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Prevalence, Incidence, and Mortality of Myasthenia Gravis and Myasthenic Syndromes: A Systematic Review

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Keywords
Myasthenia gravis · Epidemiology · Prevalence · Incidence · Mortality

Abstract

Introduction: No systematic reviews were published in the last years investigating epidemiological data, involving myasthenia gravis (MG) and related myasthenic syndromes. This systematic review aimed to estimate the prevalence, incidence, and mortality of all MG types and myasthenic syndromes worldwide. ***Methods:*** All literature published up to February 2024 was retrieved by searching the databases "Medline," "Embase," "ISI Web of Science" and "CINAHL" using the following search terms: (epidemiolog* OR frequency OR prevalence OR incidence OR mortality) AND (myasth* OR "anti-acetylcholine receptor antibody" OR "AChR" OR "MuSK" OR "anti-muscle specific kinase antibody" OR "LRP4" OR "seronegative MG"). ***Results:*** A total of 94 studies, performed between 1952 and 2022, were included. Prevalence of MG ranged from 20 to 475 cases per million, with a mean prevalence of 173.3 (95% confidence interval [CI]: 129.7–215.5) cases per million and a median prevalence of 129.6 cases per million. Incidence rates ranged from 2.3 to 61.3 cases per million person-years, with a mean incidence of 15.7 (95% CI: 11.5–19.9) and a median of 13.3 cases. Mortality rates showed a mean of 1.4 (95% CI: 0.8–2.1) cases per million person-years. Acetylcholine receptor (AChR)-MG was the clinical subtype more frequent in terms of prevalence and incidence. ***Discussion:*** The prevalence and incidence of MG have significantly increased over the last years worldwide, probably due to the improvement of epidemiological methodologies and current advances in diagnosis. However, we observed a significant variation in frequencies of MG between and within countries because

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of methodological biases and complex heterogeneity of the disease characterized by several phenotypes and different clinical responses.

Introduction

Myasthenia gravis (MG) is one of the main neuromuscular disorders, defined as an autoimmune disorder caused by pathogenic autoantibodies to components of the postsynaptic muscle endplate. From a clinical point of view, the altered function of the neuromuscular junction leads to characteristic fatigable weakness, increased with continued muscle activity and a fluctuating course, even during the day [1]. MG is a heterogeneous disease, with several subgroups into which patients can be divided based on serological status, clinical phenotype, age at onset, and association with thymic pathology. Thus, patients with MG are typically divided into subgroups, which are classified according to the age of onset (juvenile-onset, ≤18 years; early-onset, 19–50 years; late-onset, >50 years), the presence of a thymoma (thymoma-associated MG), and the clinical phenotype (ocular or generalized MG) [2]. These divisions mainly regard the clinical subtype characterized by the presence of the antibodies affecting the nicotinic acetylcholine receptor (AChR) which represents the most frequent form of seropositive MG (AChR-MG) [2]. Approximately 85% of patients with generalized disease and 50–60% of patients with ocular disease are classified as having AChR-MG, and among patients with AChR-negative MG, 30–60% have muscle-specific tyrosine kinase (MuSK) antibodies [2]. MUSK-MG represents a less common subtype of seropositive MG, together with the lipoprotein receptor-related protein 4 (LRP4)-MG that is characterized by the presence of antibodies targeting the low-density lipoprotein receptor-related protein 4 [1].

MG associated with both AChR and MuSK antibodies is very rare and is mostly present in childhood or adolescence. The detection of MuSK antibodies in this group of patients typically coincides with a clinical worsening of bulbar weakness [3], while LRP4-MG accounts for about 1–2% of total cases of the disease, and this group is often characterized by female patients with mild generalized or ocular, early-onset disease [3]. Despite the autoimmune nature of the disease, antibodies to AChR, MuSK, and LRP4 could not be detected, thus having a seronegative form of MG (seronegative MG). This occurs probably due to the reduced sensitivity of the test methods in use or the presence of antibodies to as yet undetermined postsynaptic membrane antigens [4]. In addition to these aforementioned autoimmune subtypes, MG can also be congenital and associated with genetic abnormalities [4].

Myasthenic syndromes exhibit clinical characteristics similar to those observed in MG patients, despite showing different prognoses or autoimmune responses [5]. Lambert-Eaton myasthenic syndrome (LEMS) is considered one of the most important myasthenic syndromes. Conversely to MG, in patients with LEMS, the weakness tends to spread in a caudal-to-cranial direction, and the presentation with only ocular symptoms is very rare [5]. Moreover, LEMS is 46 times less frequent than MG [6]. Compared to LEMS, a larger number of MG epidemiological studies have been performed worldwide over the years with marked variability in observed incidence and prevalence of the disease. In this regard, Carr et al. [7] provided the most recent systematic review, estimating the incidence and prevalence of MG at 5.3 per million and 77.7 per million, respectively, with a large number of epidemiological studies, mainly in Western Europe and Asia, reporting significant differences in incidence ranging from 1.7 to 30 per million per year [7]. However, Carr et al. [7] provided their data more than 10 years ago, and the number of MG patients has grown, and it has more than doubled in the last 20 years, probably due to a greater MG incidence in the elderly, and because of the better diagnosis, treatment, and increasing longevity of the population [8]. Also, there is a need to investigate the prevalence, incidence, and mortality of the different etiologies and subtypes that distinguish MG and myasthenic syndromes. To our knowledge, no systematic reviews were published in the last years investigating these epidemiological data, involving all MG types (autoimmune and congenital) and related myasthenic syndromes like LEMS. In light of this, the present systematic review aimed to estimate the prevalence, incidence, and mortality of MG and myasthenic syndromes worldwide. This work was performed as part of a project funded by the Italian Medicines Agency in the context of the pharmacovigilance call 2012-2013-2014 ("Comparative Effectiveness and Safety of Drugs used in Rare Neuromuscular and Neurodegenerative Diseases – the CAESAR study").

Materials and Methods

This systematic literature review was reported based on the PRISMA statement for reporting systematic reviews and meta-analyses [9]. Additionally, the study protocol was registered in the International Prospective

Register for Systematic Reviews (PROSPERO) with the following code: CRD42023415272. All literature published up to February 2024 was retrieved by searching the databases "Medline", "Embase", "ISI Web of Science" and "CINAHL" using the following search terms: (epidemiolog* OR frequency OR prevalence OR incidence OR mortality) AND (myasth* OR "anti-acetylcholine receptor antibody" OR "AChR" OR "MuSK" OR "anti-muscle specific kinase antibody" OR "LRP4" OR "seronegative MG").

No limitations in the search strategy were applied to the date of publication, study design, or language. References of considered studies were also searched to identify any further relevant data.

Using the Rayyan web tool for systematic reviews [10], the titles and abstracts of the identified records were initially screened and selected by six groups composed of two independent and blinded reviewers based on their expertise on the review topic. Conflicts and disagreements were resolved by consensus.

The following set of predefined inclusion criteria were then individually applied to the selected articles in their full-text version: (i) studies enrolling subjects with a clinical diagnosis of MG or myasthenic syndromes or any other type of MG subgroup; (ii) studies reporting data on prevalence, incidence, or mortality of any type of MG; (iii) clearly defining a denominator population; (iv) reporting enough data to allow for data extraction; (v) studies published in English. Case reports, case series, reviews, letters, conference proceedings, abstracts, and editorials were excluded. Systematic reviews were considered separately to check the consistency of the data.

Data Extraction and Quality Assessment

Data extraction from the included studies was performed by independent reviewers using standardized tables. For each study, the following data were extracted: country, MG type, source type, period of the study, number of MG cases, mean age, gender, denominator, prevalence (crude and standardized), incidence (crude and standardized), and mortality (crude and standardized).

Statistical analyses were performed by examining the mean and median values of prevalence, incidence, and mortality rates of MG and relative clinical subgroups, and 95% confidence intervals (CIs) were calculated. Globally, there were no significant differences between crude and standardized rates, and not all the studies reported standardized data. So, crude rates are used throughout this review.

The quality assessment of each study was independently evaluated by six groups, each composed of two independent reviewers using the Methodological Evaluation of Observational REsearch (MORE) checklist [11]. The MORE tool includes 26 items, referring to both external and internal validity, assessing the appropriateness of sampling bias, response and exclusion rate, address bias, source of measures, reference period, severity and frequency of symptoms, validation of outcome measurement, reliability of estimates, reporting of prevalence/incidence, and precision of the estimates. For each item, a score ranging from 0 to 2 can be assigned. Higher scores are associated to worse study quality, since for each item, a score of 0 is assigned if there is no flaw, a score of 1 is assigned if there is a minor flaw, and a score of 2 is assigned if there is a major flaw. Missing items (not reported/not applicable) are not considered in the count, but their characterization is important to define the study quality. Studies with the same total score might present a different quality due to the different number of not reported or not applicable items.

Results

Bibliographic searches on literature databases yielded 6,223 records. After the first screening, 184 records were selected, and the related full texts were retrieved. Based on the full text, 90 studies were excluded, as they did not meet the inclusion criteria. Overall, 94 studies were included (flow diagram is illustrated in Fig. 1). A high agreement (>90%) was reported by the reviewers involved in the study selection process.

Most of the included studies (81.9%) examined all types of MG (ALL MG), reporting prevalence (59 studies), incidence (50 studies), and mortality (16 studies). In these studies, epidemiological data were often referred to ALL MG category, without reporting the prevalence, incidence, or mortality of MG subtypes. Moreover, 10 studies focused on AChR-MG providing incident rates (IRs), with 2 studies providing both incident and prevalence rates (PRs), while only 1 study reported mortality rates (MRs). PR and IR of MUSK-MG were analyzed in 2 studies, while LEMS was examined in 5 studies. Juvenile and congenital MG were investigated in 3 and 2 studies, respectively. No studies about the epidemiology of LRP4-MG and seronegative MG were found. A total of 80 studies (85.1%) were population-based, while the remaining (14.9%) were clinical. The period of the studies ranged from 1952 to 2022. There was a wide geographical distribution, with representation of

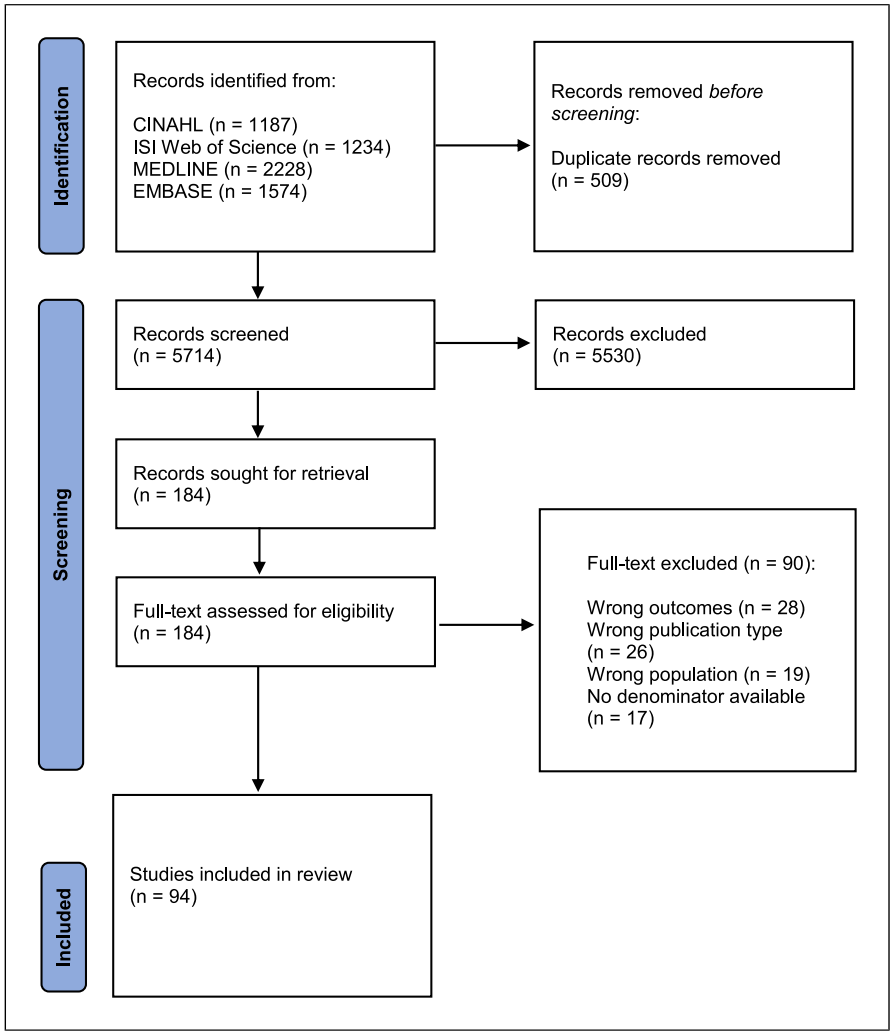

Fig. 1. PRISMA flow diagram of the included study.

all continents (Fig. 2). A total of 63 studies were performed in Europe with particular contributions from Italy (13 studies), the UK (7 studies), and Norway (7 studies).

Quality Assessment

Most of the included studies (86.2%) were retrospective and employed national health registries/databases to capture MG cases during a specific period. The quality of the studies ranged from very low to high, with most of the studies (73.3%) showing a medium quality (medium overall score: 3.4, SD 3.5). Two studies [12, 13] obtained 0 points, and the lowest score achieved was 8 [14], but many studies did not report several items concerning external validity, thus compromising their quality in terms of generalizability. The main reasons associated with poorer quality were subjects enrolled by clinical records, response, and exclusion rates often not reported in the studies, and sampling bias not addressed in the analysis. Concerning internal validity, many studies (56.4%) did not report a validation of outcome measures and the reliability of the estimates (64.9% of the studies). A total of 56 studies (59.5%) reported period prevalence/incidence rates, while the remaining studies (40.5%) described point epidemiological rates. Finally, most of the studies (74.5%) reported only crude epidemiological rates. A summary of the quality assessment of the included studies is shown in online supplementary Tables 1S and 2S (for all online suppl. material, see https://doi.org/10.1159/000539577).

Prevalence

For the ALL MG group, 59 studies [12–70] estimated prevalence, and PRs ranged from 20 to 475 cases per million (online suppl. Table 3S), with a mean PR of 173.3 (95% CI: 129.7–215.5) cases per million and a median prevalence of 129.6 cases per million. Taking into consideration all the studies and countries,

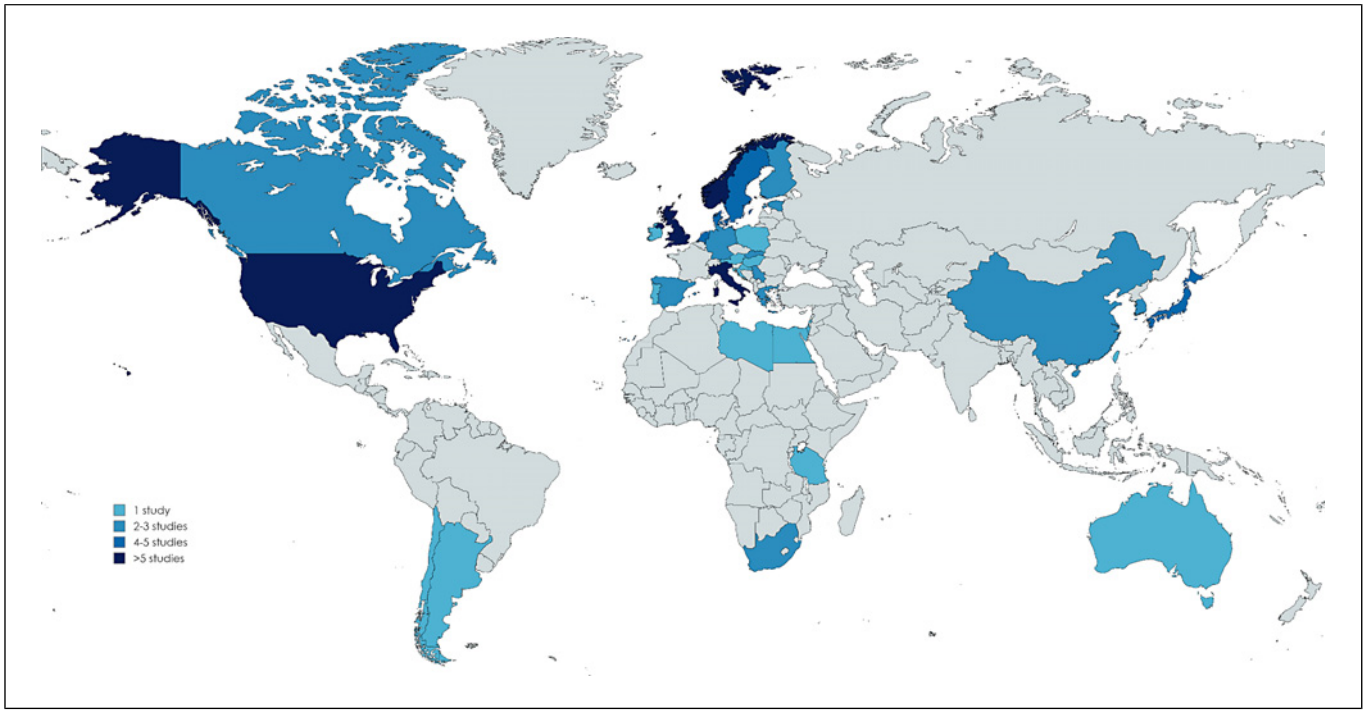

Fig. 2. Geographical distribution of the included studies. This figure offers an overview of the geographical distribution of the included studies. The gradient of blue indicates the number of studies: countries represented with darker blue are those with a higher number of studies. The gray countries are those without studies.

prevalence showed an increasing trend over the years (Fig. 3). The mean PR was 97.5 (95% CI: 59.9–141.9; range: 20–174.2) cases per million considering studies from 1952 to 2007 (the most recent period investigated by the last systematic review [7]), while the mean PR increased up to 220.1 (95% CI: 149.3–288.1; range: 78–475) cases per million considering the period 2008–2021. Also, the median PRs showed an increase from 99 (period: 1952–2007) to 196.8 (period: 2008–2021) cases per million.

Moreover, significant differences were observed between continents regarding PR, with the highest mean PR registered in the American continent (256.2 cases per million, 95% CI: 89.1–423.3; range 70–475); North America showed a mean PR of 341.4 (range: 142–475) cases per million, while studies conducted in South America revealed a lower mean PR (149.8, range: 70–367.1 cases per million). Europe and Asia provided a mean PR of 167.9 (95% CI: 117.9–217.9; range: 20–393) and 127.4 (95% CI: 92.3–162.5; range: 67–231) cases per million, respectively. No significant differences were observed between Northern Europe and Southern Europe. Only two studies [31, 41] were performed in Africa and Oceania.

For the AChR-MG group, 2 studies [71, 72] provided prevalence data (online suppl. Table 3S), depicting a slight geographical variation between the Netherlands and Greece, with a PR of 90 and 70.6 cases per million, respectively. The observed prevalence for MuSK-MG in Southern Holland was 1.9 per million, representing 2% of prevalent MG cases in the region [71], while the MuSK-MG PR in Greece was higher at 2.9 per million [73].

Five studies [67, 68, 74–76] reported PR for LEMS, showing a mean of 2.6 cases per million (range: 2.3–2.9) and a significant consistency across the countries (the USA, the Netherlands, Ireland, and Japan). Finally, 4 studies [77–80] examined PR for juvenile or congenital MG. Two studies [77, 79] reported values for juvenile MG, providing a mean of 24.6 cases per million, while the other two studies [78, 80] highlighted a mean PR of 15.7 cases per million for congenital MG.

Incidence

For the ALL MG group, 50 studies [12, 13, 16, 18–21, 24–30, 32, 35, 36, 38, 40, 41, 44, 48, 49, 52, 54, 57–61, 63–66, 68, 69, 81–94] examined incidence. IRs ranged from 2.3 to 61.3 cases per million person-years (online suppl. Table 3S), with a mean IR of 15.7 (95% CI:

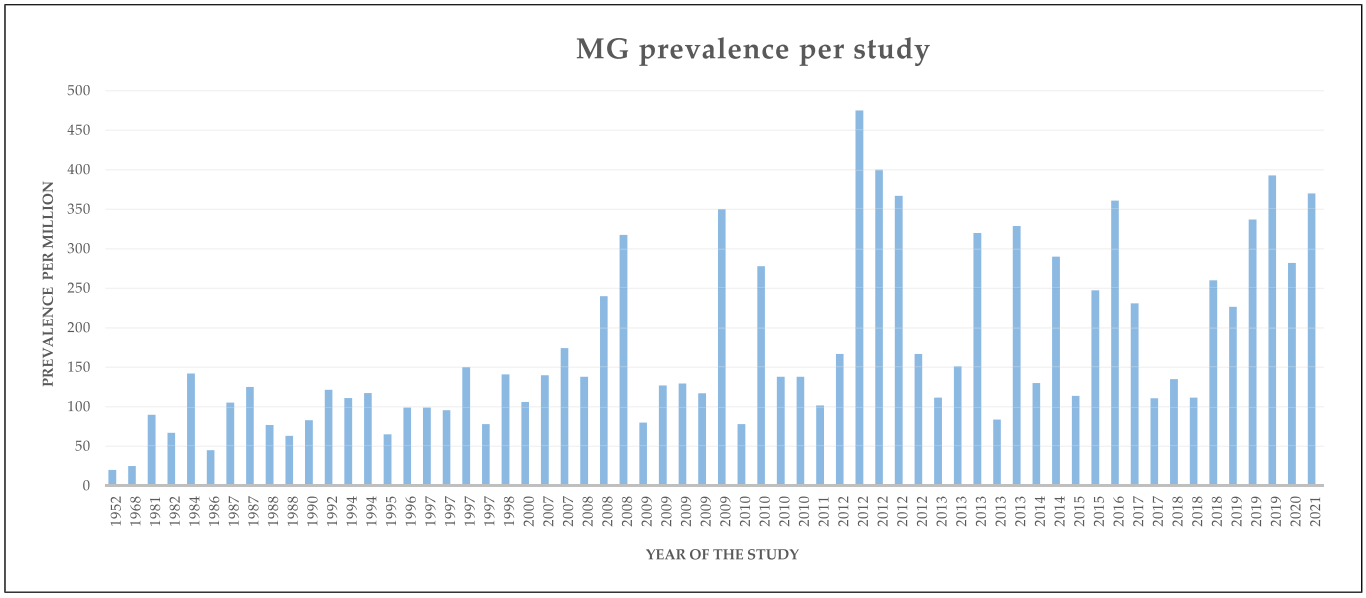

Fig. 3. Crude PRs per million reported by ALL MG studies over time. This figure reports the crude prevalence (per million) of every study that examined the prevalence of ALL MG. The years refer to the last year/period investigated by the study.

11.5–19.9) and a median IR of 13.3 cases. Studies showed increasing rates over the years (Fig. 4): considering the period 1967–2007, the mean IR was 8.7 (95% CI: 5.5–11.9; range: 2.3–21.3) cases per million person-years, and in the period 2008–2022, the mean IR has more than doubled: 22.9 (95% CI: 14.1–31.7; range: 6.3–61.3). The median IR raised from 7.3 (period: 1967–2007) to 22 (period: 2008–2022) cases per million person-years.

It was observed a difference in IRs between America and the other continents. The American countries showed the highest mean IR cases per million person-years with a value of 23.7 (95% CI: 6.5–40.9; range: 4.7–61.3). Asia and Europe exhibited lower and similar IRs: 16.9 (95% CI: 4.8–29; range: 4.2–36.6) and 17.1 (95% CI: 11.5–22.7; range: 2.3–46) cases per million person-years, respectively. Finally, a slight difference between Southern Europe (IR: 15.9, 95% CI: 9.3–22.5; range 2.5–46) and Northern Europe (IR: 11.7, 95% CI: 5.6–17.8; range: 2.3–29) was observed.

For the AChR-MG group, 10 studies [49, 71, 72, 95–101] provided incidence data (online suppl. Table 3S), reporting a mean IR of 12.4 (95% CI: 5–19.8; range: 2.6–32.7) cases per million person-years. No studies were conducted in Asian countries. Two studies [95, 96] examined IR in South Africa depicting an increasing trend between 2005 and 2012: 2.6 and 7.5 cases per million person-years, respectively.

Only two epidemiological studies have been performed to date on MuSK-MG: in the Netherlands [71] and Greece [73]. In the first study, the IR was 0.1 per million person-years and in Greece 0.3 per million person-years.

Three studies [68, 74, 76] investigated the incidence of LEMS, reporting a mean of 0.5 cases per million person-years and a consistency across countries (USA and the Netherlands) and years (1999, 2003, 2013). The IR of juvenile MG was examined by two studies in Norway [77] and in the UK [78], reporting an IR of 1.6 and 1.5 cases per million person-years, respectively.

Mortality

Sixteen studies [15, 16, 20, 24, 25, 27, 37, 44, 54, 59, 81, 89, 102–105] provided MR for ALL MG group (online suppl. Table 3S), showing a mean MR of 1.4 (95% CI: 0.8–2.1; range: 0.5–3.5) cases per million person-years. No trend was observed for MR over the years (Fig. 5). Almost all the studies were conducted in Europe, and no differences were observed between Northern and Southern Europe. The MR for AChR-MG was analyzed only in Greece [72], providing an MR of 0.4 cases per million person-years.

Age and Sex Distribution

Seventy-four (83.1%) studies provided a sex distribution for the MG cases, and in 67 of them (90.5%), a higher number of females was observed, with a ratio of

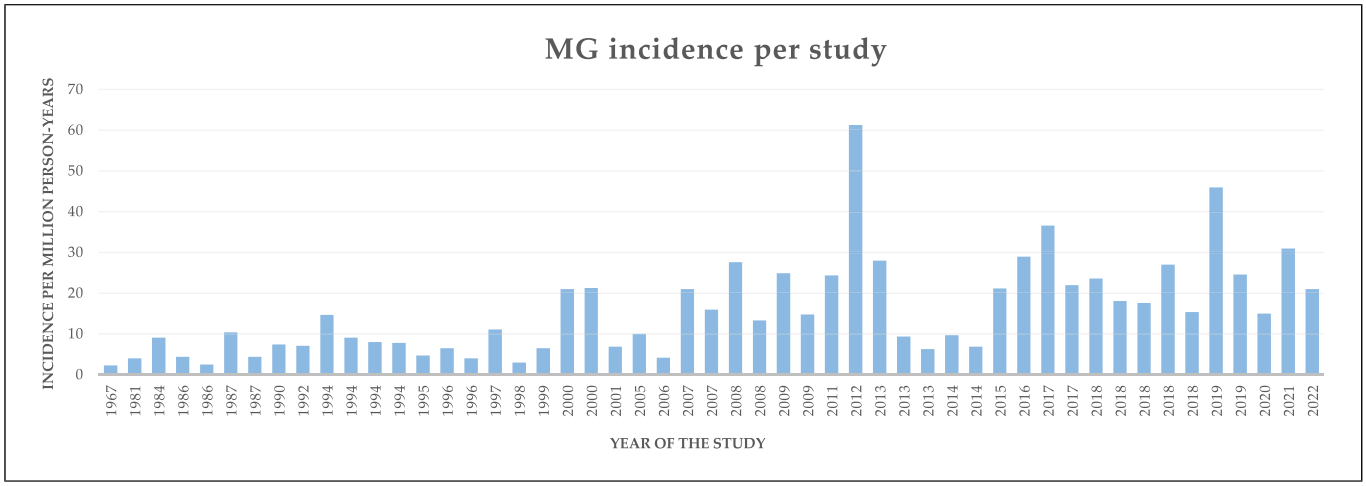

Fig. 4. Crude IRs per million person-years reported by ALL MG studies over time. This figure reports the crude incidence (per million person-years) of every study that examined the incidence of ALL MG. The years refer to the last year/period investigated by the study.

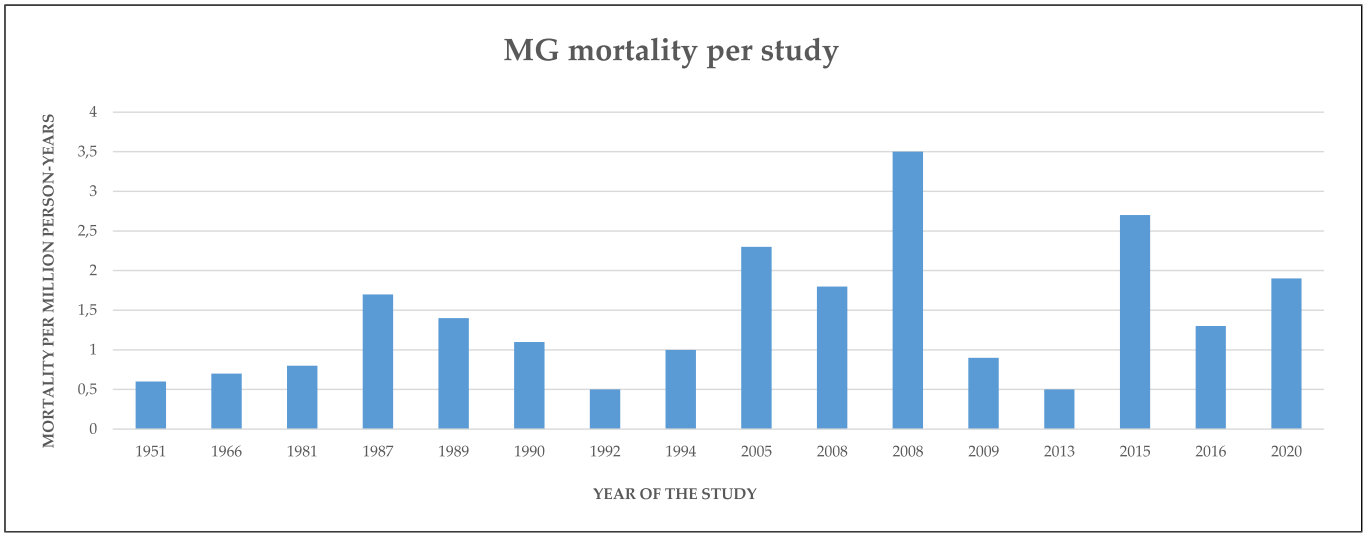

Fig. 5. Crude MRs per million person-years of the studies examining ALL MG. This figure reports the crude mortality (per million person-years) of every study that examined the mortality of ALL MG. The years refer to the last year/period investigated by the study.

F/M = 1.6/1. Figure 6 illustrates the number of males and females over the years, showing a different sex proportion only in recent studies [65, 66, 94, 105] with a higher number of males captured by national health registries. The mean age of ALL MG cases was 53.7 years (range: 25–74.9), and the age distribution stratified for gender (Fig. 7) showed that in most studies, (77.8%) males were older than females, with a mean difference of 7 years (57 years, range: 32.2–83 vs. 50.4 years, range: 21–64.6). A total of 63 studies (67%) reported the occurrence of MG among age groups, highlighting an increasing frequency of the disease with age, with a peak between 65 and 75 years. Nevertheless, females experienced an onset of MG symptoms earlier than males; indeed, most of the studies (90%) showed a higher frequency of MG in females until 50–55 years (with a peak between 25-39 years), while males were more affected after 60 years of age.

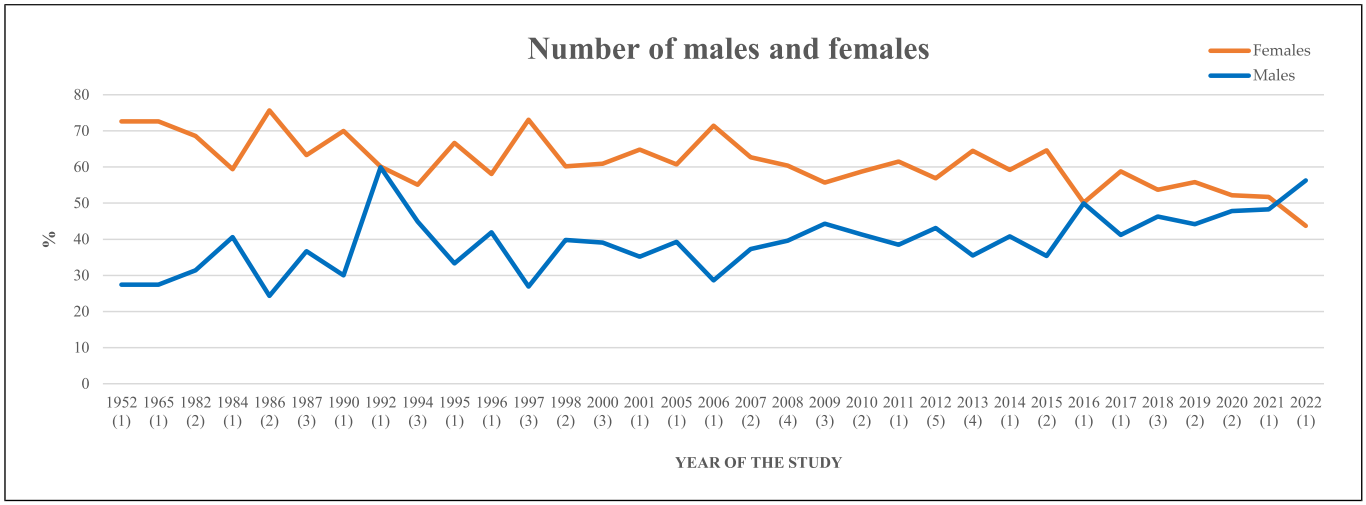

Fig. 6. Number of males and females in ALL MG studies over the years. This figure depicts the sex distribution (in percentage) in the ALL MG studies over the years. The year of the study refers to the last year examined by the studies. In brackets, the number of studies reporting these data for each year.

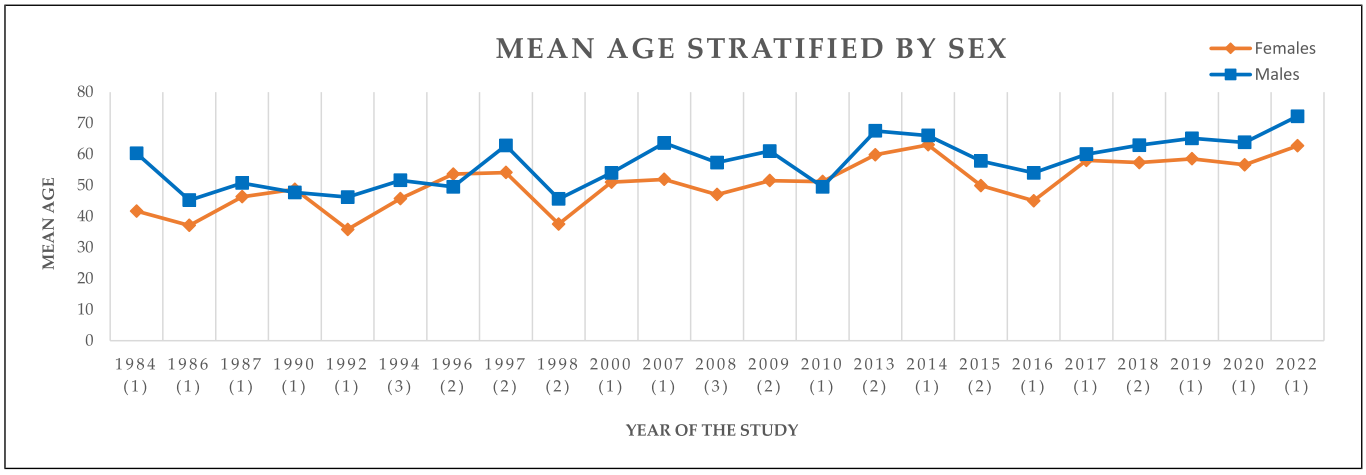

Fig. 7. Mean age of ALL MG cases over the years, stratified by sex. This figure illustrates the mean age of MG cases stratified for sex, over the years. The year of the study refers to the last year examined by the studies. In brackets, the number of studies reporting these data for each year.

The scenario in LEMS was different. In all the studies, a higher number of males was captured by sources, providing a ratio of M/F = 2.3/1. The mean age of LEMS cases was 56.5 years (range: 55–62.2).

Discussion

This systematic review examined the epidemiological trend of MG and myasthenic syndromes (LEMS) worldwide, from 1952 to 2022. Most of the studies (79.8%) reported epidemiological data referred to ALL MG group, thus not distinguishing in the analysis the different clinical subgroups of the disease. Regarding this group (ALL MG), we observed a mean IR of 15.7 (95% CI: 11.5–19.9; range: 2.3–61.3) cases per million person-years and a mean PR of 173.3 (95% CI: 129.7–215.5; range: 20–475) cases per million. We observed a notable difference with the data shown by the last systematic review [7] in which Carr et al. [7] reported a mean IR of 5.3 (95% CI: 4.4–6.1; range: 1.7–21.3) per million person-years and a mean PR of 77.7 (95% CI: 63.9–94.3; range: 15–179)

cases per million.; a slight increase was also reported in MR. The work by Carr et al. [7] focused only on population-based studies, while this review also included clinical studies, despite they were a minority (13.8%). However, the observed increase in PR and IR might be best explained by the improvement of epidemiological methodologies, particularly by the sources used to capture MG cases. Indeed, an important difference between studies performed until the early 2000s and those performed thereafter can be observed. Recent studies employed databases and national registries more often than studies until the 1980s/1990s that frequently focused on clinic surveys and hospital records, thus having a lower chance of intercepting all the MG diagnoses in the countries. Hospital records rarely include patients with mild symptoms, and patients diagnosed and only treated as outpatients are not included at all [1]. Moreover, another important role could be played by the increasing influence of anti-AChR antibody receptor assay upon ascertainment, improved in recent years [1].

Concerning the geographical distribution of ALL MG group, we observed a significant pattern in America that showed the highest mean prevalence (256.2 cases per million) and incidence (23.7 cases per million person-years) compared to the other continents. Specifically, North American studies provided the highest prevalence worldwide, with PRs also higher than 400 cases per million [50, 51]. This finding might be explained by a higher use of national databases, but also by specific environmental or genetic factors. In this regard, a hypothesis could be related to the high presence of Afro-Americans in North America (especially in the USA), since some studies suggested that rates of autoimmune diseases are higher among these people [18, 106]. However, this finding needs to be investigated, and more studies are needed to examine any ethnic or racial differences regarding MG. Moreover, a great heterogeneity was observed in these studies, showing wide ranges of PR (70–475) and IR (4.7–61.3), associated with wide 95% CIs: 89.1–423.3 for PR and 6.5–40.9 for IR. This variability reflects significant differences in studies that need to be highlighted.

Studies from Asia report the lowest prevalence in the ALL MG group (127.4) and the highest prevalence of juvenile MG [79] with a PR of 45.6 cases per million compared to the mean PR of 20.6 cases worldwide. This finding is coherent with the literature that described Asian populations with a higher frequency of juvenile-onset and particularly infantile-onset ocular MG [107], probably associated with the role of the human leukocyte antigen (HLA) [107].

Regarding seropositive MG, the included studies showed that AChR-MG exhibited significantly higher rates of both prevalence and incidence, compared to MuSK-MG. These data are in accordance with the literature that described the AChR-MG as the most frequent clinical subgroup of the disease [2]. The higher frequency of this MG subgroup could be explained not only by a clinical perspective but also by the different timing about the availability of serological testing: tests for AChR antibodies became available earlier (1980s/1990s), than those for MuSK (2000s), and LRP4 (2010) [3]. At the same time, studies on AChR-MG revealed great heterogeneity although using identical methodologies and sources (medical records from immunology laboratories). IRs in these studies ranged from 2.6 cases per million person-years in South Africa to 32.7 cases per million person-years in Argentina. These differences could be explained by population genetics and environmental factors, as also reported for MuSK-MG studies. Literature shows that epidemiological values of MuSK-MG could follow a north-south latitude gradient which might result partly from differences in genetic or unknown environmental factors [2]. Accordingly, the included studies of this review depicted a different prevalence and incidence of MuSK-MG between the Netherlands and Greece, particularly reporting an IR 3 times higher in Southern Europe. Nevertheless, not only the genetic and environmental factors but also the different levels of access to neurologist and serological tests among populations also need to be taken into account to explain these heterogeneities [4]. Conversely, studies focused on LEMS were those with the greatest homogeneity in prevalence and incidence, providing PRs and IRs much lower than those observed in MG. However, the epidemiology of LEMS could be underestimated, in particular the incidence of disease associated with small-cell lung cancer, given that LEMS is often misdiagnosed initially [5].

Several observations suggest that biological factors are important in describing differences in MG epidemiology. In this regard, sex is also considered a significant biological factor that determines differences in MG epidemiology. MG affects all ages, but it is considered "a disease of young women and old men" [8]. Several studies showed that MG typically affects women at younger ages compared to men: the most common onset age is between 20 and 39 years in women [108] and between 50 and 70 years in men [108]. This typical pattern was confirmed by the analysis of the studies included in this work, revealing that women with MG had a mean age of 50.4 years and a peak of the disease often between 25-39 years, while

the men captured by the sources had a mean age of 57 years and were characterized by a later onset. Moreover, we observed a ratio of F/M = 1.6/1, indicating women have a higher risk of developing MG, as yet suggested in the literature [109]. Female sex is an epidemiological risk factor for the development of autoimmune diseases, including MG [8, 110]. This risk has been related to thymic hyperplasia that mainly affects females (ratio 9:1) and to the role of estrogen receptors which are expressed on thymic cells and thymocytes. Indeed, an increased expression of estrogen receptors was found in the thymocytes and T cells from peripheral blood mononuclear cells in MG patients [110]. However, studies included in our review examining another autoimmune disease, the LEMS, showed a different trend characterized by a higher number of men compared to women (ratio: 2.3/1). These studies intercepted cases of LEMS associated with small-cell lung carcinoma. In the literature, this association is reported in about 60% of patients [5] and small-cell lung carcinoma is described as a pathology more frequent in men [111]. In this regard, Yoshikawa et al. [75] showed a predominance in men with LEMS associated with tumors (paraneoplastic LEMS, P-LEMS), with women having a higher frequency of LEMS without tumors (primary autoimmune form of LEMS, AI-LEMS); also other studies [112–114] confirmed these findings, indicating the presence of tumors as a characteristic more frequent in men with LEMS than in women.

Overall, this systematic review outlined a significant epidemiological increase in MG over the years, mainly concerning the ALL MG group. Compared to the latest systematic review that examined MG epidemiology [7], PRs and IRs are more than doubled. Accordingly, the included studies depicted a scenario characterized by low mortality associated with this syndrome (mean MR: 1.4 cases per million person-years). This trend is also confirmed by a recent population-based study [115] that examined MG epidemiology in Denmark, Sweden, and Finland reporting a steady increase of prevalence and incidence in the countries between 2000 and 2020. At the same time, the authors observed a stable pattern regarding MRs, with values ranging from 1.25 to 1.4 [115]. Nevertheless, it is important to point out that studies included in this review exhibited significant variability across countries, but also within the same countries; these discrepancies might be related to methodological biases and the consequent quality of studies, but they could also be associated with different cures, mortality patterns, and relative life expectancies in the diverse continents. Moreover, this variability could also be explained by the complex heterogeneity of the disease characterized by several phenotypes and different clinical responses. Precisely regarding the different phenotypes and clinical subgroups of the disease, it must be underlined that only a minority of the included studies (19%) reported epidemiological rates referred to long/early-onset MG, thymoma-associated MG, and ocular or generalized MG. One of these studies [60] showed an increasing PR between 2006 and 2016 of late-onset MG and early-onset MG (EOMG) in Sweden, differing from the thymoma-associated MG that exhibited a stable trend. Nevertheless, in this systematic review, a thorough and accurate analysis of the trend over the years of these clinical subgroups was not possible principally due to the small number of studies and the heterogeneity of the subgroups investigated.

In the future, limitations about the quality need to be improved to reveal real geographical trends. Many studies (74.5%) reported only crude epidemiological rates, and different sources of data were used to intercept MG cases, thus resulting in different estimates not always related to geographical or genetic characteristics and not allowing a correct comparison between studies. More studies examining epidemiological trends of MG subtypes (EOMG, late-onset MG, ocular/generalized MG, MuSK-MG, juvenile MG, LRP4-MG, seronegative MG) are warranted, and, similarly, more research examining MG trends in Africa and Oceania are needed to have a more global view of MG epidemiology. Finally, validated nationwide databases, including the whole population, are recommended to enhance the quality and the estimates of MG and myasthenic syndromes. Also, it is crucial to perform research with an accurate sampling of the subjects and an accurate validation of the outcome measures.

Conclusions

Prevalence and incidence of MG have significantly increased over the last years worldwide, probably due to the improvement of epidemiological methodologies and current advances in diagnosis. In this work, we reported a mean PR and IR more than over doubled compared to those shown 14 years ago by Carr et al. [7], along with great geographical variability. Accordingly, the included studies depicted a scenario characterized by low mortality associated with this disease. A higher number of studies using standardized data are recommended to better investigate and compare the epidemiological trend of MG

across different countries. More studies examining MG subtypes and myasthenic syndromes are warranted, together with research in Africa and Oceania to have a broader global view of MG epidemiology. Study quality limitations should be enhanced to reveal any real geographical or genetic trends.

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Statement of Ethics

Ethics approval was not required. Consent to participate statement was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.S.: writing – original draft preparation; E.L. and S.V.: methodology; and all authors: data interpretation and review and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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