# PART ONE
# GENERAL APPROACH TO MYASTHENIA GRAVIS

# 1.1

# EPIDEMIOLOGY AND NATURAL HISTORY OF MYASTHENIA GRAVIS

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Myasthenia gravis (MG) is classified as a rare disease. It has been estimated that "a typical neurologist (*i.e.* not dedicated to neuromuscular diseases) might expect to encounter a new case of MG every 3 to 4 years."[1] Rare diseases have been defined as those affecting less than 1 in 2000 individuals in the European Union and 1 in 1250 in the United States, meaning that up to 4-6 million people worldwide may be affected by a rare disease such as MG. However, the reported prevalence and incidence rates of MG vary widely among countries. It is still unclear whether this heterogeneity mainly reflects methodological differences, such as case ascertainment and inclusion criteria,[2] or true differences in the frequency of the disease based on ethnic or other demographic factors.[1] Despite the variability, there are some commonalities in MG throughout the world (*e.g.*, distribution by age of onset, gender and immunological features) that help to define clinical subclasses and improve understanding of the pathophysiology of the disease. In addition, comparison of epidemiological data over time can help us understand the real effect of treatment evolution on the course of the disease in terms of morbidity and mortality. Finally, some basic observations on the natural history of the disease and known treatment outcomes may be useful in MG prognostication. The purpose of this chapter is to

provide a comprehensive exploration of the main points in the field of epidemiological data on MG throughout the world.

## Incidence and prevalence

Studies on MG epidemiology have been conducted since the early 1950s.[1] Two systematic reviews of population-based epidemiological studies were published in 2010. The first examined 55 studies conducted in 23 countries between 1950 and 2007; the authors found a prevalence rate of 15-179 per million people and an incidence rate of 1.7-21.3 per million people per year.[2] The second evaluated the incidence of MG reported in 31 studies published between 1984 and 2004 (most of them from European countries) that, in total, covered a study period of about 50 years, from 1951 to 2000. The reported incidence rate was 3-30 per million/year, with marked variations between studies.[3]

Since 2009, 33 studies (30 retrospective and 3 prospective) have assessed the frequency of MG in North America (the United States and Canada), South America (Argentina and Colombia), Israel, Africa (Egypt and South Africa), East Asia (South Korea and Taiwan), Australia, and Europe (Table 1.1.I).[4-36] In Europe, there have been epidemiological studies in relatively extensive regions of 15 countries. Together, the studies covered a period of about 40 years, from 1979 to 2020.[21-36] The studies have been quite heterogeneous, even in the context of the same country, with data derived from hospital/medical records, pyridostigmine prescriptions, National Health Service (NHS) exemption codes, clinical/laboratory data, door-to-door surveys, disease registry, or exclusively antibody tests. Some studies included all patients with MG, while others only included patients older than 16 or 18 years. In addition, the authors reported incidence or prevalence rates that were either crude or standardized or both. Moreover, standardization, when performed, was done with respect to different factors (age, sex, population of the nation, continent, or based on World Health Organization [WHO] data). That said, the considerable variability of epidemiological data in different studies is unsurprising. Based on the findings, the global crude incidence rate recorded between 1990 and 2020 in 21 countries ranged from 6.3 to 47.7 per million per year. The prevalence rate, registered in 20 countries at different prevalence points between 2000 and 2020, ranged from 17.8 to 393 per million. In Europe, the incidence rate ranged from 6.3 to 46 per million per year and the prevalence rate from 111.7 to 393 cases per million.

## Changes in incidence and prevalence over time

A question addressed in many epidemiological studies is whether the incidence and prevalence of MG have changed over time. A survey of the epidemiologic literature between 1950 and 1990 revealed a slight, nonsignificant increase in the incidence of

**Table 1.1.I** All the studies that have assessed the frequency of MG in North America, South America, Israel, Africa, East Asia, Australia, and Europe.

| Country | Reference | Patients | Study | Data source | Study period | Inc cases | IR per million | Prev point | Prev cases | PR per million | Death % or MR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **AMERICA** | | | | | | | | | | | |
| Canada (Ontario) | Breiner 2016[4] | >18yrs | R | Administrative health data system | 1996-2013<br>2013 | 6750 | 28<br>23* | 2013 | 3611 | 320<br>263* | |
| USA | Alshekhlee 2009[5] | All MG | R | National inpatient database | 2000-2005 | 5502 | 10* | | | | 2.2% |
| | Hendricks 2019[6] | All MG | R | Medical records in Olmsted | 1990-2017 | 65 | 22* | | | | |
| | Rodrigues 2023[7] | All MG | R | US claims and electronic health records database | 2021 | 4214 | 31 | 2021 | 78225 | 370 | |
| | Ye 2024 §a[8] | >18yrs | R | Administrative claims data (Commercial and Medicare) | 2016-2017 | 692 | 54.5<br>68.5* | 2017 | 4187 | 197.1<br>316.4* | |
| | Ye 2024 §b[8] | >18yrs | R | Administrative claims data (Medicaid) | 2016-2017 | 176 | 47.7<br>49.7* | 2017 | 1266 | 181.8<br>203.7* | |
| Colombia | Mateus 2017[9] | All MG | R | Orphan disease registry | 2015 | | | 2015 | 839 | 17.8 | |
| Argentina | Bettini 2017[10] | All MG | R | Hospital Medical Care Program | 2006-2012 | 60 | 61.3<br>38.8* | 2012 | | 367.1 | |
| **AFRICA** | | | | | | | | | | | |
| South Africa | Mombaur 2015[11] | AChR+ | R | Laboratory AChRab+ | 2011-2012 | 890 | 8.5 | | | | |
| Egypt (Al Kharga) | El Tallawy 2010[12] | All MG | R | Door-to-door questionnaire | 2005-2009 | | | 2007 | 2 | 32 | |

*(To be continued)*

| Country | Reference | Patients | Study | Data source | Study period | Inc cases | IR per million | Prev point | Prev cases | PR per million | Death % or MR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **MEADDLE AND FAR EAST** | | | | | | | | | | | |
| Israel | Lotan 2020[13] | AChR+ | R | Laboratory AChRab+ | 2004-2013<br>2013 | 1371<br>147 | 18.5<br>18.2 | | | | |
| Japan | Murai 2011[14] | All MG | R | Questionnaire sent to the hospitals | 2006 | | | 2006 | 8542 (rec)<br>15100 (est) | 118* | |
| | Yoshikawa 2022[15] | All MG | R | Questionnaire sent to the hospitals | 2018 | | | 2018 | 2708 (rec)<br>29210 (est) | 231* | |
| South Korea | Lee SH 2016[16] | All MG | R | National Health I Insurance Claims database | 2011-2014 | 1316 | 6.9 | 2010<br>2014 | 5001<br>6551 | 104.2<br>129.9 | |
| | Park SY 2016[17] | All MG | R | National Health I Insurance Claims database | 2010-2011 | 1236 | 24.4* | 2010<br>2011 | 4907<br>5410 | 96.7*<br>106.6* | |
| | Park JS 2022[18] | All MG | R | National Health I Insurance Claims database | 2010<br>2018 | 683<br>1232 | 11.8*<br>18.1* | 2010<br>2018 | 7668 | 75.0*<br>111.5* | |
| Australia | Gattellari 2012[19] | All MG | R | Pyridostigmine Prescription | 2009 | 545 | 24.9<br>19.1* | 2009 | 2574 | 117.7<br>87.8* | |
| Taiwan | Lai 2009[20] | All MG | R | National Health Insurance database | 2000-2007<br>2000<br>2007 | 5211<br>466<br>501 | 21<br>21<br>22 | <br>2000<br>2007 | <br>1875<br>3205 | <br>84<br>140 | |
| **EUROPE** | | | | | | | | | | | |
| Portugal (Northern) | Santos 2016[21] | All MG | R/P | Pyridostigmine prescription/ hospital records | 2013 | 23 | 6.3 | 2013 | 407 | 111.7 | 2.6%<br>0.5 (MR) |

| Country | Reference | Patients | Study | Data source | Study period | Inc cases | IR per million | Prev point | Prev cases | PR per million | Death % or MR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Spain (Ourense) | Estevez 2023[22] | >20yrs | R | Pyridostigmine prescription/ hospital records | 2009-2018 | 48 | 15,4 | 2018 | 80 | 260 | |
| UK (East Midlands) | Maddison 2019[23] | All MG | P | Clinical, laboratory, neurophysiology | 2014-2018 | 120 | 17.6<br>17.3* (UK)<br>16.4* (EU) | | | | |
| The Netherland | Boldingh 2015[24] | >16 yrs | R | Hospital records | 2011-2012 | | | 2012 | 671 | 167* (NL)<br>110* (EU) | |
| Denmark | Pedersen 2012[25] | All MG | R | Diagnosis and prescription from National Registers | 1996-2009 | 693 | 9.2*# | | | | |
| Norway | Andersen 2014[26] | All MG | R | Pyridostigmine prescription database | 2004-2007 | 74 | 16 | 2008 | 619 | 131 | |
| | Andersen 2014[26] | AChR+ | R | AChRab+ database | 2004-2007 | 35 | 8.8 | 2008 | 479 | 145 | |
| | Boldingh 2015[24] | >16 yr | R | Hospital records | 2009-2010 | | | 2010 | 534 | 138*(NW)<br>97*(EU) | |
| Sweden | Westerberg 2020[27] | > 18yr | R | Diagnosis and prescription from National Registers | 2006-2016<br>2016 | 2598 | 21-29<br>29 | 2016 | 4736<br>3607 | 237-361<br>361 | |
| Finland | Sipila 2019[28] | >16 yr | R | Hospital admission for MG and Health Care database | 2004-2014 | | | 2014 | 1321 | 290 | 1%** |
| Latvia | Zieda 2018[29] | All MG | R | Neuromuscular Hospital records | 2010-2014 | 99 | 9.7<br>8.4*(EU)<br>7.6*(WHO) | 2015 | 226 | 113,8 | |
| Serbia (Belgrade) | Lavrnic 2013[30] | >16 yrs | R | Hospital records and MG registry | 1979-2008 | 562 | 13.3 | 2008 | 425 | 317.6 | |

| Country | Reference | Patients | Study | Data source | Study period | Inc cases | IR per million | Prev point | Prev cases | PR per million | Death % or MR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Slovakia | Martinka 2018[31] | All MG | R | Medical records | 2010-2015 | 554 | 17.4 | 2015 | | 247.5 | 1.3 (MR)°° |
| Italy | Antonini 2023[32] | >18 yrs | R | Pyridostigmine prescription | 2011-2018 | | | 2018 | 4397 | 293 | |
| | Antonini 2023[32] | >18 yrs | R | Pyridostigmine prescription/ hospital records/ exemption | 2011-2018 | | | 2018 | 2026 | 135 | |
| | Sechi 2024[33] | AChR+/ MuSK+ | R | Lab records in Sardinia | 2010-2019 | 107 | 32.6<br>18.4* | 2019 | 180 | 553<br>316* | |
| France | Salort-Campana 2023[34] | All MG | R | National Health data system and hospital records | 2008-2020 | 13912 | 25 | 2020 | 22979 | 342 | |
| Faroe Islands | Joensen 2014[35] | All MG | P | Clinical, laboratory, neurophysiology | 1986-2013 | 12 | 9.4 | 2013 | 9 | 187 | 3.9 (MR) |
| Germany | Mevius 2023[36] | All MG | R | Statutory Health Insurance | 2015-2019<br>2019 | 156 | 51<br>46* (G) | 2018 | 1247 | 392<br>360* (G) | 5.7% |

R: retrospective study; P: prospective study; IR: incidence rate may be reported for time intervals (average or range) and/or for a year of the study period; PR: prevalence rate related to the prevalence point; (rec): recorded cases; (est): estimated cases; MR: mortality rate; G: German.
*Standardized Data: IR and PR are standardized for age, gender and, where indicated, for country/EU/WHO population.
§a. Databases covered healthcare service use within fee-for-service plans among an employed population and their families, as well as Medicare-eligible employees and their families with employer-sponsored supplemental plans.
§b. Medicaid provides healthcare coverage to millions of Americans, including eligible low-income individuals of all ages as well as people with disabilities.
# Direct standardization of all incidence rates by gender and age using the 2002 population of Denmark as the standard population had minimal impact on these results.
**In-hospital mortality rate.
°°Incidence rate of patients deceased for myasthenic crisis. Average mortality rate per year 1977-2015: 2.7/million.