (0·39; 0·34 to 0·45). Prevalence was higher in males than females at all ages (figure 2), with the peak of prevalence for males at age 85–89 years, and for females at age 80–84 years. The male to female ratio of age-standardised prevalence was 1·22 (1·19 to 1·24) in 1990 and 1·25 (1·23 to 1·28) in 2016.

The YLL rate curve peaked in the group aged 0–1 year and again in the group aged 70–74 years (figure 3). YLD rates showed a steady increase to a plateau at age 80–84 years (figure 3). The YLD rates were much lower than the YLL rates, reflecting the high case fatality of motor neuron disease.

The expected age-standardised DALY rates increased with SDI (figure 4), from about five per 100 000 population in countries with a very low SDI to about 30 per 100 000 population in countries with a high SDI. The change in DALYs as SDI increased was greatest at high SDIs. The rates in high-income North America, western Europe, and Australasia were higher than expected based on their SDI levels. By contrast, the age-standardised DALY rates in the high-income Asia Pacific region were lower than expected based on its SDI. None of the 84 risk factors analysed in GBD 2016 were shown to have sufficient evidence of association with motor neuron disease incidence or deaths.

Discussion

More than half of global deaths and close to half of all prevalent cases of motor neuron diseases occurred in three high-income regions: North America, western Europe, and Australasia. Motor neuron disease cases and deaths were far fewer in other parts of the world. Globally, from 1990 to 2016, the all-age prevalence increased more than the age-standardised prevalence, indicating that the largest part of the global prevalence increase was due to ageing.

The geographical differences in age-standardised incidences might be partly due to more accurate case ascertainment and diagnosis of motor neuron disease in high SDI countries compared with countries with low and middle SDIs. For example, a significant geographical difference in motor neuron disease prevalence was observed in the USA and western Europe between regions with different levels of quality of access to health-care systems. However, high SDI countries in the Asia Pacific region, where an accurate diagnosis of motor neuron disease is more probable than in low SDI countries, had a lower incidence than high SDI
countries in western Europe and North America. This geographical heterogeneity suggests that the differences in the prevalence and incidence of motor neuron disease might be due to ethnicities and ancestries, and that the apparent relationship with SDI might be spurious. In a 2017 study in which subcontinents were considered as surrogates of ancestries, a higher prevalence of amyotrophic lateral sclerosis was reported in Europe, the USA, and New Zealand than in east Asia.8

The increase in age-standardised incidence of motor neuron diseases in the high SDI regions during the study period might, in part, be due to improved diagnosis, whereas the increase in age-standardised prevalence is probably due to improved survival. In particular, non-invasive ventilation can prolong survival21 and has been increasingly included in the usual practice of multidisciplinary motor neuron disease centres. The improvement of quality and reduction of time to certainty of amyotrophic lateral sclerosis diagnosis might also appear to increase the duration of disease.22 Additional contributing factors could include an increase in the public awareness of amyotrophic lateral sclerosis (including that generated by major clinical trials launched since the early 1990s in Europe and the USA), and increased awareness that progressive weakness is not a normal part of ageing.

We found that the prevalence of motor neuron disease increases particularly after age 50 years, with a peak at around age 85 years, followed by a rapid decline in males, while in females the curve is flat between age 70 and 85 years, followed by a decline (figure 2). The rapid decline in the oldest age group (ie, ≥85 years) could be due to poor ascertainment because of more complex clinical features or comorbidities, competing mortality from other causes (eg, cardiovascular disease, dementia), or both. Older people are less frequently referred to tertiary neurological care11 and are less likely to get a correct diagnosis than are younger patients. Another factor that might play a part in the observed decline in the prevalence of motor neuron disease in the older population relates to different clinical expression of the disease, with a greater case fatality in this age group (eg, more frequent bulbar motor neuron disease cases).11,23

Our findings suggest that the prevalence of motor neuron disease is consistently higher in males than females across all age groups, with no changes in the male to female ratio between 1990 and 2016. The ratio is similar to that in studies from European registries, although in those studies incidence of amyotrophic lateral sclerosis in females increased over time.10 The reported change in sex ratio of amyotrophic lateral sclerosis in the earlier study10 has been attributed to changes of exposure for females to possible environmental factors, such as smoking. In GBD, however, the evidence for an association of smoking with all motor neuron disease was considered insufficient.21

![Figure 2: Global prevalence of motor neuron diseases by age and sex, 2016](#)

Prevalence is expressed as the percentage of the population that is affected by the disease. Shaded areas show 95% uncertainty intervals. Values are plotted at the midpoint of 5-year age categories.

![Figure 3: Global years lived with disability (YLDs) and years of life lost (YLLs) rates per 100 000 population due to motor neuron diseases by age, 2016](#)

Shaded areas show 95% uncertainty intervals. Values are plotted at the midpoint of 5-year age categories.
Previously reported prevalence per 100 000 population for amyotrophic lateral sclerosis (5·40 in Europe, 3·40 in the USA, and 2·34 in Asia) are lower than the GBD 2016 estimates of overall motor neuron disease prevalence per 100 000 population (10·00 in Europe, 19·37 in the USA, and 3·13 in Asia), as expected, because we included additional motor neuron diseases.

This study explored motor neuron diseases in all age groups. About 14% of cases were younger than age 20 years, an approximate estimate of the genetic forms with early clinical onset. The inclusion of spinal muscular atrophy, including all of its clinical and genetic phenotypes, has had an effect on DALYs, with the presence of a peak in the first year of life in addition to the second peak in people aged 70 years and older due to amyotrophic lateral sclerosis. However, the inclusion of spinal muscular atrophy and other motor neuron diseases of early life has not produced a substantial change in the age prevalence curve compared with studies including only amyotrophic lateral sclerosis.

Incidence and prevalence of motor neuron disease in early childhood (ie, spinal muscular atrophy and hereditary spastic paraplegia) seems to be lower in GBD 2016 estimates than previous estimates. For example, a prevalence of approximately one to two per 100 000 population and incidence of one in 10 000 livebirths per year have been estimated with spinal muscular atrophy type 1 (60% of cases). A previous report in England, Finland, Norway, and Hungary estimated a birth incidence of spinal muscular atrophy of ten per 100 000 livebirths. A larger survey, done in 2015, which took data from 27 population-based studies from Europe, Middle East, North America, Asia, South America, Africa, and Australia, reported a similar range, from 5·1 to 16·6 cases per 100 000 livebirths. We found an incidence of 1·9 per 100 000 person-years in the group aged 28 days to 1 year, indicating a relevant risk and burden in the first year of life (see the GBD 2016 online results tool). Age-specific incidence in this age group varied notably among locations: from 0·9 (sub-Saharan Africa) to 13·1 (Australia) per 100 000 person-years. The prevalence of spinal muscular atrophy is established, as for other genetic diseases of early years of life, by several factors, including family size of the proband, the availability of genetic counselling, prenatal diagnosis with genetic testing, and access to and willingness to have pregnancy termination. Additionally, spinal muscular atrophy frequency seems higher in white populations compared with other ethnic groups, similar to amyotrophic lateral sclerosis.

Several limitations of the study should be considered. First, given the diagnostic challenges of motor neuron diseases, some categories of motor neuron disease are probably still underdiagnosed, especially in older people and ethnic minority groups. Although the criteria for amyotrophic lateral sclerosis diagnosis in adults changed several times over the study period, we did not detect a systematic bias between data based on El Escorial criteria and data based on alternative case definitions. Second, data are scarce from large parts of the world, including sub-Saharan Africa, most of Latin America, eastern Europe, and south and central Asia. Despite the fact that the Asian population constitutes more than 50% of the world population, few epidemiological studies of motor neuron diseases have been done outside Europe and North America. The data indicate a difference in the prevalence and incidence of motor neuron disease, with lower estimates in Asia, Latin America, and Africa, as compared with the rest of the world. This difference might, at least in part, reflect missed diagnosis because of the absence of appropriate diagnostic instruments. Third, mortality rate estimations were based on data classified using ICD-9 and ICD-10. Although both versions of the ICD are highly congruent in the field of motor neuron disease, we cannot exclude an influence of the classification evolution, even if unlikely. As prevalence is related to incidence and disease duration, we should consider that variation in prognosis between geographical area, especially due to variation in care, might explain part of the prevalence variation. For example, tracheostomy is done in about 30% of Japanese...
patients, whereas in the USA and Europe proportions range between 0% and 10%. Conversely, use of non-invasive ventilation appears much higher in the USA (15–35% of cases) as compared with Japan and Europe.

This report is one of the most accurate so far on motor neuron disease epidemiology, but is still based on inference for large areas. Therefore, further improvements in estimates of the burden of motor neuron disease will require new research in these areas of the world; prevalence and possibly incidence studies in low-middle-income and low-income countries, particularly in sub-Saharan Africa, Latin America, the Caribbean, and Asia, are needed. Epidemiological studies of subpopulations of countries with diverse ethnicities are also important, given the supposed lower motor neuron disease incidence in mixed populations as compared with homogeneous populations.

Our estimate of the severity of disability is based on the PRO-ACT database and therefore indicative of disability in amyotrophic lateral sclerosis and not in spinal muscular atrophy and other motor neuron diseases. Another limitation is that participants in randomised trials are characterised by a less severe form of amyotrophic lateral sclerosis than are participants from population-based studies. Finally, no data exist on the effect of cognitive impairment on disability, an important clinical trait of amyotrophic lateral sclerosis that affects about 50% of individuals at diagnosis, and this might have led to underestimation of the overall motor neuron disease disability.

Unfortunately, no effective treatment for motor neuron diseases exists. The only licensed drugs for amyotrophic lateral sclerosis are riluzole and, more recently, edaravone. Even if these drugs change the survivorship, the effect is limited to a few more months of life, and the effect on the disability caused by amyotrophic lateral sclerosis is not clear. Conversely, a promising new approach exists for gene-modifying therapy for spinal muscular atrophy.

These data show that, with ageing of the world population, the burden of motor neuron diseases on health services is likely to increase substantially in coming decades. New epidemiological studies in areas without data are needed. Epidemiological studies in diverse populations might improve estimates of motor neuron disease frequency, understanding of disease phenotypes and risk factors, and the completeness of case ascertainment and referral. In the meantime, with limited possibilities for effective medical intervention, these GBD 2016 data are of relevance to health-care planning and resource allocation for the extensive care needs of people with motor neuron diseases.
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Contributors
GL, MP, and BM prepared the first draft. EN, VF, and TV analysed the manuscript, and approved the final version of the manuscript. All other authors provided data, developed models, reviewed results, provided guidance on methodology, or reviewed the manuscript, and approved the final version of the manuscript.

Declaration of interests
We declare no competing interests.

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