RESEARCH ARTICLE

Demographic and Geographic Trends in Myasthenia Gravis–Related Mortality in the United States, 1999–2022

Ali Al-Salahat,[1] Ali Bin Abdul Jabbar,[2] Rohan Sharma,[1] Yu-Ting Chen,[1] and Evanthia Bernitsas[1]

Neurology® 2025;104:e213505. doi:10.1212/WNL.0000000000213505

Correspondence
Dr. Al-Salahat
alsalahatmd@gmail.com

Abstract

Background and Objectives

The prevalence and incidence of myasthenia gravis (MG) have been increasing, globally and in the United States. The literature lacks data on MG-related mortality (MGRM) and its trends in the United States. We aimed to examine nationwide demographic and geographic trends of MGRM from 1999 to 2022.

Methods

This retrospective population-based study used data regarding MG-related deaths (MGRD) from Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research mortality records. The International Classification of Diseases (ICD) code, G70.0, was used to identify MG. We stratified deaths by sex, age groups (25–64 years and older than 64 years), race and ethnicity, and geographical location. Joinpoint regression was performed to examine trends in age-adjusted mortality rates (AAMRs). Sensitivity analysis was performed using MG as an underlying cause of death (UCD).

Results

During the study period, there were 37,075 MGRD (89.6% were older than 64 years, and 44.7% were female individuals). From 1999 to 2022, the MG-related AAMR increased significantly from 6.21 (95% CI 5.58–6.58) per 1 million population to 9.51 (95% CI 9.14–9.88) per 1 million population, with an average annual percent change of +2.42 (95% CI 1.98–2.87). The increase in MGRM was observed regardless of age group, sex, region, or race and ethnicity. The MG-related AAMR increased by 66.3% in male individuals and 29.6% in female individuals over the study period. For individuals aged 65 years or older, there was a concerning increase in MG-related AAMR by 82.35% from 28.23 to 47.36. There was a peak in MGRM during the coronavirus disease 2019 pandemic (2020–2022), and sensitivity analysis revealed that the trend in MGRM remained consistent as both UCD and contributing cause of death.

Discussion

The rising MGRM over the 23-year period is concerning and warrants investigation into the underlying causes for this trend. This increase was most prominent in older and male individuals. The growing burden of MG in the United States and globally might pose a serious challenge to health care in the future. Limitations of this study include reliance on ICD codes. Future work needs to take these trends and disparities into consideration and focus on improving MGRM.

Introduction

Myasthenia gravis (MG), an autoimmune neurologic condition, has been steadily increasing in prevalence and burden.[1] A systematic review estimated the global prevalence of MG at around 12.4 per 100,000 people.[2] Another recent large population data study in the United States estimated that the prevalence of MG is around 32.02 per 100,000 people and its incidence

[1]Neurology Department, Creighton University, Omaha, NE; and [2]Department of Internal Medicine, Creighton University, Omaha, NE.

Glossary

AAMR = age-adjusted mortality rate; **AAPC** = average annual percent change; **APC** = annual percent change; **CDC WONDER** = Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research; **COVID-19** = coronavirus disease 2019; **EOMG** = early-onset MG; **ICD** = International Classification of Diseases; **ICI** = immune-checkpoint inhibitor; **LOMG** = late-onset MG; **LRP4** = low-density lipoprotein receptor-related protein 4; **MG** = myasthenia gravis; **MG-AAMR** = MG-related AAMR; **MGRD** = MG-related death; **MGRM** = MG-related mortality; **MuSK** = muscle-specific kinase; **NH** = non-Hispanic; **UCD** = underlying cause of death.

around 54 per million person-years.[3] Globally, epidemiologic studies from different regions show that the incidence and prevalence of MG have been steadily increasing over the past several years.[4-6]

Remarkable advances in understanding the pathophysiology of MG and its treatment have occurred over the past 2 decades.[7-9] However, MG-related mortality (MGRM) rates remain high compared with the general population, with 1 study in Denmark showing a mortality rate ratio of 1.41.[10] Another large study from the Nordic countries showed that the standardized mortality ratios for MG ranged between 1.20 and 1.32 and were stable from 2000 to 2020.[11] Data from the United States focused on in-hospital mortality rates from MG, which were reported around 1.8%–2.2%.[11,12] These studies and others have reported older age, specifically 65 years or older, as a strong predictor of mortality in MG.[11-13]

The current literature on MGRM primarily focuses on mortality rates in hospitals, excluding deaths that occur outside of the inpatient setting. In addition, there is a lack of national-level data on MGRM trends and disparities in the United States. This study aims to analyze MGRM trends from 1999 to 2022 in the United States and explore demographic and geographical disparities using data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) mortality records. The findings from this study can play a crucial role in guiding future research in MG and can be valuable for neurologists, neuromuscular specialists, policymakers, and health care administrators.

Methods

Study Design and Database

This study followed the RECORD reporting guidelines. CDC WONDER, a comprehensive online database with a wide variety of public health data, was used to identify MG-related deaths (MGRDs) in the United States. Mortality data from the CDC WONDER database are derived from death certificates filed in state vital statistics offices and collected from all states and the District of Columbia into a national database by the National Center for Health Statistics.[14] The denominator for the mortality data is the entire US population based on US Census Bureau estimates.[14,15] The Multiple Cause of Death Files for 1999–2020 and 2018–2022 were queried separately to extract data from 1999 to 2020 and 2021 to 2022, respectively, and merged for analysis.[16,17] The Multiple Cause of Death Files Use death certificate records to find MG listed as an underlying or contributing cause on nationwide death certificate records.

We extracted data regarding MGRD and population sizes from 1999 to 2022. The International Classification of Diseases (ICD), 10th Revision, Clinical Modification codes G70.0 was used to analyze data regarding MGRM[18]; this code showed high positive predictive value (>98%) in a validity study.[19]

Demographic and Geographical Stratification Groups

Specifically, data extracted for analysis included biological sex, race and ethnicity, age groups, region, state, and urban-rural classification. Biological sex included male or female. Race and ethnicity groups were divided into non-Hispanic (NH) White, NH Black, and Hispanic individuals based on what was listed on the patient's death certificate. Other racial and ethnic groups (NH Asian or Pacific Islander, NH American Indian or Alaska Native individuals, etc.) could not be analyzed because of suppressed data for many years in each subgroup. CDC suppresses the counts of fewer than 10 in CDC WONDER data to protect confidentiality, and death rates are marked unreliable for a count less than 20. Age groups were segregated into young adults (aged 25–64 years) and older adults (65 years or older) to compare trends between the younger and older populations. For urban-rural classifications, the National Center for Health Statistics Urban-Rural Classification Scheme was used to divide the population into urban (population >50,000) and rural (population <50,000) counties per the 2013 US census classification.[20] Rural-urban stratified analysis was only conducted from 1999 to 2020 because the database does not report the population in rural and urban areas and mortality rates from 2021 onward. Regions were classified into Northeast, Midwest, South, and West according to the Census Bureau definitions.

Statistical Analysis

MG-related crude number of deaths and age-adjusted mortality rates (AAMRs) per 1,000,000 were calculated. AAMR controls for the population's variation in age distribution, allowing data comparison, and was standardized using the 2,000 US standard population.[21] The Joinpoint Regression Program (Joinpoint version 4.9.0.0 available from National

Cancer Institute, Bethesda, MD) was used to determine trends in mortality within the study period.[22] This program identifies significant changes in annual mortality trends over time through Joinpoint regression, which fits models of linear segments where significant temporal variation occurred. Annual percentage change (APC) with 95% CIs for the AAMRs were calculated for the line segments linking a Joinpoint using the Monte Carlo permutation test. The weighted average of the APCs was calculated and reported as AAPCs and corresponding 95% CIs to summarize the reported mortality trend for the entire study period. APC and AAPCs were considered to increase or decrease if the slope describing the change in mortality over the time interval significantly differed from zero using a 2-tailed *t* test. Statistical significance was set at $p \leq 0.05$.[23] Sensitivity analyses were performed using MG only as an underlying cause of death, which refers to the disease or injury that initiated the sequence of events leading directly to death. The analysis took place in October 2024.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was exempt from institutional review board approval because the CDC WONDER database contains anonymized, publicly available data, and participants cannot be identified.

Data Availability

The data analyzed in this study are publicly available from the CDC WONDER on request.

Results

Overall Mortality

During the study period, there were 37,075 MGRD (eTable 1). Between 1999 and 2022, the MGRD increased by around 135% (Table 1). The MG-related AAMR (MG-AAMR) increased significantly from 6.21 per 1 million people in 1999 to 9.51 per 1 million in 2022 (Figure 1). From 1999 to 2016, the APC for MG-AAMR was +0.96, further accelerating to +6.69 between 2016 and 2022.

Age-Related Disparities

Although most MGRD involved people 65 years or older (33,208, 89.6%), only 3,867 (10.43%) involved people between 25 and 64 years. Over the study period, the MGRD increased by 143% for people 65 years or older and by 70% for people aged 25–64 years (Table 1). Similarly, the MG-AAMR increased from 28.23 to 47.36 for those 65 years or older (Figure 2A) and from 0.87 to 1.06 for those 25–64 years, with an AAPC of +2.49 for the former group and +1.64 for the latter group (eTable 2). For the younger group, the MG-AAMR was stable from 0.87 in 1999 to 0.78 in 2015. However, the MG-AAMR for the younger group increased from 0.78 in 2015 to 1.06 in 2022 (Table 1). For the older group, the MG-AAMR increased from 28.3 in 1999 to 33.42 in 2016 and accelerated from 33.42 in 2016 to 44.3 in 2022.

Sex-Related Disparities

Of the total MGRD from 1999 to 2022, 20,507 (55.3%) were male individuals and 16,568 (44.7%) were female individuals. MGRD increased by 87.5% for female individuals and by 183% for male individuals (Table 1). In female individuals, MG-AAMR increased from 5.13 in 1999 to 6.65 in 2022 (eTable 3). The MG-AAMR was stable for female individuals from 5.13 in 1999 to 4.86 in 2014 but increased from 4.86 in 2014 to 6.65 in 2022. In male individuals, MG-AAMR increased from 8.21 in 1999 to 13.65 in 2022 (Figure 2B). The MG-AAMR for male individuals increased from 8.21 in 1999 to 10.16 in 2017, and it continued increasing from 10.16 in 2017 to 13.65 in 2022.

Race and Ethnicity-Related Disparities

Regarding race and ethnicity, of all MGRD over the study period, 32,671 (88.12%) were NH White individuals, 1,918 (5.17%) were NH Black individuals, and 1,727 (4.66%) were Hispanic individuals. In NH White individuals, MGRD increased by 124% from 1999 to 2022 (Table 1). The MG-AAMR for NH White individuals increased from 6.64 in 1999 to 7.88 in 2016, and it continued increasing from 7.88 in 2016 to 10.88 in 2022 (Figure 2, eTable 4). In NH Black individuals, MGRD increased from by 160% with the MG-AAMR increasing from 3.18 to 5.09 over the study period. However, the MG-AAMR for NH Black individuals remained stable from 3.18 in 1999 to 2.52 in 2013, and it accelerated significantly from 2.52 in 2013 to 5.09 in 2022. In Hispanic individuals, MGRD increased by 281% with the MG-AAMR increasing from 4.2 to 5.38 from 1999 to 2022.The MG-AAMR for Hispanic individuals remained stable from 4.2 in 1999 to 3.86 in 2018 but accelerated from 3.86 in 2018 to 5.38 in 2022.

Region-Based Disparities

In terms of region, MGRD occurred over the study period in the following order: (1) South (14,068, 37.9%), (2) Midwest (8,960, 24.17%), (3) West (7,241, 19.53%), and (4) Northeast (6,806, 18.36%). The number of MGRD increased over the study period by 167% in the South, 93% in the Midwest, 190% in the West, and 85% in the Northeast. In the South, the MG-AAMR (Figure 2D, eTable 5) increased from 6.52 from 1999 to 10.53 in 2022; it remained stable from 1999 to 2015 but increased from 7.01 in 2015 to 10.53 in 2022. In the Midwest, the MG-AAMR increased from 6.64 in 1999 to 9.38 in 2022; it remained stable from 1999 to 2016 and increased from 7.35 in 2016 to 9.38 in 2022. In the West, the MG-AAMR increased from 5.34 in 1999 to 8.85 in 2022; it remained stable between 1999 and 2012 but accelerated from 5.29 in 2012 to 8.85 in 2022. In the Northeast, the MG-AAMR increased from 6.06 in 1999 to 8.32 in 2022; it remained stable between 1999 and 2015 but increased from 6.48 in 2015 to 8.32 in 2022.

Rural-Urban Disparities

The MG-AAMR in urban areas remained stable from 6.16 in 1999 to 6.89 in 2015 (APC +0.69, 95% CI −0.12 to 1.22) and increased from 6.89 in 2015 to 9.24 in 2020 (APC +5.35, 95% CI 3.10–11.60) (eTable 6). Similarly, the MG-AAMR in rural areas remained stable from 6.16 in 1999 to 5.58 in 2006

Table 1 Temporal Trends in MG Mortality Rates, Stratified by Age Group, Biological Sex, Race and Ethnicity, and Region in the United States, 1999 to 2022

	1999		2022				
Characteristic	n	AAMR	n	AAMR	AAPC (95% CI)	APC segment 1 (95% CI, years)	APC segment 2 (95% CI, years)
Total	1,099	6.21	2,584	9.51	2.42 (1.98–2.87)	0.96 (0.04 to 1.60, 1999–2016)	6.69 (4.45–12.28, 2016–2022)
Age group							
25–64	126	0.87	218	1.06	1.64 (0.78–2.51)	−0.085 (−2.83 to 0.39, 1999–2015)	7.59 (4.16–15.88, 2015–2022)
>64	973	28.23	2,366	47.36	2.49 (2.09–2.91)	1.12 (0.30 to 1.72, 1999–2016)	6.46 (4.43–11.43, 2016–2022)
Sex							
Female	552	5.13	1,035	6.65	1.59 (1.19–2.01)	−0.13 (−1.13 to 0.57, 1999–2014)	4.90 (3.42–7.82, 2014–2022)
Male	547	8.21	1,549	13.65	2.76 (2.23–3.30)	1.36 (0.38 to 2.06, 1999–2017)	7.96 (4.79–15.86, 2017–2022)
Race and ethnicity							
NH Black individuals	51	3.18	133	5.09	1.51 (0.12–2.97)	−1.28 (−11.78 to 1.16, 1999–2013)	6.02 (2.41–21.24, 2013–2022)
Hispanic individuals	37	4.2	141	5.38	2.75 (0.79–4.70)	0.75 (−10.33 to 5.87, 1999–2018)	12.80 (2.48–34.42, 2018–2022)
NH White individuals	994	6.64	2231	10.88	2.74 (2.24–3.23)	1.32 (0.23 to 2.00, 1999–2016)	6.88 (4.40–13.81, 2016–2022)
Region							
Northeast	228	6.06	421	8.32	1.94 (1.22–2.61)	0.85 (−3.47 to 1.77, 1999–2015)	4.47 (2.10–12.46, 2015–2022)
Midwest	282	6.64	545	9.38	2.06 (1.39–2.66)	0.95 (−1.38 to 1.71, 1999–2016)	5.27 (2.54–13.04, 2016–2022)
South	403	6.52	1078	10.53	2.55 (2.09–3.05)	0.63 (−0.46 to 1.42, 1999–2015)	7.08 (5.15–11.13, 2015–2022)
West	186	5.34	540	8.85	2.42 (1.64–3.28)	0.41 (−5.58 to 1.99, 1999–2012)	5.10 (3.38–12.14, 2012–2022)

Abbreviations: AAMR = age-adjusted mortality rate; AAPC = average annual percent change; APC = annual percent change; MG = myasthenia gravis.

(APC −1.25, 95% CI −11.01 to 1.92) and increased from 5.58 in 2006 to 10.17 in 2020 (APC +3.49, 95% CI 2.54–8.39).

Place of Death Differences

Overall, over the study period, most MGRD occurred at medical facilities (18,226, 49.16%), followed by home or hospice facilities (10,241, 27.62%), nursing/long-term care facilities (7,343, 19.81%), and other/unknown places (1,271, 3.43%). The crude number of MGRD at medical facilities increased from 691 in 1999 to 1214 in 2022 (176%), but the percentage of deaths at medical facilities out of all MGRD decreased from 62.88% in 1999 to 46.98% in 2022 (eTables 7 and 8). For deaths at home or hospice facilities, the number increased from 169 in 1999 to 855 in 2022 (506%), and the percentage of MGRD at home or hospice facilities increased from 15.38% in 1999 to 33.09% in 2022. The number of MGRD at nursing/long-term facilities increased from 220 in 1999 to 411 in 2022, with the percentage decreasing from 20.02% in 1999 to 15.91 in 2022. Finally, the place of death was unknown for 19 deaths in 1999 and 106 deaths in 2022, with the percentage increasing from 1.73% in 1999 to 4.10% in 2022.

State-Level Differences

There were differences in MG-AAMR at the state level across the United States (Figure 3). For the period between 1999 and 2019, the lowest MG-AAMR was found in the District of Columbia at 3.99 and the highest was in Vermont at 8.66. However, between 2020 and 2022, the highest AAMR was in West Virginia at 9.09 and the lowest was in Hawaii at 3.16 (eTables 9 and 10).

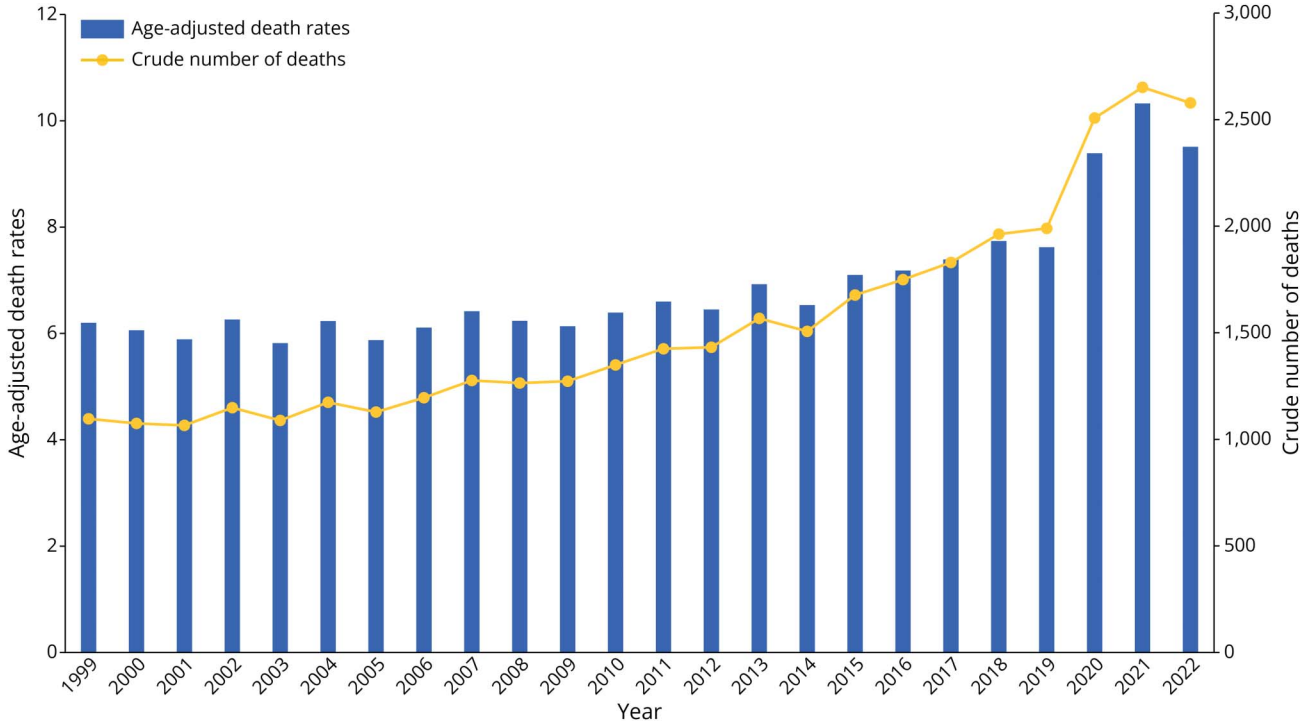
Sensitivity Analysis: MG as an Underlying Cause of Death

Of the 37,075 MGRD, 16,963 (45.75%) had MG listed as the underlying (primary) cause of death (UCD). In 1999, 488 (44.40%) of all MGRD had MG also listed as UCD, which increased to 986 (38.16%) by 2022 (AAPC 1.74, 95% CI 1.46–2.05). An interesting finding to note is that the proportion of death with MG listed as the primary cause of death was markedly high before the pandemic years (2020–2022), with nearly half of the MGRD having MG as UCD but decreased to 38%–39% during the pandemic years (2020–2022). eTable 11 presents a sensitivity analysis comparing MG listed as a contributing cause of death to that of the underlying cause.

Discussion

This 23-year nationwide analysis of MGRM data from the CDC showed several important findings. First, there was a significant and steady increase in MGRM from 1999 to 2022

Figure 1 Overall Trend of Myasthenia Gravis–Related Age-Adjusted Death Rate and Crude Number of Deaths from 1999 to 2022



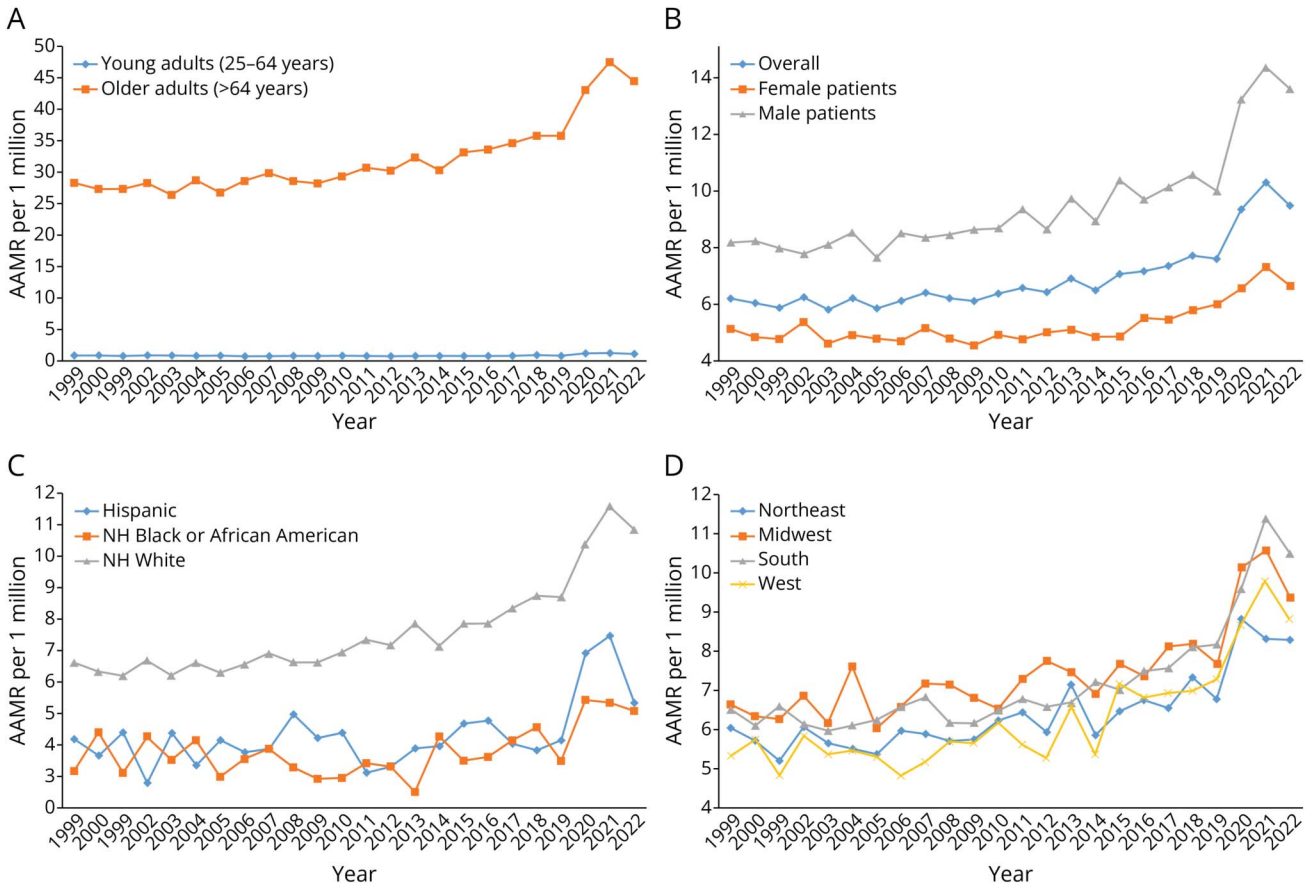
across all age groups, racial and ethnic groups, and regions, with a sharp increase around 2020. The annual number of MGRD more than doubled across the study period, and the AAMR increased from 6.21 to 9.51 per million people. The MGRM trend showed the most marked increase among those aged 65 years or older, with almost 90% of deaths occurring in this age group over the study period. The number of MGRD nearly tripled in male individuals and doubled in female individuals. This study also found significant racial and ethnic and geographical disparities in MGRM and its trend. In addition, we found significant changes in the place of MGRD, with home or hospice facilities doubling and medical facilities decreasing proportionately over the study period. Finally, our findings revealed a sharp increase of MGRM around the coronavirus disease 2019 (COVID-19) pandemic (2020–2022) across all groups and regions.

The up-trend in MGRM over the 23-year period of this study is concerning and warrants investigation. There are multiple possible interpretations for these findings. A growing body of evidence suggests that the prevalence and incidence of MG have been increasing over the past 2 decades.[4,6] This increase in prevalence and incidence of MG could partially account for the increasing mortality. Although MG is known to have a bimodal age distribution, the incidence has been increasing in older people, especially with the aging population.[4,6,24] This leads to more MG occurring in older patients and, hence, increased mortality. However, these factors alone do not explain the increasing mortality, given that our results were adjusted for age. Other factors that might explain the growing incidence of MG are increased access to and better diagnostic tests for MG, including the discovery of anti–muscle-specific kinase (MuSK) and anti–low-density lipoprotein receptor-related protein 4 (LRP4) antibodies.[25] These factors also lead to improvement in awareness of MG among clinicians and the public and, accordingly, as a contributing cause of death.[25,26]

Over the past 2 decades, there have been remarkable advances in the treatment and management of MG.[9] However, clinical trials in MG mostly focused on functional and quality-of-life outcomes, not long-term mortality.[27] Therefore, our findings indicate the need to target long-term mortality in MG research. Nevertheless, long-term mortality benefit from the newly approved medications for MG, such as efgartigimod (2021), is yet to be evaluated.[28] Moreover, recent evidence shows that older patients with MG have an increased risk of fatal adverse effects from immunosuppressants, which can lead to higher mortality as the MG population grows older.[29]

The pathophysiology and prognosis of early-onset MG (EOMG) and late-onset MG (LOMG) differ remarkably.[30] Multiple studies have shown that LOMG is characterized by severe presentations with frequent emergency visits and crises.[30-32] These aforementioned factors combined might also explain the higher mortality in male individuals compared with female individuals, as the former group is more affected by LOMG than the latter. In addition, cases of immune-checkpoint inhibitor (ICI)–related MG were first reported

Figure 2 Myasthenia Gravis–Related AAMR, Stratified by (A) Age Group, (B) Sex, (C) Race and Ethnicity, and (D) Region



AAMR = age-adjusted mortality rate.

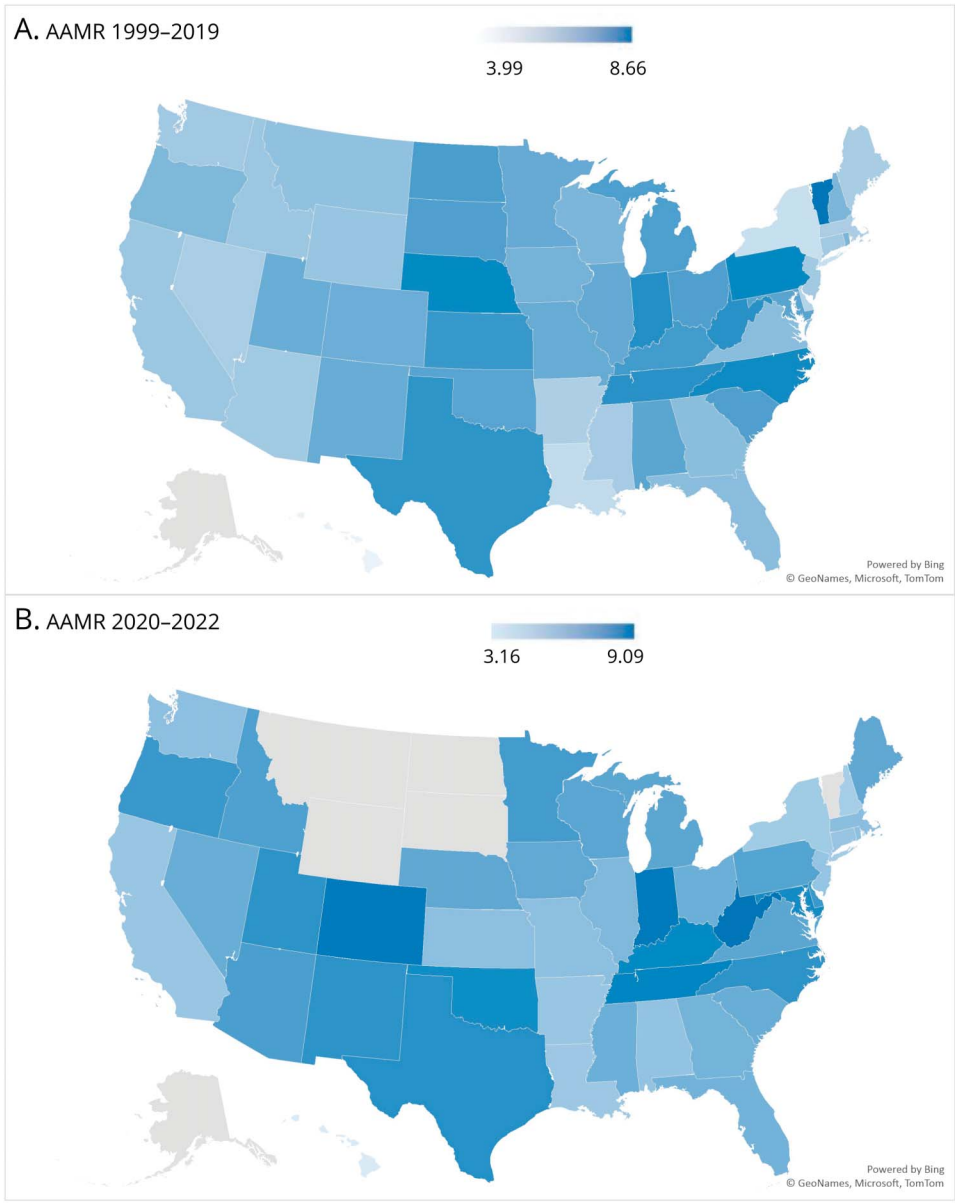
starting from 2017.[33] ICI-related MG has a more rapid and severe presentation and is usually accompanied by ICI-related myocarditis and myositis, contributing to an increase in MGRM.[34] Finally, anti-MuSK and anti-LRP3 have only been recently discovered, and these antibodies entail a higher degree of severity and risk of mortality from MG, given the severity of presentation and the frequency of crises associated with these forms of MG.[35,36]

Our findings differ drastically from previous studies examining MGRM. A recent large European study showed relatively stable MGRM from 2000 to 2020 despite increasing incidence and prevalence.[14] This is a clearly contrasting finding from our study in the United States. The study included nationwide data from 3 Nordic countries that have universal, publicly funded, and high-quality health care available to all citizens. This might have been a factor in stabilizing MGRM, although the incidence of MG increased. Studies in the United States that showed stable MGRM primarily focused on in-hospital mortality and were limited to short periods. Our study involved extensive nationwide mortality data and examined MGRM over 23 years. Another factor that may account for the difference in MGRM between the United States and Europe is the presence of other comorbidities including obesity, cardiac, and pulmonary diseases.[37,38] Studies comparing trends of overweight prevalence in the United States showed a rapid and more pronounced increase than European countries.[37] Obesity has been shown to carry a higher risk for complications from MG.[39,40]

The increasing MGRM evidenced from this study and the growing burden of MG globally might pose a serious challenge to health care in the future. It also indicates an increasing need for more research and neurologists specialized in managing MG. Given that our findings indicated the increasing MGRM was most significant in older people, future research can be directed toward improving mortality in this group of people suffering from MG.

Our study showed significant racial and ethnic disparities in MGRM trends. Although all racial and ethnic groups in the study showed a significant increase in MGRM over the study period, deaths in NH White individuals accounted for the majority (88.12%) of the total MGRD. The MG-AAMR was highest in NH White individuals, followed by Hispanic and then NH Black individuals. Multiple reasons may account for these disparities. First, studies showed racial and ethnic

Figure 3 Myasthenia Gravis–Related AAMRs Stratified by State, (A) 1999–2019 and (B) 2020–2022



AAMR = age-adjusted mortality rate.

disparities in the access to neurologic care and specialized neurologic testing.[41,42] This can lead to underdiagnosis of MG in Black or Hispanic individuals. In addition, a recent study found disparities in the access to MG-specific testing and treatment.[43] Eventually, these factors can lead to underestimation and under-documentation of MG and its mortality in racial and ethnic minority groups. These differences can help guide policymakers and health care administrators in addressing these issues related to access to neurologic testing and care. Second, genetic studies found that White individuals, carrying certain HLA-DRB1 alleles, have higher risk for LOMG, while African Americans are more likely to develop EOMG.[44,45] In addition, a study on a Spanish population cohort found that certain HLA alleles (DQB105:02, DQB105:03, and DQB1*03:01) were associated with EOMG in female individuals.[46] These studies suggest that NH White individuals are more likely to develop LOMG leading to higher mortality risk from MG compared with other racial and ethnic groups.[30-32,44-46]

All regions in the United States experienced a similar up-trend in MGRM. The South had the largest proportion of MGRD, followed by the Midwest, West, and Northeast. This distribution mirrors findings of studies on the incidence and prevalence of MG being the highest in the South and then the Midwest as second, followed by the West and Northeast.[4,6] The high AAMR in West Virginia also mirrors the high prevalence of the disease in this state.[47] These data can be valuable in resource allocation aimed at the diagnosis and management of MG.

We also saw significant changes over the study period regarding the place of MGRD. The findings suggest that more MGRDs are occurring at home or hospice facilities rather than medical facilities, pointing again to the aging MG population. Deaths at home or hospice facilities reached a peak just before the COVID-19 pandemic.

Our study shows that MGRM saw a sharp increase during the COVID-19 pandemic across all groups and regions. This is consistent with several studies that showed patients with MG suffered from more crises and exacerbations during the pandemic.[48] These studies also showed that severe MG-related symptoms at baseline correlated with worse infections with COVID-19.[49] In addition, our sensitivity analysis examined MG as UCD, showing that the pandemic spike in MGRM was largely due to MG as a contributing cause of death. Nevertheless, the analysis showed that the steady up-trend in MGRM remained for MG as primary cause of death (UCD) and as contributing cause of death.

Owing to CDC WONDER data being collected from a public health database, this study may have some limitations. Variables such as social determinants of health could contribute to the patient's death and were not reported on the website or death certificate. We were only able to analyze racial and ethnic disparities for NH White, NH Black or Hispanic individuals, and other racial and ethnic groups (NH Asian or Pacific Islander, NH American Indian or Alaska Native individuals, etc.) could not be analyzed because of suppressed data for many years in each subgroup. CDC suppresses the counts of fewer than 10 in CDC WONDER data to protect confidentiality, and death rates are marked unreliable for a count less than 20 per the CDC WONDER data use agreement. Rural-urban stratified analysis could only be conducted from 1999 to 2020 because the database does not report the age group-specific populations in rural and urban areas and mortality rates from 2021 onward. In addition, given that the CDC WONDER data is reliant on ICD codes, it can be subject to misclassification, and it also lacks information on potential confounders.

Our study revealed concerning findings regarding MGRM trends in the United States from nationwide data across the period 1999–2022. There was a steady and consistent up-trend in MGRM in all groups and regions, with an obvious spike during the pandemic years (2020–2022). The increase in MGRM is most marked in the older age group (64 years and older). These data warrant further investigation and monitoring to understand the underlying causes of these trends. Future research may focus on reducing MGRM, especially in the older MG population.

Author Contributions

A. Al-Salahat: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. A.B. Abdul Jabbar: major role in the acquisition of data; analysis or interpretation of data. R. Sharma: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. Y.-T. Chen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. E. Bernitsas: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data.

Study Funding

No targeted funding reported.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* November 5, 2024. Accepted in final form January 23, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Brian C. Callaghan, MD, MS, FAAN.

References

1. Rodrigues E, Umeh E, Aishwarya , Navaratnarajah N, Cole A, Moy K. Incidence and prevalence of myasthenia gravis in the United States: a claims-based analysis. *Muscle Nerve*. 2024;69(2):166-171. doi:10.1002/mus.28006
2. Salari N, Fatahi B, Bartina Y, et al. Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis. *J Transl Med*. 2021;19(1):516. doi:10.1186/s12967-021-03185-7
3. Ye Y, Murdock DJ, Chen C, Liedtke W, Knox CA. Epidemiology of myasthenia gravis in the United States. *Front Neurol*. 2024;15:1339167. doi:10.3389/fneur.2024.1339167
4. Tsai NW, Chien LN, Hung C, et al. Epidemiology, patient characteristics, and treatment patterns of myasthenia gravis in Taiwan: a population-based study. *Neurol Ther*. 2024;13(3):809-824. doi:10.1007/s40120-024-00619-4
5. Breiner A, Widdifield J, Katzberg HD, Barnett C, Bril V, Tu K. Epidemiology of myasthenia gravis in Ontario, Canada. *Neuromuscul Disord*. 2016;26(1):41-46. doi:10.1016/j.nmd.2015.10.009
6. Yoshikawa H, Adachi Y, Nakamura Y, et al. Two-step nationwide epidemiological survey of myasthenia gravis in Japan 2018. *PLoS One*. 2022;17(9):e0274161. doi:10.1371/journal.pone.0274161
7. Kaminski HJ, Sikorski P, Coronel SI, Kusner LL. Myasthenia gravis: the future is here. *J Clin Invest*. 2024;134(12):e179742. doi:10.1172/JCI179742
8. Saccà F, Pane C, Espinosa PE, Sormani MP, Signori A. Efficacy of innovative therapies in myasthenia gravis: a systematic review, meta-analysis and network meta-analysis. *Eur J Neurol*. 2023;30(12):3854-3867. doi:10.1111/ene.15872
9. Jordan A, Freimer M. Recent advances in understanding and managing myasthenia gravis. *F1000Res*. 2018;7:F1000 Faculty Rev-1727. doi:10.12688/f1000research.15973.1
10. Hansen JS, Danielsen DH, Somnier FE, et al. Mortality in myasthenia gravis: a nationwide population-based follow-up study in Denmark. *Muscle Nerve*. 2016;53(1):73-77. doi:10.1002/mus.24697
11. Vissing J, Atula S, Savolainen M, et al. Epidemiology of myasthenia gravis in Denmark, Finland and Sweden: a population-based observational study. *J Neurol Neurosurg Psychiatry*. 2024;95(10):919-926. doi:10.1136/jnnp-2023-333097
12. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology*. 2009;72(18):1548-1554. doi:10.1212/WNL.0b013e3181a41211
13. Habib AA, Sacks N, Cool C, et al. Hospitalizations and mortality from myasthenia gravis: trends from 2 US national datasets. *Neurology*. 2024;102(2):e207863. doi:10.1212/WNL.0000000000207863
14. Kochanek KD, Murphy SL, Xu J, Arias E. Deaths: final data for 2020. *Natl Vital Stat Rep*. 2023;72(10):1-92.
15. Ahmad FB, Cisewski JA, Xu J, Anderson RN. Provisional mortality data: United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(18):488-492. doi:10.15585/mmwr.mm7218a3
16. Centers for Disease Control and Prevention, National Center for Health Statistics. *National Vital Statistics System, Mortality 1999-2020 on CDC WONDER Online Database, released in 2021. Data are from the Multiple Cause of Death Files, 1999-2020, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program*. Accessed October 19, 2024. wonder.cdc.gov/mcd-icd10.html.
17. Centers for Disease Control and Prevention, National Center for Health Statistics. *National Vital Statistics System, Mortality 2018-2022 on CDC WONDER Online Database, released in 2024. Data are from the Multiple Cause of Death Files, 2018-2022, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital*

Statistics Cooperative Program. Accessed October 19, 2024. wonder.cdc.gov/mcd-icd10-expanded.html.
18. World Health Organization. *ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision*, 2nd ed. WHO; 2004.
19. Lee BN, Kim K, Shin HY, et al. Validation and proposal of case definitions for identifying patients with myasthenia gravis. *Curr Med Res Opin*. 2024;40(11):1985-1991. doi:10.1080/03007995.2024.2416984
20. Rothwell C, Madans J, Arispe I. NCHS urban–rural classification scheme for counties. *National Center for Health Statistics*. 2013;2:166.
21. Anderson R, Rosenberg H. Age standardization of death rates; implementation of the year 2000 standard. *Natl Vital Stat Rep*. 1998;47(3):1-16, 20.
22. Kim H, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2001;20:655.
23. *Joinpoint Regression Program, Version 5.0.2*. Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute; 2023.
24. Aarli JA. Myasthenia gravis in the elderly: is it different? *Ann NY Acad Sci*. 2008;1132:238-243. doi:10.1196/annals.1405.040
25. Yoganathan K, Stevenson A, Tahir A, Sadler R, Radunovic A, Malek N. Bedside and laboratory diagnostic testing in myasthenia. *J Neurol*. 2022;269(6):3372-3384. doi:10.1007/s00415-022-10986-3
26. Yang J, Wu J, Han T, et al. Global research hotspots and frontiers of myasthenia gravis from 2002 to 2021: a bibliometric study. *Medicine (Baltimore)*. 2023;102(24):e34002. doi:10.1097/MD.0000000000034002
27. Howard JF Jr, Bril V, Vu T, et al. Long-term safety, tolerability, and efficacy of efgartigimod (ADAPT+): interim results from a phase 3 open-label extension study in participants with generalized myasthenia gravis. *Front Neurol*. 2023;14:1284444. doi:10.3389/fneur.2023.1284444
28. Heo YA. Efgartigimod: first Approval [published correction appears in Drugs. 2022;82(5):611. doi:10.1007/s40265-022-01712-4]. *Drugs*. 2022;82(3):341-348. doi:10.1007/s40265-022-01678-3
29. Chanson JB, Bouhour F, Aubé-Nathier AC, et al. Myasthenia gravis treatment in the elderly presents with a significant iatrogenic risk: a multicentric retrospective study. *J Neurol*. 2023;270(12):5819-5826. doi:10.1007/s00415-023-11925-6
30. Fan L, Ma S, Yang Y, Yan Z, Li J, Li Z. Clinical differences of early and late-onset myasthenia gravis in 985 patients. *Neurol Res*. 2019;41(1):45-51. doi:10.1080/01616412.2018.1525121
31. Cortés-Vicente E, Álvarez-Velasco R, Segovia S, et al. Clinical and therapeutic features of myasthenia gravis in adults based on age at onset. *Neurology*. 2020;94(11):e1171-e1180. doi:10.1212/WNL.0000000000008903
32. de Meel RH, Lipka AF, van Zwet EW, Niks EH, Verschuuren JJ. Prognostic factors for exacerbations and emergency treatments in myasthenia gravis. *J Neuroimmunol*. 2015;282:123-125. doi:10.1016/j.jneuroim.2015.03.018
33. Makarious D, Horwood K, Coward JIG. Myasthenia gravis: an emerging toxicity of immune checkpoint inhibitors. *Eur J Cancer*. 2017;82:128-136. doi:10.1016/j.ejca.2017.05.041
34. Qin Y, Chen S, Gui Q, et al. Prognosis of immune checkpoint inhibitor-induced myasthenia gravis: a single center experience and systematic review. *Front Neurol*. 2024;15:1372861. doi:10.3389/fneur.2024.1372861
35. König N, Stetefeld HR, Dohmen C, et al. MuSK-antibodies are associated with worse outcome in myasthenic crisis requiring mechanical ventilation. *J Neurol*. 2021;268(12):4824-4833. doi:10.1007/s00415-021-10603-9
36. Rivner MH, Quarles BM, Pan JX, et al. Clinical features of LRP4/agrin-antibody-positive myasthenia gravis: a multicenter study. *Muscle Nerve*. 2020;62(3):333-343. doi:10.1002/mus.26985
37. Janssen F, Bardoutsos A, Vidra N. Obesity prevalence in the long-term future in 18 European countries and in the USA. *Obes Facts*. 2020;13(5):514-527. doi:10.1159/000511023
38. Solé-Auró A, Michaud PC, Hurd M, Crimmins E. Disease incidence and mortality among older Americans and Europeans. *Demography*. 2015;52(2):593-611. doi:10.1007/s13524-015-0372-7
39. Liu XD, Shao MR, Sun L, Zhang L, Jia XS, Li WY. Influence of body mass index on postoperative complications after thymectomy in myasthenia gravis patients. *Oncotarget*. 2017;8(55):94944-94950. doi:10.18632/oncotarget.19189
40. Wilcke H, Glaubitz S, Kück F, et al. Female sex and overweight are associated with a lower quality of life in patients with myasthenia gravis: a single center cohort study. *BMC Neurol*. 2023;23(1):366. doi:10.1186/s12883-023-03406-0
41. Perez MA, Reyes-Esteves S, Mendizabal A. Racial and ethnic disparities in neurological care in the United States. *Semin Neurol*. 2024;44(2):178-192. doi:10.1055/s-0043-1778639
42. Saadi A, Himmelstein DU, Woolhandler S, Mejia NI. Racial disparities in neurologic health care access and utilization in the United States. *Neurology*. 2017;88(24):2268-2275. doi:10.1212/WNL.0000000000004025
43. Suresh S, Watanabe M, Reynolds EL, Callaghan BC. Possible sex and racial disparities in myasthenia gravis care. *Muscle Nerve*. 2024;70(4):791-799. doi:10.1002/mus.28215
44. Ling CS, Shen ML, Wang Y, et al. The associations of HLA-DRB1 gene polymorphisms with late-onset myasthenia gravis: a meta-analysis. *Neurol Sci*. 2020;41(5):1041-1049. doi:10.1007/s10072-019-04213-7
45. Maniaol AH, Elsais A, Lorentzen ÅR, et al. Late onset myasthenia gravis is associated with HLA DRB1*15:01 in the Norwegian population. *PLoS One*. 2012;7(5):e36603. doi:10.1371/journal.pone.0036603
46. Salvado M, Caro JL, Garcia C, et al. HLA-DQB1*05:02, *05:03, and *03:01 alleles as risk factors for myasthenia gravis in a Spanish cohort. *Neurol Sci*. 2022;43(8):5057-5065. doi:10.1007/s10072-022-06102-y
47. Phillips LH II, Torner JC, Anderson MS, Cox GM. The epidemiology of myasthenia gravis in central and western Virginia. *Neurology*. 1992;42(10):1888-1893. doi:10.1212/wnl.42.10.1888
48. De León AM, Aban I, McPherson T, et al. Impact of the COVID-19 pandemic on patients with myasthenia gravis: a survey of the Myasthenia Gravis Foundation of America MG patient registry. *Muscle Nerve*. 2023;67(1):25-32. doi:10.1002/mus.27743
49. Li J, Zheng Y, Zhao Y, et al. COVID-19 in patients with myasthenia gravis: a single-center retrospective study in China. *Neurol Sci*. 2024;45(7):2969-2976. doi:10.1007/s10072-024-07518-4