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REVIEW

Global burden of motor neuron disease: unraveling socioeconomic disparities, aging dynamics, and divergent future trajectories (1990–2040)

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Abstract

Background and objectives Motor neuron disease (MND) is a progressive neurodegenerative disorder associated with high morbidity and mortality. With global aging, the burden of MND is expected to increase, particularly in regions with rapidly aging populations. This study utilizes Global Burden of Disease (GBD) 2021 data to assess the global and regional MND burden from 1990 to 2021, examining trends by age, sex, and socio-demographic index (SDI), and projecting future trends to 2040.

Methods Data from the GBD 2021 database for the years 1990–2021 were analyzed to evaluate age-standardized prevalence rates (ASPR), incidence rates (ASIR), mortality rates (ASMR), and disability-adjusted life years (DALYs) for MND across SDI regions, age groups, and sexes. Temporal trends were explored using joinpoint regression analysis, while future projections were generated using the Bayesian age–period–cohort (BAPC) model for 2021–2040.

Results From 1990 to 2021, global MND prevalence increased by 68.43%, reaching 272,732 cases, while the age-standardized prevalence rate (ASPR) slightly declined, reflecting the influence of population aging. Although global incidence increased by 74.54%, the age-standardized incidence rate (ASIR) showed a modest decline, suggesting improvements in diagnostic practices. Mortality and DALY rates continued to rise globally, with high-SDI regions bearing the highest burden. Projections indicate that by 2040, global MND prevalence will decline slightly, while incidence, mortality, and DALYs will continue to rise in low- and middle-SDI regions due to aging populations.

Discussion The global MND burden is heavily influenced by aging, particularly in high-SDI regions. Although incidence rates have slightly decreased, mortality and disability burdens are increasing, highlighting ongoing challenges in disease management and treatment. The findings stress the importance of age-targeted interventions, improving healthcare access, and addressing socio-economic disparities to mitigate the future impact of MND, particularly in low- and middle-SDI regions.

Keywords Motor neuron disease · Global burden of disease · Aging population · Socio-demographic index · Incidence · Mortality · Future projections

Abbreviations

ALS	Amyotrophic Lateral Sclerosis
AAPC	Average annual percent change
APC	Age-period-cohort
ASDR	Age-Standardized DALY Rate
APC	Annual Percentage Change
ASDR	Age-standardized death rate
ASIR	Age-standardized incidence rate

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ASMR	Age-standardized mortality rate
ASPR	Age-standardized prevalence rate
ASR	Age-standardized rate
BAPC	Bayesian age-period-cohort
BMI	Body mass index
CI	Confidence Interval
CODEm	Cause of Death Ensemble Model
DALYs	Disability-adjusted life years
DisModMR	Disease Modeling Meta-Regression
EAPC	Estimated annual percentage change
GBD	Global Burden of Disease
HAQ	Healthcare Access and Quality Index
HICs	High-Income Countries
LMICs	Low- and Middle-Income Countries
MND	Motor neuron disease
MR-BRT	Meta-Regression Bayesian, Regularized, Trimmed
SDI	Sociodemographic index
UI	Uncertainty interval
WHO	World Health Organization
YLL	Years of Life Lost
YLD	Years Lived with Disability

Introduction

Motor Neuron Disease (MND) is a group of rare yet severe neurodegenerative disorders that primarily affect the upper and lower motor neurons, leading to progressive muscle weakness, loss of voluntary muscle control, and ultimately respiratory failure and death [1, 2]. The group includes amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, progressive muscular atrophy, hereditary spastic paraplegia, pseudobulbar palsy, and spinal muscular atrophy [3, 4]. Among these, ALS is the most common and fatal form, with approximately 50% of patients dying from respiratory failure within 2 years of diagnosis [5]. Although MND primarily affects adults, with peak onset between ages 50 and 70, it poses a significant challenge to global healthcare systems due to its rapid progression, poor prognosis, and the socioeconomic burden it places on patients and caregivers [6, 7].

Despite being relatively rare, the burden of MND varies across regions and socioeconomic groups. Epidemiological studies from high-income regions such as North America and Western Europe report relatively high incidence and prevalence, while data from low- and middle-income countries are limited due to underdeveloped healthcare infrastructure and diagnostic capabilities [8]. The etiology of MND is complex and multifactorial, involving genetic susceptibility, environmental exposures, and potentially modifiable lifestyle factors [9]. These factors not only drive the progression of the disease but also highlight the disparities in disease burden among different populations.

Previous analyses using the Global Burden of Disease (GBD) framework have provided valuable insights into the epidemiology of MND, particularly regarding its prevalence, incidence, mortality, and disability-adjusted life years (DALYs). For example, the 2019 GBD study estimated approximately 268,673 prevalent MND cases globally, emphasizing the increasing disease burden in high-income regions [10]. The study also highlighted the geographic heterogeneity of the disease burden, suggesting that sociodemographic factors, healthcare access, and genetic background may influence the global distribution of MND. Although the age-standardized rates (ASRs) of MND have remained relatively stable over time, the absolute burden continues to rise due to population growth and aging, underscoring the need for timely, evidence-based healthcare planning.

To date, a comprehensive assessment of the global, regional, and national burden of MND using the latest GBD 2021 data has not been conducted. This updated analysis is crucial for understanding the evolving trends in MND burden and its association with sociodemographic factors. In this study, we utilized the GBD 2021 estimates to quantify the global, regional, and national burden of MND from 1990 to 2021. We analyzed prevalence, incidence, mortality, and DALYs, stratified by sex, age, and SDI quintiles, to identify differences and trends in disease burden. In addition, we predicted future trends in MND incidence using the Bayesian age–period–cohort (BAPC) model. These findings not only provide scientific evidence for the development of targeted public health strategies and optimized healthcare resource allocation but also offer forward-looking guidance for disease prevention and resource planning, helping to manage this devastating disease more effectively.

Methods

Data sources

This study utilized data from the 2021 Global Burden of Disease, Injuries, and Risk Factors Study (GBD), which provides comprehensive global, regional, and national estimates for 369 diseases and 88 risk factors across 204 countries and regions [11]. The GBD methodology integrates various data sources, including population surveys, hospital records, mortality registries, and scientific literature, and employs advanced statistical techniques to address bias, inconsistencies, and data gaps. The burden of disease indicators—such as prevalence, incidence, mortality, and disability-adjusted life years (DALYs)—were estimated using DisMod-MR 2.1, a Bayesian meta-regression tool that accounts for differences in study design, geographical location, and age distribution [12]. Mortality estimates were generated through the Cause of Death Ensemble modeling (CODEm) framework, which

integrates multiple models to enhance the accuracy of cause-specific mortality estimates [13].

For rare diseases like motor neuron disease (MND), which exhibit significant data heterogeneity, the GBD framework utilized predictive modeling and expert consultations to synthesize sparse data [14, 15]. Prevalence and incidence estimates were derived by coordinating data from various sources, addressing gaps in data availability, and combining prior distributions based on established epidemiological patterns [12]. Mortality estimates, in conjunction with life expectancy data, were used to calculate Years of Life Lost (YLL), while DALYs were calculated by adding YLL to Years Lived with Disability (YLD). YLD was derived by multiplying MND prevalence by standardized disability weights. All estimates are accompanied by uncertainty intervals (UIs), ensuring the robustness and reproducibility of the global and regional burden assessments for MND [16, 17]. The specific calculation methods can be found in Supplementary Method 1. This rigorous methodology aligns with GBD standards, enhancing the validity of the findings for scientific and policy applications.

Socio-demographic index

The sociodemographic index (SDI) serves as a composite metric integrating per capita income, educational attainment, and total fertility rate to assess regional development levels. This index, scaled from 0 to 1, reflects a gradient of sociodemographic progress, with higher values denoting advanced socioeconomic conditions. Epidemiological analyses have consistently demonstrated SDI's utility in predicting global health disparities, particularly in disease incidence and mortality patterns [18, 19]. In this investigation, we stratified 204 countries into quintiles (low, low–medium, medium, medium–high, and high SDI) to systematically evaluate associations between motor neuron disease (MND) burden and developmental disparities.

Decomposition analysis

We employed the Das Gupta decomposition method to dissect the changes in prevalence, incidence, mortality, and DALYs from 1990 to 2021 into contributions from aging, population growth, and epidemiological changes. This approach enabled us to decompose the overall changes in burden into these key factors, thereby gaining a clearer understanding of how demographic and epidemiological shifts have shaped trends over time. Unlike traditional methods, such as linear regression, which primarily focus on establishing relationships between variables, decomposition analysis allows for a detailed assessment of the independent contributions of each factor to the overall changes in disease burden. By breaking down these trends, we have obtained a more transparent picture of the underlying drivers of the global burden of motor neuron disease.

Forecasting and projections

Future trends in the burden of motor neuron disease (MND) for the period 2021–2040 were projected using a Bayesian age–period–cohort (BAPC) model, an advanced statistical framework widely utilized in GBD studies. The BAPC model integrates historical data trends with age-specific rates to provide robust predictions of future disease outcomes while accounting for temporal and demographic dynamics. To improve the precision of the projections, integrated nested Laplace approximations were employed, a method designed to optimize computational efficiency and accuracy. All projections were accompanied by 95% uncertainty intervals (UIs) to reflect variability in the input data, modeling assumptions, and inherent uncertainties, ensuring a transparent and comprehensive evaluation of future MND burden trends.

Statistical analysis

The statistical analysis in this study was conducted using R software (version 4.4.2) and GlobalBurdenR package for data analysis and visualization. Joinpoint regression analysis was performed using the Joinpoint Regression Program (version 5.3.0), developed by the National Cancer Institute, USA. The statistical significance level for all analyses was set at $p < 0.05$. To assess long-term trends, the Estimated Annual Percentage Change (EAPC) was calculated by fitting a linear regression to the natural logarithm of annual rates. Each year was assigned a sequential value ($t = 0,1,2\ldots\ldots31$), with 1990 designated as the reference year. The regression model is represented as: $\mathrm{Ln}(Rt) = \alpha + \beta t + \varepsilon$, where Rt represents the rate in year t, α denotes the intercept, β is the regression coefficient, and ε is the error term. The EAPC was calculated as: $\mathrm{EAPC} = (e^{\beta} - 1) \times 100\%$. 95% confidence intervals for the EAPC were derived from the standard error of β. Trends were considered statistically significant if the confidence interval excluded zero. This approach allows for the quantification of long-term trends in health metrics, providing essential insights into temporal changes in disease burden.

To identify significant changes in temporal trends and characterize recent pattern shifts, joinpoint regression analysis was performed using the Joinpoint Regression Program (version 5.3.0, National Cancer Institute, USA). This method identifies joinpoints, or points, where the linear trend changes significantly in either magnitude or direction, providing a more detailed understanding of temporal trends compared to the single EAPC summary measure. The procedure for the joinpoint analysis was as follows: 1) the program

tested the optimal number of join-points (up to a maximum of five) to best characterize the trend, starting with the null hypothesis of zero joinpoints. 2) For each segment between join-points, the annual percent change (APC) was calculated using the formula: APC = $(e^{\beta} - 1) \times 100\%$. Where β is the slope coefficient from the segmented regression of logarithmically transformed data. 3) The final model was selected using the Monte Carlo Permutation method, with the significance of join-points determined at a threshold of $p < 0.05$. 4) The analysis produced: 1) the optimal number and temporal location of joinpoints; 2) segment-specific APCs with corresponding 95% confidence intervals; and 3) tests for parallelism between different series where applicable. This methodology allows for a more nuanced interpretation of temporal trends and the identification of significant shifts in the data, which is vital for assessing changes in disease burden over time.

Results

Global level

In 2021, MND remained a substantial global health concern, with 272,732 prevalent cases (95% UI 236,194–313,676), representing a 68.43% increase since 1990. However, the ASPR showed a marginal decline from 3.36 per 100,000 (95% UI 2.87–3.92) in 1990 to 3.31 per 100,000 (95% UI 2.86–3.80) in 2021, with an estimated annual percentage change (EAPC) of 0.11 (95% CI 0.03–0.19) (Table 1; Fig. 1). Globally, 64,178 incident cases (95% UI 58,506–70,270) were reported in 2021, reflecting a 74.54% rise compared to 1990. Despite this increase in absolute numbers, the ASIR exhibited a modest reduction from 0.81 per 100,000 (95% UI 0.72–0.90) in 1990 to 0.77 per 100,000 (95% UI 0.70–0.84) in 2021, with an EAPC of −0.19 (95% CI −0.15 to −0.05), suggesting a sustained downward trend in incidence (Table 2; Fig. 1). Mortality due to MND reached 39,082 deaths (95% UI 35,757–42,433) in 2021, corresponding to an ASMR of 0.46 per 100,000 (95% UI 0.42–0.49). The ASMR demonstrated an upward trend, with an EAPC of 0.69 (95% CI 0.56–0.81) (Table 3; Fig. 1). The global ASDR attributable to MND in 2021 were estimated at 1,040,566 (95% UI 963,064–1,123,956). The ASDR was 12.17 per 100,000 (95% UI 11.24–13.15), with an EAPC of 0.3 (95% CI 0.22–0.37) (Table 4; Fig. 1), indicating a persistent disease burden over time.

Regional level

Between 1990 and 2021, the burden of MND varied significantly across regions with differing socio-demographic index (SDI) categories. High SDI regions had the highest ASPR (7.81 per 100,000 [95% UI 7.01–8.68]) and ASIR (1.66 per 100,000 [95% UI 1.58–1.75]), while low SDI regions had the lowest ASPR (1.32 per 100,000 [95% UI 1.03–1.64]) and ASIR (0.4 per 100,000 [95% UI 0.34–0.48]) (Tables 1, 2, Figs. 1, 2A, B). High SDI regions also exhibited the highest ASMR (1.24 per 100,000 [95% UI 1.14–1.33]) and ASDR (34.39 per 100,000 [95% UI 32.48–36.49]), whereas low SDI regions showed the lowest ASMR (0.01 per 100,000 [95% UI 0–0.01]) and ASDR (0.47 per 100,000 [95% UI 0.31–0.65]) (Tables 3, 4; Figs. 1, 2C, D). Notably, low SDI regions experienced the highest increase in ASMR (EAPC: 5.07 [95% CI 4.65–5.49]), while low–middle SDI regions had the largest increase in ASDR (EAPC: 2.83 [95% CI 2.75–2.91]) (Tables 3, 4, Figs. S6, S7). In contrast, high SDI regions saw the greatest increase in ASPR (EAPC: 0.67 [95% CI 0.55–0.78]) and ASIR (EAPC: 0.41 [95% CI 0.38–0.44]) (Tables 1, 2, Figs. S4, S5).

At the regional level, Western Europe had the highest ASPR (7.81 per 100,000 [95% UI 7.01–8.68]) and ASDR(34.39 per 100,000 [95% UI 32.48–36.49]), while West Africa had the lowest ASPR (1.32 per 100,000 [95% UI 1.03–1.64]) and ASMR (0.01 per 100,000 [95% UI 0–0.01]) (Table 1; Fig. 1A). North America had the highest ASIR (1.66 per 100,000 [95% UI 1.58–1.75]), and South Asia had the lowest (0.4 per 100,000 [95% UI 0.34–0.48]) (Table 2; Fig. 1B). Eastern Europe had the highest ASMR (1.24 per 100,000 [95% UI 1.14–1.33]), while Western Europe had the highest ASDR (41.57 per 100,000 [95% UI 38.3–45.31]) (Tables 3, 4; Fig. 1C, D).

Regional trends revealed that West Africa and South Asia showed the highest increases in ASMR and ASDR (EAPCs: 5.07 [95% CI 4.65–5.49] and 2.83 [95% CI 2.75–2.91], respectively), while Western Europe and North America exhibited the greatest increases in ASPR and ASIR (EAPCs: 0.67 [95% CI 0.55–0.78] and 0.41 [95% CI 0.38–0.44], respectively) (Tables 1–4; Figs. S4–S7).

Correlation analysis showed a significant positive correlation between SDI and ASPR ($\rho = 0.862$, $p < 0.001$), ASIR, ASMR, and ASDR globally and across the 21 GBD regions ($\rho = 0.726, 0.855, 0.863$, all $p < 0.001$) (Fig. 3A–D). In addition, SDI was positively correlated with these rates across the 204 countries ($\rho = 0.880, 0.546, 0.761, 0.793$; all $p < 0.001$) (Figs. S8–11).

Temporal joinpoint analysis

The temporal joinpoint regression analysis revealed significant differences in disease burden indicators stratified by the Socio-Demographic Index (SDI). The global ASPR exhibited slight fluctuations (AAPC = 0.04%), with a notable decline between 1990 and 1991 (APC = −1.85%), followed by stabilization after 2016 (2016–2018: APC = 0.43%) and a recent downturn (2019–2021: APC = −0.54%). High SDI

Table 1 Age-standardized rates (per 100,000) and absolute numbers (in hundreds) for MND prevalence globally from 1990 to 2021

Location	1990		2021		EAPC (95% CI)
	Numbers (95% UI)	ASPR (95% UI)	Numbers (95% UI)	ASPR (95% UI)	
Global	1619.26 [1370.06–1892.63]	3.36 [2.87–3.92]	2727.32 [2361.94–3136.76]	3.31 [2.86–3.8]	0.11 [0.03–0.19]
Sex					
Female	773.82 [652.87–908.53]	3.13 [2.66–3.66]	1272.53 [1094.71–1465.1]	3.02 [2.6–3.52]	0.02 [−0.05 to 0.1]
Male	845.44 [716.37–988.25]	3.61 [3.11–4.21]	1454.79 [1263.64–1667.87]	3.64 [3.16–4.16]	0.19 [0.11–0.28]
SDI					
High SDI	684.74 [594.29–786.27]	6.88 [6.01–7.86]	1231.01 [1097.97–1382.56]	7.81 [7.01–8.68]	0.67 [0.55–0.78]
High–middle SDI	356.51 [299.22–419.4]	3.34 [2.83–3.91]	531.88 [452.04–620.47]	3.6 [3.05–4.19]	0.33 [0.27–0.39]
Middle SDI	339.16 [267.44–418.92]	1.97 [1.58–2.4]	513.87 [409.66–622.41]	2.06 [1.65–2.5]	0.18 [0.14–0.23]
Low–middle SDI	175.73 [135.72–219.99]	1.56 [1.23–1.93]	309.37 [243.26–386.15]	1.6 [1.27–1.97]	0.11 [0.06–0.16]
Low SDI	61.58 [47.23–77.62]	1.35 [1.05–1.68]	138.98 [106.12–175.65]	1.32 [1.03–1.64]	−0.07 [−0.13 to −0.02]
Region					
Andean Latin America	6.05 [4.79–7.49]	1.7 [1.37–2.07]	12.29 [9.99–14.76]	1.87 [1.53–2.24]	0.42 [0.37–0.46]
Australasia	15.2 [13.15–17.44]	6.83 [5.95–7.8]	39.33 [33.79–45.36]	9 [7.78–10.12]	1 [0.9–1.09]
Caribbean	8.63 [6.91–10.41]	2.49 [2.02–2.97]	13.06 [11–15.27]	2.66 [2.24–3.12]	0.31 [0.28–0.34]
Central Asia	17.56 [14.08–21.36]	2.56 [2.07–3.09]	23.75 [19.02–28.83]	2.49 [2.02–3.02]	−0.02 [−0.1 to 0.06]
Central Europe	45.12 [37.77–53.19]	3.56 [2.97–4.18]	50.63 [42.99–59.06]	4 [3.37–4.68]	0.47 [0.43–0.51]
Central Latin America	36.04 [28.23–44.27]	2.25 [1.8–2.72]	63.12 [51.68–75.25]	2.46 [2.04–2.93]	0.39 [0.35–0.42]
Central Sub-Saharan Africa	5.58 [4.28–7.05]	1.17 [0.91–1.45]	13.81 [10.47–17.62]	1.11 [0.87–1.39]	−0.14 [−0.19 to −0.09]
East Asia	267.78 [212.82–331.89]	2.15 [1.74–2.62]	348.09 [282.96–420.72]	2.31 [1.85–2.81]	0.27 [0.2–0.34]
Eastern Europe	77.13 [62.01–93.19]	3.44 [2.76–4.12]	75.88 [63.09–89.78]	3.58 [2.91–4.21]	0.27 [0.18–0.36]
Eastern Sub-Saharan Africa	21.06 [15.95–26.75]	1.27 [0.98–1.58]	48.07 [36.18–61.42]	1.23 [0.95–1.53]	−0.11 [−0.17 to −0.05]
High-income Asia Pacific	83.52 [70.38–97.21]	4.45 [3.75–5.16]	143.61 [122.91–167.4]	5.05 [4.33–5.83]	0.43 [0.33–0.53]
High-income North America	254.8 [222.1–291.53]	8.13 [7.1–9.25]	474.31 [438.62–515.37]	9.23 [8.59–10.02]	1.07 [0.82–1.33]
North Africa and Middle East	85.42 [69.09–102.99]	2.64 [2.16–3.15]	162.3 [130.99–195.4]	2.63 [2.15–3.14]	0.04 [0.01–0.07]
Oceania	0.91 [0.71–1.14]	1.44 [1.16–1.75]	1.8 [1.4–2.25]	1.33 [1.07–1.64]	−0.3 [−0.35 to −0.25]
South Asia	160.34 [122.16–203.77]	1.49 [1.15–1.86]	298.96 [232.74–378.06]	1.58 [1.24–1.97]	0.2 [0.14–0.26]
Southeast Asia	70.13 [54.48–87.77]	1.51 [1.2–1.87]	107.65 [84.71–133.31]	1.53 [1.21–1.89]	0.01 [–0.04 to 0.06]
Southern Latin America	18.89 [15.75–22.19]	3.86 [3.23–4.53]	37.07 [31.58–42.77]	5 [4.25–5.77]	0.9 [0.85–0.95]
Southern Sub-Saharan Africa	9.03 [6.94–11.31]	1.78 [1.39–2.21]	13.68 [10.62–17.29]	1.7 [1.33–2.11]	−0.14 [−0.2 to −0.08]
Tropical Latin America	37.87 [29.99–46.44]	2.53 [2.03–3.04]	68.2 [56.88–79.9]	2.89 [2.4–3.39]	0.56 [0.52–0.59]
Western Europe	375.72 [327.1–430.82]	7.74 [6.73–8.88]	675.63 [582.35–783.65]	9.66 [8.43–11.03]	0.77 [0.69–0.84]
Western Sub-Saharan Africa	22.51 [17.12–28.51]	1.31 [1.01–1.63]	56.11 [42.27–71.39]	1.26 [0.98–1.57]	−0.1 [−0.16 to −0.05]

SD socio-demographic index

regions showed the steepest increase (AAPC = 0.42%), with a notable acceleration in growth from 2000 to 2004 (APC = 1.31%) (Fig. 4). In contrast, low SDI regions experienced the most significant rise in ASMR (AAPC = 4.82%), peaking between 1999 and 2002 (APC = 5.19%). Notably, high–middle SDI regions exhibited a bimodal increase in ASMR (1990–1994: APC = 4.17%; 2013–2015: APC = 3.79%, $p <$ 0.05), marking them as the regions with the highest mortality burden (Fig. S2).

Both ASIR and ASMR showed SDI gradient effects: ASIR continued to rise in high SDI regions (AAPC = 0.35%), with the fastest growth from 2001 to 2007 (APC = 0.52%), while ASMR in low SDI regions continued to

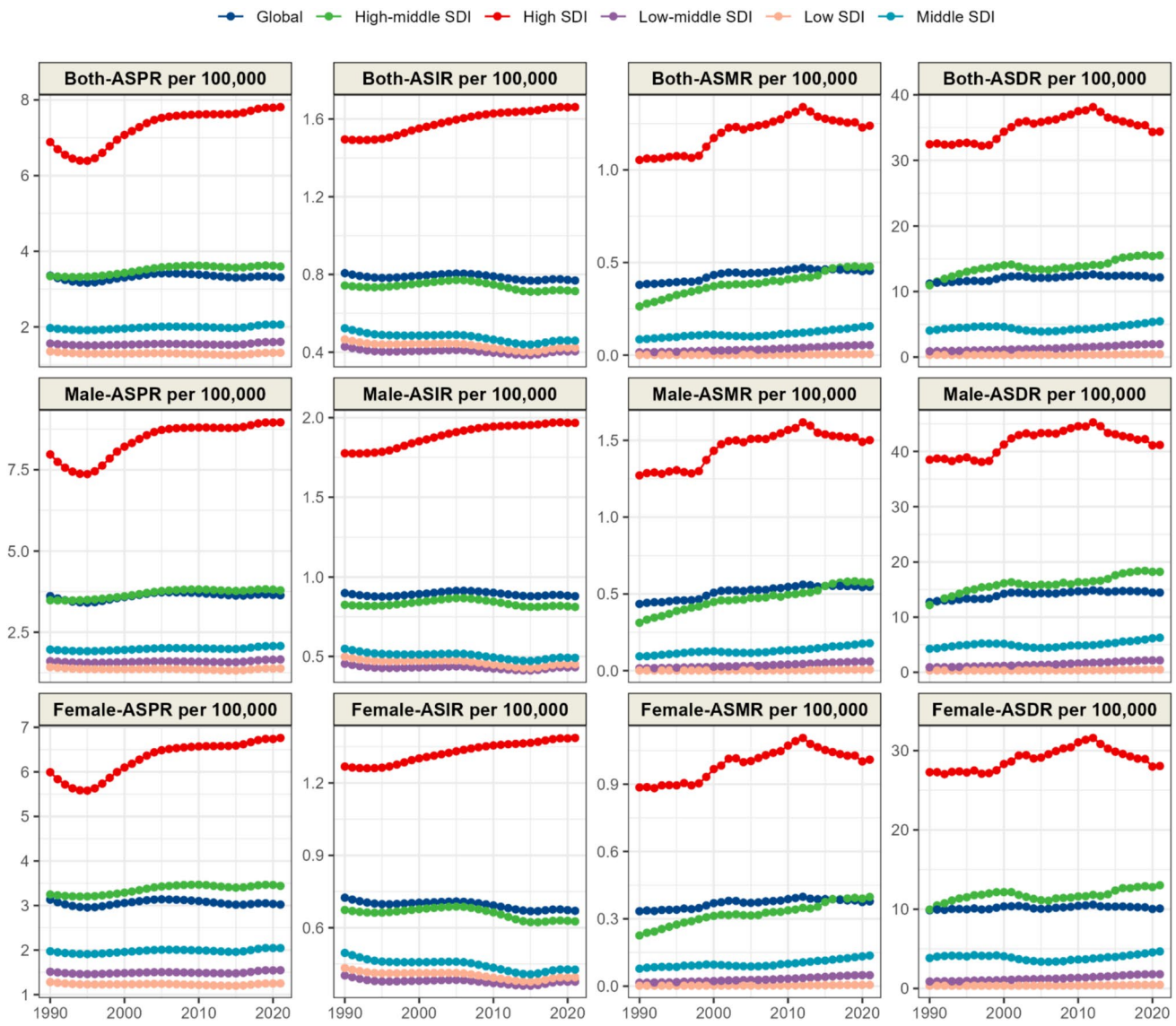

Fig. 1 Temporal trends in sex-specific age-standardized prevalence, incidence, mortality, and DALY rates of motor neuron disease across socio-demographic index regions from 1990 to 2021

climb until 2018 (1994–2001: APC = 2.80%). Key turning points revealed epidemiological shifts, with 2012 emerging as a common inflection point across multiple global indicators. After 2012, ASIR significantly declined (2012–2021: APC = −0.52%) (Fig. S1), and the growth rate of ASMR also slowed (2012–2021: APC = 0.34%). ASDR trends highlighted the effectiveness of prevention and control measures, with a significant decline in ASDR in high SDI regions post-2012 (2012–2014: APC = −1.64%), while high–middle SDI regions experienced a counter-trend rise from 2013 to 2015 (APC = 2.76%, $p < 0.05$; Fig. S3), reflecting the regional imbalance in disease burden shifts.

Sex patterns

The 2021 global epidemiological analysis of MND demonstrated notable gender-based disparities. The ASPR for males was 3.61 per 100,000 (95% UI 3.11–4.21), higher than females, which was 3.13 per 100,000 (95% UI 2.66–3.66). The EAPC in male ASPR (0.19, 95% CI 0.11–0.28) was significantly faster than that for females (0.02, 95% CI −0.05 to 0.1) (Table 1). Regarding incidence rates, the ASIR for males was 0.9 per 100,000 (95% UI 0.81–1), while for females it was 0.72 per 100,000 (95% UI 0.65–0.81). Female incidence showed a negative growth trend (EAPC = −0.21, 95% CI −0.26 to −0.16), whereas male incidence remained stable (EAPC = 0, 95% CI −0.06 to 0.05) (Table 2).

Table 2 Age-standardized rates (per 100,000) and absolute numbers (in hundreds) for MND incidence globally from 1990 to 2021

Location	1990		2021		EAPC (95% CI)
	Numbers $*10^2$ (95% UI)	ASIR (95% UI)	Numbers $*10^2$ (95% UI)	ASIR (95% UI)	
Global	367.69 [330.68–413]	0.81 [0.72–0.9]	641.78 [585.06–702.7]	0.77 [0.7–0.84]	−0.1 [−0.15 to −0.05]
Sex					
Female	170.84 [153–190.87]	0.72 [0.65–0.81]	290.4 [263.9–318.66]	0.67 [0.61–0.74]	−0.21 [−0.26 to −0.16]
Male	196.85 [176.93–221.83]	0.9 [0.81–1]	351.38 [321.51–384.98]	0.88 [0.81–0.96]	0 [−0.06 to 0.05]
SDI					
High SDI	152.72 [143.64–162.47]	1.5 [1.4–1.59]	301.84 [287.11–315.79]	1.66 [1.58–1.75]	0.41 [0.38–0.44]
High-middle SDI	74.79 [66.13–84.84]	0.74 [0.66–0.84]	116.19 [104.86–128.02]	0.71 [0.64–0.79]	−0.13 [−0.22 to −0.04]
Middle SDI	78.87 [67.4–92.6]	0.52 [0.44–0.62]	116.1 [98.09–136.44]	0.46 [0.39–0.54]	−0.43 [−0.51 to −0.35]
Low-middle SDI	42.65 [35.34–51.26]	0.43 [0.35–0.53]	70.26 [58.82–83.63]	0.4 [0.34–0.48]	−0.17 [−0.24 to −0.1]
Low SDI	18.35 [15.22–22.12]	0.47 [0.38–0.58]	36.86 [30.54–44.34]	0.42 [0.35–0.52]	−0.35 [−0.43 to −0.27]
Region					
Andean Latin America	1.28 [1.08–1.49]	0.43 [0.36–0.5]	3.05 [2.65–3.43]	0.49 [0.43–0.55]	0.61 [0.56–0.67]
Australasia	4.78 [4.53–5.02]	2.11 [2–2.22]	12.74 [12.25–13.29]	2.6 [2.49–2.72]	0.75 [0.68–0.81]
Caribbean	1.82 [1.55–2.07]	0.59 [0.5–0.67]	3.77 [3.4–4.12]	0.75 [0.68–0.82]	0.91 [0.86–0.97]
Central Asia	2.99 [2.48–3.57]	0.48 [0.39–0.59]	4.11 [3.39–5.03]	0.44 [0.36–0.53]	−0.31 [−0.37 to −0.25]
Central Europe	8.54 [7.36–9.84]	0.67 [0.58–0.76]	11.64 [10.46–12.81]	0.75 [0.67–0.82]	0.41 [0.38–0.44]
Central Latin America	6.97 [5.97–8.07]	0.51 [0.44–0.59]	15.75 [13.93–17.46]	0.63 [0.56–0.7]	0.86 [0.8–0.91]
Central Sub-Saharan Africa	1.75 [1.43–2.12]	0.45 [0.36–0.56]	4.13 [3.37–5]	0.42 [0.34–0.52]	−0.24 [−0.32 to −0.16]
East Asia	70.89 [61.27–82.24]	0.65 [0.57–0.75]	77 [63.2–91.2]	0.47 [0.4–0.54]	−1.29 [−1.48 to −1.11]
Eastern Europe	13.19 [10.97–15.78]	0.56 [0.47–0.67]	17.27 [15.21–19.37]	0.66 [0.57–0.73]	0.73 [0.65–0.8]
Eastern Sub-Saharan Africa	6.6 [5.4–8.05]	0.5 [0.4–0.63]	13.24 [10.79–16.4]	0.44 [0.35–0.56]	−0.49 [−0.59 to −0.39]
High-income Asia Pacific	16.45 [14.7–18.08]	0.88 [0.79–0.96]	32.68 [30.42–34.91]	0.91 [0.84–0.99]	0.18 [0.15–0.2]
High-income North America	59.26 [56.06–62.88]	1.82 [1.71–1.93]	126.57 [121.44–131.95]	2.1 [2.02–2.19]	0.57 [0.53–0.62]
North Africa and Middle East	16.87 [14.47–19.4]	0.57 [0.48–0.67]	31.11 [26.45–36.32]	0.55 [0.47–0.63]	−0.11 [−0.16 to −0.06]
Oceania	0.23 [0.19–0.27]	0.44 [0.37–0.52]	0.47 [0.39–0.55]	0.39 [0.32–0.46]	−0.49 [−0.56 to −0.41]
South Asia	37.54 [30.86–46.07]	0.4 [0.32–0.49]	63.11 [51.88–76.23]	0.37 [0.31–0.44]	−0.21 [−0.29 to −0.13]
Southeast Asia	15.32 [12.62–18.4]	0.4 [0.33–0.48]	23.81 [19.49–29.05]	0.35 [0.29–0.42]	−0.45 [−0.53 to −0.37]
Southern Latin America	3.81 [3.31–4.31]	0.8 [0.69–0.9]	8.15 [7.54–8.81]	1.05 [0.96–1.13]	0.92 [0.86–0.99]
Southern Sub-Saharan Africa	1.89 [1.55–2.31]	0.45 [0.37–0.57]	2.9 [2.33–3.59]	0.4 [0.33–0.5]	−0.42 [−0.52 to −0.32]
Tropical Latin America	8.04 [6.92–9.16]	0.65 [0.56–0.74]	21.13 [19.21–22.94]	0.86 [0.79–0.93]	1.14 [1.07–1.21]
Western Europe	82.99 [77.96–88.2]	1.64 [1.54–1.75]	154.72 [146.97–162.54]	2 [1.9–2.12]	0.7 [0.66–0.75]
Western Sub-Saharan Africa	6.5 [5.41–7.79]	0.44 [0.36–0.54]	14.44 [12.04–17.32]	0.39 [0.32–0.47]	−0.37 [−0.45 to −0.3]

SD socio-demographic index

Gender differences in mortality continued to widen. The ASMR for males was 0.44 per 100,000 (95% UI 0.4–0.46), with an EAPC of 0.84 (95% CI 0.7–0.97), which was 1.7 times higher than that for females (0.33 per 100,000, 95% UI 0.31–0.35; EAPC = 0.5, 95% CI 0.39–0.61) (Table 3). In addition, the male ASDR was 12.73 per 100,000 (95% UI 11–13.82), with an EAPC of 0.45 (95% CI 0.36–0.54), significantly higher than the female ASDR of 9.86 per 100,000 (95% UI 9.38–10.36; EAPC = 0.1, 95% CI 0.05–0.16) (Table 4).

Decomposition analysis

This decomposition analysis highlights that population growth is the most influential factor affecting the prevalence, incidence, mortality, and disability-adjusted life years (DALYs) of MND both globally and across different SDI regions. Aging plays a significant role in increasing the burden of MND, especially in high SDI regions (Fig. 5; Table S1). Epidemiological changes have varying impacts depending on the region and health metric, with more

Table 3 Age-standardized rates (per 100,000) and absolute numbers (in hundreds) for MND deaths globally from 1990 to 2021.

Location	1990		2021		
	Numbers (95% UI)	ASMR (95% UI)	Numbers (95% UI)	ASMR (95% UI)	EAPC (95% CI)
Global	152.6 [143.67–160.43]	0.38 [0.36–0.4]	390.82 [357.57–424.33]	0.46 [0.42–0.49]	0.69 [0.56–0.81]
Sex					
Female	72.48 [68.19–75.77]	0.33 [0.31–0.35]	173.79 [154.19–196.38]	0.38 [0.34–0.43]	0.5 [0.39–0.61]
Male	80.12 [71.37–85.79]	0.44 [0.4–0.46]	217.03 [196.23–233.71]	0.55 [0.5–0.59]	0.84 [0.7–0.97]
SDI					
High SDI	113.65 [108.53–116.32]	1.05 [1.01–1.08]	249.11 [225.01–268.48]	1.24 [1.14–1.33]	0.73 [0.56–0.89]
High–middle SDI	26.26 [22.2–30.25]	0.26 [0.22–0.3]	90.23 [80.08–100.86]	0.48 [0.42–0.53]	1.73 [1.57–1.9]
Middle SDI	11.33 [8.11–13.32]	0.09 [0.06–0.1]	42.66 [36.75–49.18]	0.16 [0.13–0.18]	1.63 [1.41–1.86]
Low–middle SDI	1.21 [1–1.54]	0.02 [0.01–0.02]	8.09 [6.86–9.4]	0.05 [0.05–0.06]	4.37 [4.28–4.47]
Low SDI	0.05 [0.03–0.08]	0 [0–0]	0.36 [0.14–0.65]	0.01 [0–0.01]	5.07 [4.65–5.49]
Region					
Andean Latin America	0.01 [0.01–0.02]	0 [0–0.01]	1.6 [1.23–1.96]	0.27 [0.21–0.32]	13.85 [11.17–16.61]
Australasia	3.75 [3.54–3.91]	1.6 [1.52–1.67]	9.6 [8.46–10.68]	1.84 [1.64–2.03]	0.6 [0.3–0.91]
Caribbean	0.03 [0.03–0.04]	0.01 [0.01–0.01]	2.23 [1.88–2.62]	0.42 [0.35–0.49]	10.45 [7.06–13.95]
Central Asia	0.03 [0.03–0.05]	0.01 [0–0.01]	0.26 [0.23–0.3]	0.03 [0.02–0.03]	6.55 [5.64–7.47]
Central Europe	3.1 [2.99–3.25]	0.23 [0.22–0.24]	11.25 [10.26–12.38]	0.57 [0.52–0.63]	3.38 [3.09–3.68]
Central Latin America	1.86 [1.81–1.9]	0.19 [0.18–0.19]	11.09 [9.73–12.61]	0.43 [0.38–0.49]	2.81 [2.66–2.96]
Central Sub-Saharan Africa	0.01 [0–0.01]	0 [0–0]	0 [0–0.01]	0 [0–0]	−3.96 [−5.15 to −2.75]
East Asia	15.89 [9–20.17]	0.15 [0.09–0.19]	36.31 [23.96–49.67]	0.18 [0.12–0.25]	−0.52 [−1.08 to 0.04]
Eastern Europe	2.26 [1.63–3.12]	0.09 [0.06–0.12]	21.75 [19.97–23.66]	0.64 [0.59–0.7]	6.23 [5.59–6.87]
Eastern Sub-Saharan Africa	0.01 [0.01–0.02]	0 [0–0]	0.01 [0.01–0.02]	0 [0–0]	−3.28 [−4.16 to −2.39]
High-income Asia Pacific	10.95 [10.46–11.3]	0.54 [0.52–0.56]	32.9 [28.82–36.14]	0.72 [0.64–0.78]	0.95 [0.79–1.11]
High-income North America	43.28 [41.1–44.55]	1.27 [1.21–1.3]	95.71 [88.09–100.51]	1.5 [1.39–1.57]	0.64 [0.31–0.97]
North Africa and Middle East	1.79 [1.06–3.02]	0.06 [0.03–0.1]	6.99 [4.82–9.81]	0.14 [0.1–0.2]	3.12 [2.86–3.38]
Oceania	0 [0–0]	0.01 [0–0.01]	0 [0–0]	0 [0–0]	−2.51 [−3.28 to −1.73]
South Asia	0.32 [0.16–0.69]	0 [0–0.01]	3.48 [1.68–5.22]	0.02 [0.01–0.03]	5.23 [5.05–5.4]
Southeast Asia	0.26 [0.13–0.39]	0.01 [0–0.01]	1.37 [0.91–1.95]	0.02 [0.01–0.03]	2.73 [2.58–2.88]
Southern Latin America	0.35 [0.34–0.36]	0.07 [0.07–0.08]	6.37 [5.79–7.04]	0.75 [0.68–0.83]	6.18 [4.53–7.87]
Southern Sub-Saharan Africa	0.05 [0.01–0.09]	0.01 [0–0.02]	0.05 [0.02–0.09]	0.01 [0–0.01]	−2.23 [−2.42 to −2.05]
Tropical Latin America	3.14 [3.04–3.25]	0.3 [0.29–0.31]	18.77 [17.48–20.1]	0.73 [0.68–0.78]	3.18 [3.06–3.29]
Western Europe	65.49 [62.89–67.11]	1.2 [1.16–1.23]	131 [116.85–145.14]	1.49 [1.35–1.64]	1.03 [0.87–1.19]
Western Sub-Saharan Africa	0.02 [0.01–0.02]	0 [0–0]	0.08 [0.06–0.11]	0 [0–0]	1.97 [1.61–2.32]

SD socio-demographic index

pronounced effects observed in middle and high–middle SDI regions (Fig. 5; Table S1). These findings suggest that strategies to address MND should account for population growth trends and demographic shifts, particularly aging, while adapting to regional epidemiological changes to effectively reduce the burden of MND.

National level

According to the 2021 Global Burden of Disease (GBD) study data: United States of America (USA) had the highest number of MND cases, with 40,495.4 cases (95% UI 37,645.4–43,576.3), while Niue had the fewest cases, with 0 cases (95% UI 0–0).Ireland had the highest ASPR at 13.7 per 100,000 (95% UI 11.7–15.5), while Somalia had the lowest ASPR at 0.9 per 100,000 (95% UI 0.7–1.2). Uruguay showed the highest EAPC at 1.17 (95% CI 1.10–1.24), while Guam had the lowest EAPC at −1.39 (95% CI −1.54 to −1.23) (Table S3; Figs. 2A, S4). In 2021, the country with the highest number of new cases was China (7324.8 cases, 95% UI 5993.2–8709.1), while several countries (such as Nauru and Niue) reported zero cases. The country with the highest ASIR was Finland (2.5 per 100,000, 95% CI 2.4–2.7), while multiple countries (such as Indonesia and Malaysia) had an ASIR of 0.3. The country with the highest EAPC was Costa Rica (2.39, 95% CI 2.12–2.66), while Guam had the

Table 4 Age-standardized rates (per 100,000) and absolute numbers (in hundreds) for MND DALYs globally from 1990 to 2021

Location	1990		2021		EAPC (95% CI)
	Numbers (95% UI)	ASDR (95% UI)	Numbers (95% UI)	ASDR (95% UI)	
Global	5061.46 [4620.35–5450.5]	11.22 [10.39–11.98]	10,405.66 [9630.64–11,239.56]	12.17 [11.24–13.15]	0.3 [0.22–0.37]
Sex					
Female	2308.98 [2190.91–2434.19]	9.86 [9.38–10.36]	4485.17 [4132.28–4967.21]	10.08 [9.33–11.14]	0.1 [0.05–0.16]
Male	2752.49 [2302.89–3051.86]	12.73 [11–13.82]	5920.49 [5296–6428.11]	14.45 [12.93–15.76]	0.45 [0.36–0.54]
SDI					
High SDI	3201.52 [3112.04–3280.59]	32.46 [31.58–33.26]	5967.97 [5554.83–6363.42]	34.39 [32.48–36.49]	0.4 [0.25–0.56]
High–middle SDI	1097.42 [901.46–1303.38]	10.96 [9.02–13.09]	2595.3 [2301.26–2907.27]	15.52 [13.52–17.57]	0.79 [0.63–0.95]
Middle SDI	647.13 [457.75–765.98]	4.05 [2.95–4.75]	1454.05 [1246.27–1696.76]	5.45 [4.64–6.39]	0.46 [0.15–0.77]
Low–middle SDI	95.86 [80.17–115.93]	0.89 [0.74–1.08]	333.86 [285.73–388.86]	1.97 [1.7–2.29]	2.83 [2.75–2.91]
Low SDI	15.65 [11.19–21.64]	0.34 [0.24–0.46]	44.43 [30.35–60.08]	0.47 [0.31–0.65]	1.06 [0.88–1.24]
Region					
Andean Latin America	1.61 [1.16–2.25]	0.49 [0.36–0.67]	49.63 [38.23–60.19]	8 [6.17–9.71]	9.97 [8.35–11.62]
Australasia	102.81 [98.51–107.01]	46.81 [44.95–48.65]	227.58 [205.2–249.87]	49.54 [45.12–54.17]	0.44 [0.15–0.74]
Caribbean	3.05 [2.45–3.83]	0.92 [0.74–1.13]	66.37 [56.11–77.56]	12.75 [10.76–14.89]	7.91 [5.49–10.38]
Central Asia	5.72 [4.31–7.45]	0.82 [0.62–1.05]	14.92 [12.84–17.45]	1.56 [1.35–1.82]	2.67 [2.2–3.13]
Central Europe	133.98 [128.74–140.34]	11.09 [10.64–11.63]	321.48 [294.68–351.5]	19.82 [18.27–21.71]	2.3 [2.05–2.54]
Central Latin America	85.04 [81.63–88.92]	6.76 [6.55–7]	359.95 [315.64–408.71]	13.92 [12.2–15.83]	2.44 [2.31–2.56]
Central Sub-Saharan Africa	1.53 [1.11–2.12]	0.31 [0.22–0.42]	3.16 [2.11–4.56]	0.26 [0.18–0.36]	−0.62 [−0.8 to −0.45]
East Asia	904.18 [527.78–1149.63]	7.96 [4.73–10.09]	1286.89 [869.39–1732.35]	7.73 [5.03–10.02]	−1.43 [−2.04 to −0.81]
Eastern Europe	100.39 [76.04–128.52]	4.16 [3.2–5.31]	642.76 [593.71–694.94]	21.06 [19.54–22.69]	4.94 [4.39–5.5]
Eastern Sub-Saharan Africa	5.22 [3.68–7.34]	0.3 [0.22–0.42]	10.71 [6.95–15.55]	0.28 [0.19–0.39]	−0.37 [−0.46 to −0.27]
High-income Asia Pacific	319.36 [304.22–331.71]	16.35 [15.46–17.01]	682.95 [615.66–739.32]	18.11 [16.76–19.47]	0.39 [0.21–0.56]
High-income North America	1238.74 [1195.04–1272.52]	39.82 [38.6–40.85]	2372.12 [2248.79–2470.51]	41.58 [39.69–43.26]	0.3 [0.03–0.57]
North Africa and Middle East	131.11 [84.21–219.78]	3.57 [2.33–5.66]	289.17 [217.68–384.91]	5.27 [3.93–7.02]	1.66 [1.45–1.87]
Oceania	0.26 [0.19–0.35]	0.46 [0.35–0.59]	0.47 [0.35–0.64]	0.37 [0.28–0.5]	−0.91 [−1.11 to −0.72]
South Asia	48.01 [34.29–65.68]	0.47 [0.33–0.67]	184.5 [121.13–247.84]	1.08 [0.69–1.45]	2.75 [2.56–2.93]
Southeast Asia	25.43 [18.72–32.85]	0.61 [0.44–0.8]	67.39 [49.64–86.44]	0.95 [0.7–1.21]	1.38 [1.31–1.45]
Southern Latin America	15.43 [14.17–16.88]	3.21 [2.96–3.51]	181.54 [166.02–197.92]	22.7 [20.73–24.72]	5.32 [3.88–6.79]
Southern Sub-Saharan Africa	4.23 [2.66–6.71]	0.89 [0.53–1.4]	5.57 [3.46–8.03]	0.68 [0.44–0.97]	−1.03 [−1.13 to −0.92]
Tropical Latin America	131.76 [126.88–138.25]	10.87 [10.5–11.31]	568.16 [532.79–607.14]	22.24 [20.86–23.76]	2.61 [2.47–2.74]
Western Europe	1797.55 [1740.02–1836.5]	38.34 [37.36–39.13]	3054 [2788.25–3344.28]	41.57 [38.3–45.31]	0.56 [0.4–0.72]
Western Sub-Saharan Africa	6.04 [4.37–8.27]	0.34 [0.25–0.45]	16.35 [12.03–22.05]	0.37 [0.28–0.49]	0.31 [0.21–0.41]

SD socio-demographic index

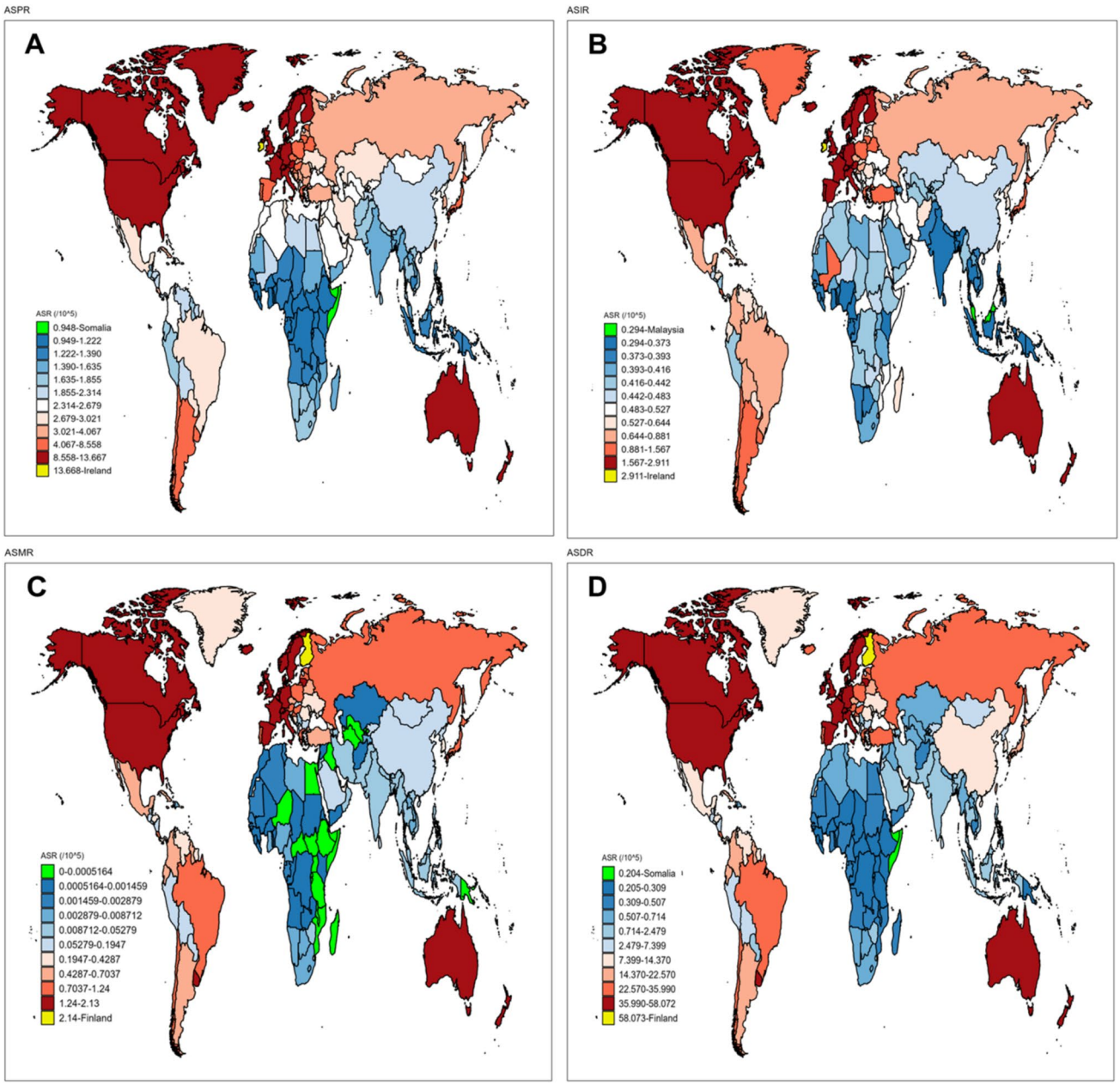

Fig. 2 Global distribution of age-standardized prevalence, incidence, mortality, and disability-adjusted life years (DALYs) rates for motor neuron disease across 204 countries and territories in 2021: **A** age-standardized prevalence rate (ASPR); **B** age-standardized incidence rate (ASIR); **C** age-standardized mortality rate (ASMR); **D** age-standardized DALY rate (ASDR). Green—lowest value; yellow—highest value

lowest EAPC at −3.57 (95% CI −3.96 to −3.17) (Table S4; Figs. 2B, S5).

In 2021, the country with the highest number of MND-related deaths was United States (8465.6 deaths, 95% UI 7799.9–8899), while several countries (such as Andorra, Antigua and Barbuda) reported zero deaths. The highest ASMR was recorded in Finland (2.1 per 100,000, 95% UI 1.8–2.6), while multiple countries (such as Afghanistan and Algeria) reported an ASMR of 0. The highest EAPC in mortality was observed in Ecuador (25.61, 95% CI 18.24–33.43), while the lowest EAPC was found in Egypt (−17.47, 95% CI −20.14 to −14.72) (Table S5; Figs. 2C, S6). In 2021, the highest number of DALYs due to MND was observed in the United States of America (210,559.4 DALYs; 95% UI 199,250.1–218,996.6), while the lowest was recorded in Nauru (0; 95% UI 0–0.1). The highest ASDR was recorded in Australia (50.5 per 100,000, 95% UI 46–55.2), while the lowest was observed in multiple

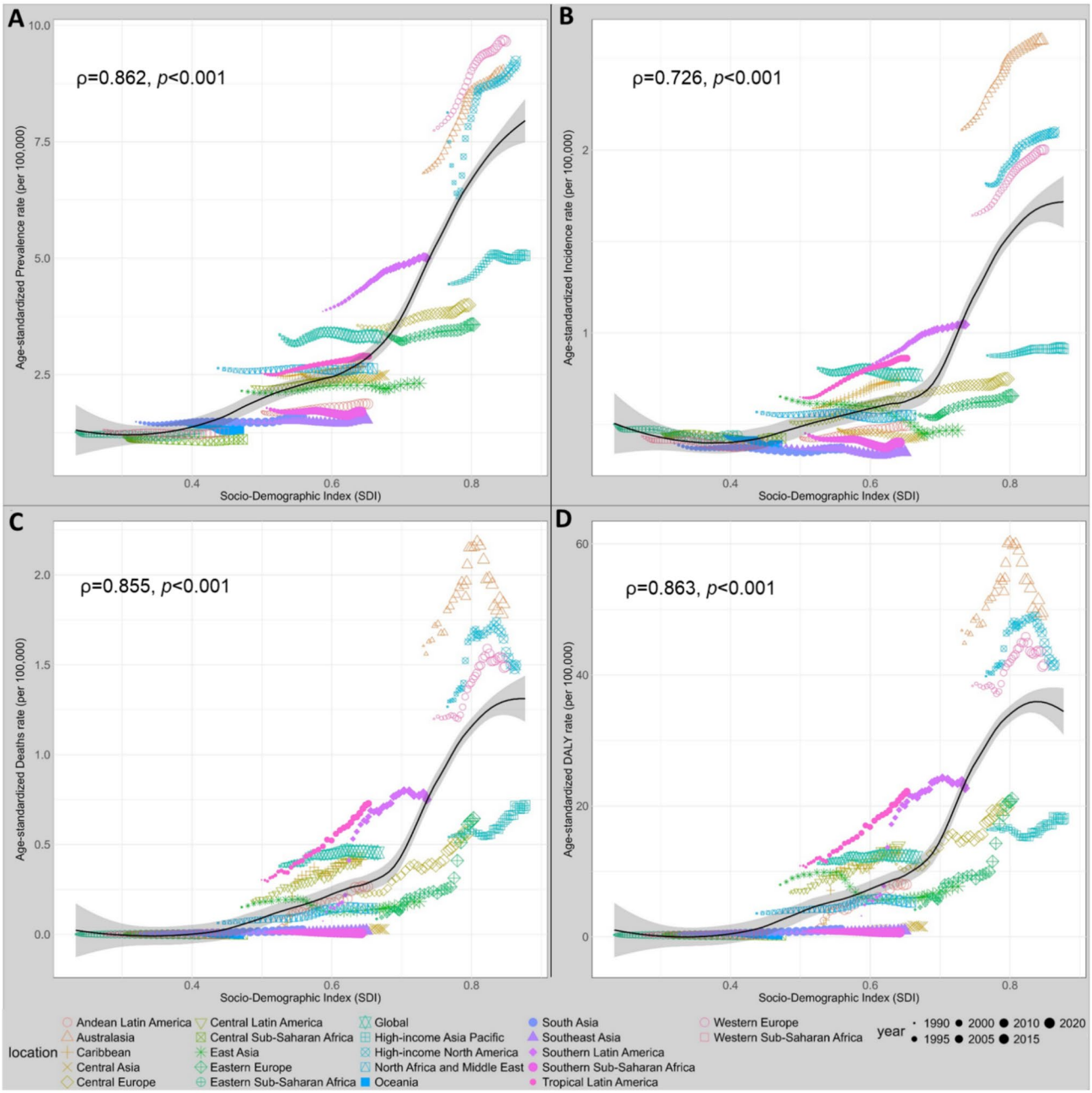

Fig. 3 Age-standardized prevalence, incidence, mortality, and DALY rates of motor neuron disease in relation to SDI in 2021 among 21 GBD regions. **A** Age-standardized prevalence rate (ASPR); **B** age-standardized incidence rate (ASIR); **C** age-standardized mortality rate (ASMR); **D** age-standardized DALY rate (ASDR)

countries, including Afghanistan (0.4; 95% UI 0.3–0.6). The highest EAPC was noted in Ecuador (13.69; 95% CI 10.69–16.78), while the lowest was observed in Guam (−7.38; 95% CI −8.31 to −6.44) (Table S6; Figs. 2D, S7).

Future forecasts for the global and five SDI regions'burden of MND

It is projected that the global burden of MND will decrease

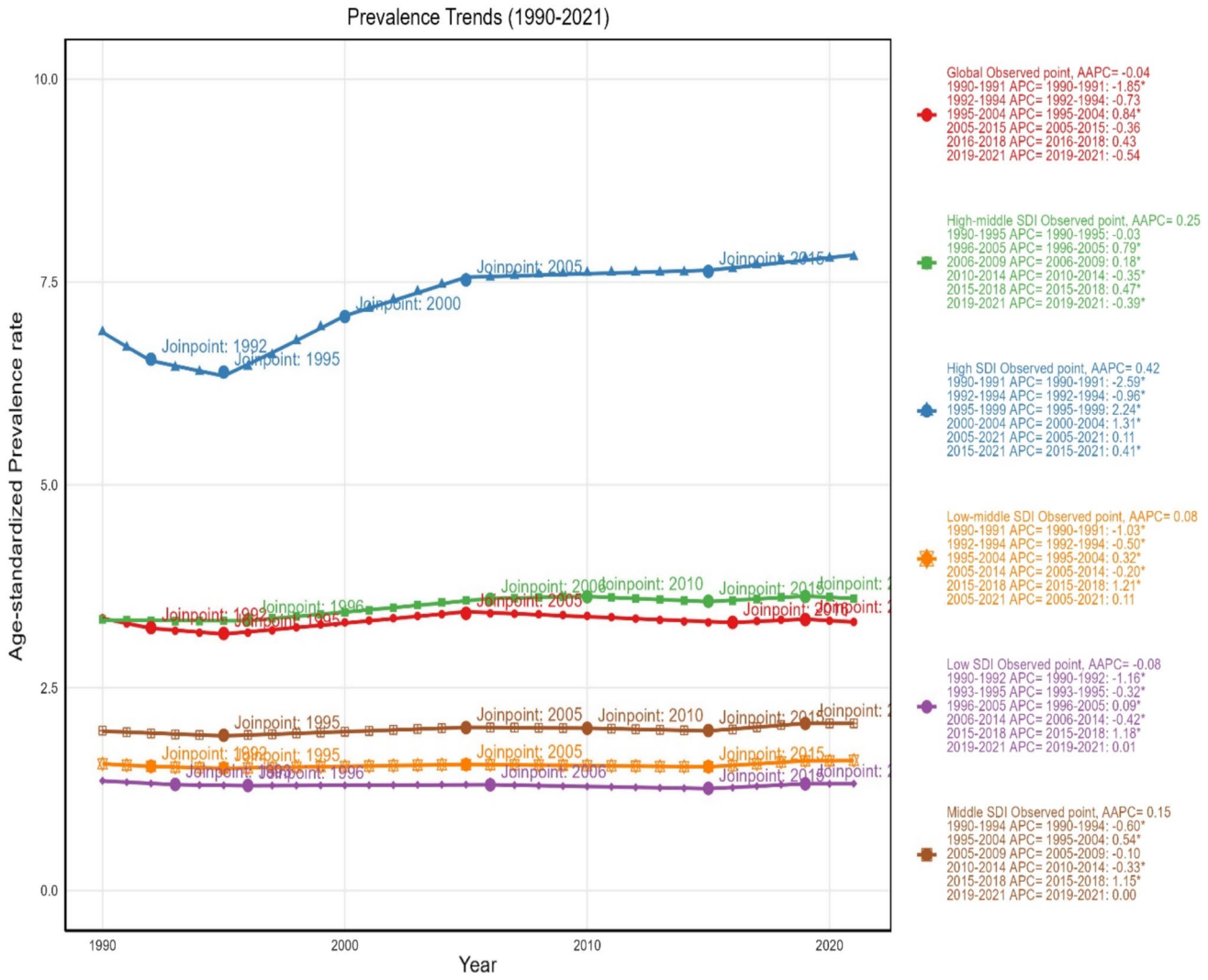

Fig. 4 Temporal trends in ASPR of MND by SDI regions: a Joinpoint regression analysis, 1990–2021. MND: motor neuron disease; ASPR: age-standardized prevalence rate; SDI, socio-demographic index; APC, annual percent change; AAPC, average annual percent change. *$p < 0.05$

from 2021 to 2040, though the trends for different indicators vary. The ASPR for both genders combined is expected to decline from approximately 3.29 per 100,000 in 2021 to around 2.75 per 100,000 in 2040 (Fig. 6A).The ASIR is projected to decrease from 0.76 per 100,000 in 2021 to approximately 0.65 per 100,000 in 2040 (Fig. 6B).The ASMR will fall from 0.45 per 100,000 in 2021 to around 0.37 per 100,000 in 2040 (Fig. 6C).The ASDR will decrease from 12.07 per 100,000 in 2021 to approximately 10.82 per 100,000 in 2040 (Fig. 6D; Table S2). However, trends in other SDI regions vary: both high SDI and high–middle SDI regions are expected to show a declining trend (Fig. S12 A–H). On the other hand, the Middle SDI region is projected to see an increase in both ASMR and ASDR, while the burden of MND is expected to rise in low–middle SDI and low SDI regions (Figs. S13, S14).

Discussion

This study highlights the key findings on the global burden of motor neuron disease (MND). Since 1990, the total prevalence, incidence, and mortality of MND have increased worldwide. However, the age-standardized rates (ASRs) have shown a slight decline, indicating a more stable trend over time. Notable regional disparities were observed: high Socio-Demographic Index (SDI) regions had the highest prevalence, incidence, mortality, and disability-adjusted life years (DALYs), while low SDI regions had the lowest. Temporal trend analysis further revealed that after 2012, the increase in MND burden slowed in high SDI areas, whereas mortality and DALYs rose significantly in low SDI regions. In terms of sex differences, males experienced a significantly higher burden of disease. Decomposition analysis

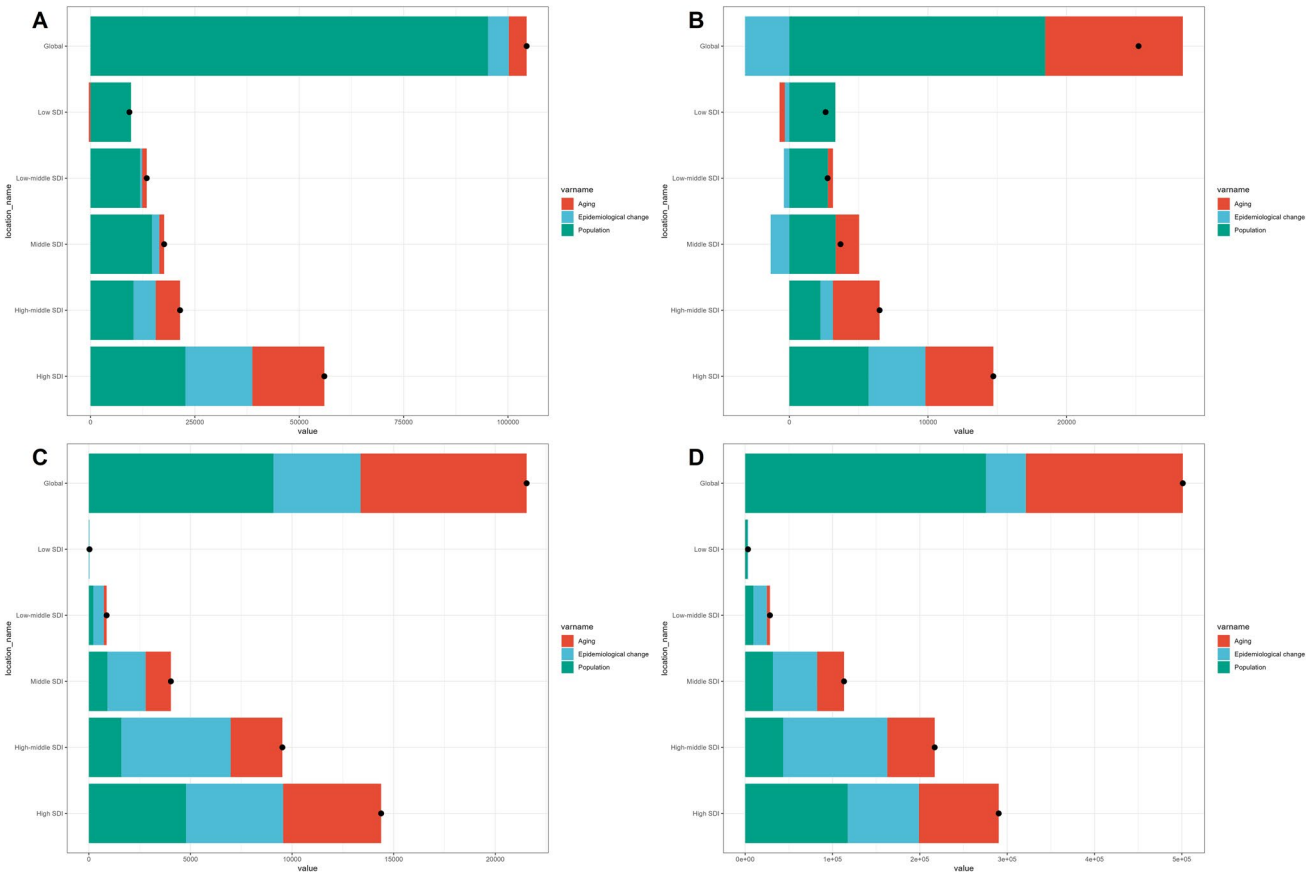

Fig. 5 Decomposition analysis of population-level determinants of motor neuron disease prevalence, incidence, mortality, and DALYs from 1990 to 2021 across global and socio-demographic index regions. **A** Age-standardized prevalence rate (ASPR); **B** age-standardized incidence rate (ASIR); **C** age-standardized mortality rate (ASMR); **D** age-standardized DALY rate (ASDR)

underscored that population growth and aging were the primary drivers of increasing MND burden in high SDI regions. Nationally, countries such as the United States reported the highest burden, whereas low SDI countries reported fewer cases and deaths. Looking forward, projections indicate a potential global decline in MND burden, but low and middle SDI countries may continue to experience increasing trends. These findings underscore the necessity of region-specific strategies to address the disparities in disease burden across countries and populations.

In 2021, the global burden of MND demonstrated substantial increases in the number of prevalent cases (68.43%) and incident cases (74.54%) since 1990, in line with trends in population aging and improved diagnostic capacity [20, 21]. However, the ASR of prevalence (ASPR) and incidence (ASIR) showed slight downward trends, which may partly reflect improved disease recognition (e.g., dissemination of diagnostic guidelines [22]) and refined coding practices. Nevertheless, caution is needed in interpreting results from low-income regions due to limitations in data availability and model uncertainty in the GBD framework [23]. Increases in mortality and DALYs highlight the long-term impact of MND. Particularly in high-income regions, improvements in diagnostic and care capacity have extended life expectancy but have not reduced overall mortality risk. These findings are in line with recent literature suggesting that while improved care may delay disease progression, it has not significantly altered the fatal outcome of MND [24].

The observed regional inequalities in MND burden are closely related to SDI levels. High SDI regions (e.g., Western Europe and North America) have the highest ASPR, ASIR, and age-standardized mortality rates (ASMR), likely due to better healthcare infrastructure, more complete disease registry systems, and population aging [25, 26]. However, despite advanced diagnostic and treatment services, ASMR continues to increase, suggesting that MND management remains a significant challenge—consistent with patterns seen in other neurodegenerative disorders [27, 28]. In contrast, low SDI regions (e.g., West Africa and South Asia) had the lowest ASPR and ASIR but showed the fastest increases in ASMR (EAPC: 5.07) and DALYs (EAPC: 2.83), likely reflecting limited healthcare

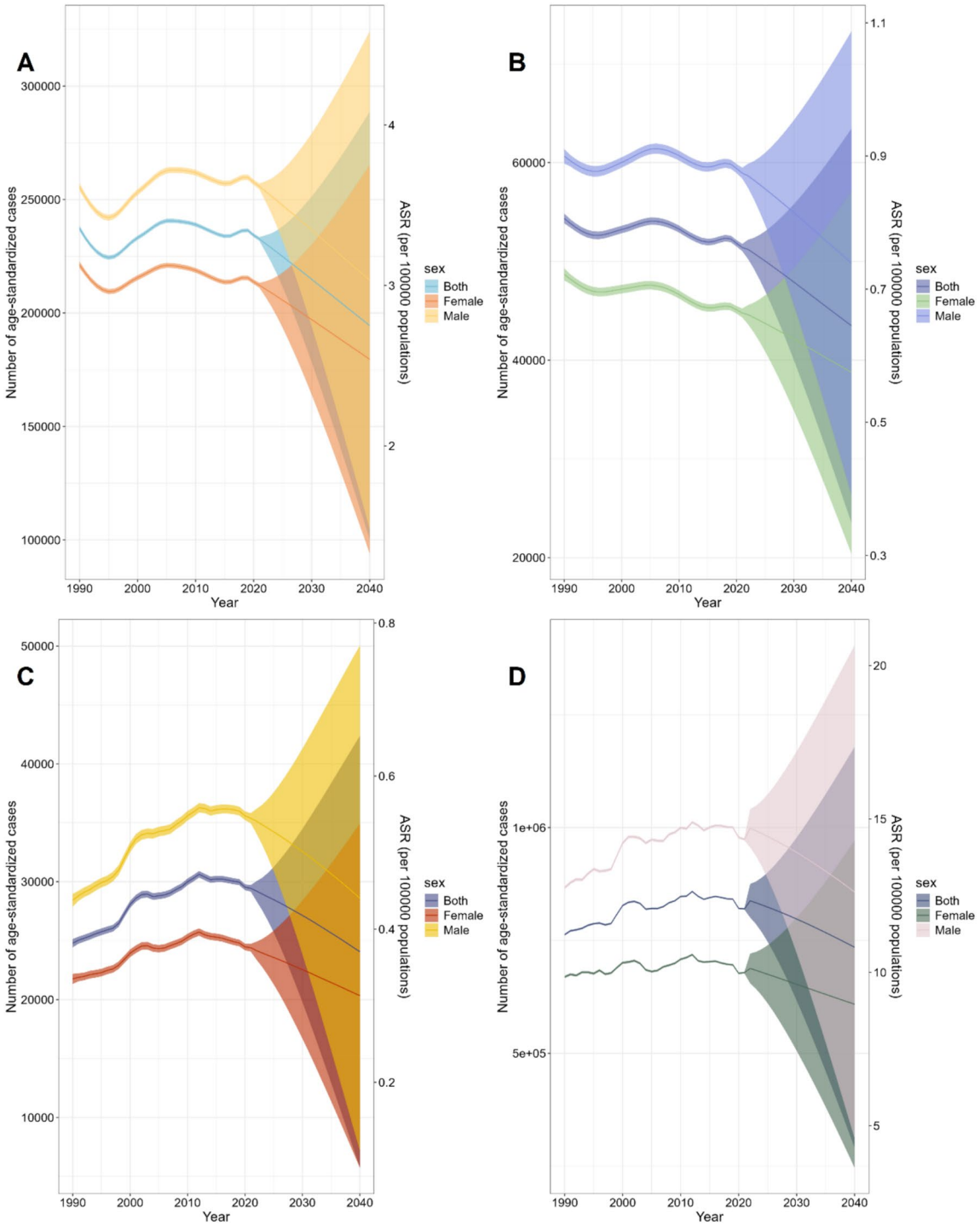

Fig. 6 Projected global trends in sex-specific age-standardized prevalence, incidence, mortality, and DALY rates of motor neuron disease from 1990 to 2040. **A** Age-standardized prevalence rate (ASPR); **B** age-standardized incidence rate (ASIR); **C** age-standardized mortality rate (ASMR); **D** age-standardized DALY rate (ASDR)

access, delayed diagnosis, and lack of palliative care resources [29, 30]. It is noteworthy that historical data gaps in these regions may result in overestimated trends. While the GBD model incorporates sparse data and expert priors to mitigate bias, uncertainty intervals (UIs) remain wider in low SDI areas, indicating potential under-reporting and surveillance limitations [31].

Time-trend analysis further revealed dynamic shifts in the MND burden. Between 2000 and 2004, high SDI regions experienced a sharp increase in prevalence (APC = 1.31%), possibly linked to improved diagnostic criteria and heightened disease awareness [32]. However, despite medical advances, ASMR continued to rise, suggesting persistent unmet needs in MND care. In low SDI regions, ASMR peaked during 1999–2002 (APC = 5.19%) but slowed significantly after 2012 (APC = 0.34%), possibly due to local healthcare improvements. Nevertheless, fundamental diagnostic and treatment capacities remain insufficient [33]. Importantly, the year 2012 marked a global turning point, with declining ASIR (APC = –0.52%) and a deceleration in ASMR, potentially reflecting progress in global surveillance and intervention systems. These findings highlight the need for region-specific MND strategies: high SDI regions should optimize long-term care systems to address aging-related disease burdens, while low SDI regions must improve early diagnostic capacity and strengthen basic healthcare infrastructure to reduce underdiagnosis and treatment delays [34, 35].

Sex-specific patterns show that men bear a significantly higher burden of MND in terms of ASMR and DALYs, consistent with previous studies suggesting that genetic and environmental factors jointly contribute to higher MND risk in males [36, 37]. These findings support the urgent need for sex-specific prevention and management strategies. Decomposition analysis revealed that population growth and aging are critical drivers of increased MND burden, particularly in high SDI areas. These demographic shifts call for tailored health policy responses that reflect local epidemiological trends. As global MND prevalence continues to rise, both high and low SDI regions must prioritize improvements in healthcare infrastructure and implement targeted interventions to mitigate the growing disease burden.

Our projections demonstrate characteristic GBD-defined epidemiological patterns, with high-SDI regions exhibiting declining age-standardized MND rates—consistent with documented improvements in diagnostic capacity and healthcare systems. Conversely, low-to-middle SDI regions show increasing burdens, reflecting the accelerated demographic transition, where population aging precedes healthcare infrastructure development. The observed SDI-dependent divergence mirrors established neurodegenerative disease patterns within the GBD framework. The projection uncertainties (Fig. 6) represent fundamental limitations in modeling rare diseases, arising from: (1) GBD-documented regional variations in data completeness, (2) inherent unpredictability of demographic transitions, and (3) potential paradigm shifts in disease management.

Limitations

The present study has several limitations. First, as with previous Global Burden of Disease (GBD) studies, there are discrepancies in data availability and quality across countries. In particular, regions with limited healthcare infrastructure and insufficient disease reporting may underestimate or misclassify cases of motor neuron disease (MND), especially in low Socio-Demographic Index (SDI) regions. Second, reliance on predictive modeling and expert judgment to fill data gaps introduces uncertainty, particularly in countries with sparse epidemiological data. Third, while the use of Bayesian statistical models to estimate MND mortality and morbidity is robust, they may not fully capture emerging trends or regional variations. Furthermore, the calculation of Years Lived with Disability (YLD) relies on standardized disability weights, which may not accurately reflect the diverse impact of MND across different cultural and healthcare contexts. Finally, although this study provides valuable insights into global and regional trends, the complex interactions between demographic, epidemiological, and healthcare factors may not be fully captured by the models, necessitating further exploration to understand the underlying causes of regional disparities in disease burden.

Conclusion

Motor neuron disease (MND) continues to be a significant global health issue, with increasing burden in high SDI regions due to aging populations and improved diagnosis. Low SDI regions, though reporting lower overall burden, face substantial rises in mortality and DALYs, highlighting gaps in healthcare and diagnosis. The decomposition analysis points to population growth and aging as major contributors to the rising MND burden. While global projections suggest a decrease in MND burden, low and middle SDI regions may experience rising trends, necessitating targeted healthcare interventions. Regional disparities in reporting may influence burden estimates, reflecting inherent GBD study limitations. Future research should focus on regional variations and strategies to reduce the MND burden effectively.

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Author contributions Kai Liu contributed to drafting/revising the article (including medical writing), study concept/design, and data analysis/interpretation; Kun Zhang participated in drafting/revising the article (including medical writing), major data acquisition, study concept/design, and data analysis/interpretation; Anquan Hu was involved in major data acquisition and data analysis/interpretation; Yumeng Li, Wei Sun, and Xian Li contributed to data analysis/interpretation; Heyan Qin assisted in major data acquisition and data analysis/interpretation; Feng Chen performed data analysis/interpretation and funding acquisition; Tao Liu participated in drafting/revising the article (including medical writing).

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Data availability The data used in this study are publicly available from the Global Burden of Disease Study 2021 (GBD 2021) database. The dataset can be accessed at [https://vizhub.healthdata.org/gbd-results/].

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval and consent to participate An ethics approval and the consent to participate was not necessary.

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