CAESAR

Comparative Effectiveness and Safety of Drugs used in Rare Neuromuscular and Neurodegenerative Diseases

ISTITUTO SUPERIORE DI SANITÀ

CENTRO NAZIONALE
PREVENZIONE DELLE MALATTIE
E PROMOZIONE DELLA SALUTE

Epidemiologia della Myasthenia Gravis

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Istituto Superiore di Sanità

CONVEGNO FINALE PROGETTO CAESAR

Roma, Complesso Monumentale Santo Spirito in Sassia, Sala Santo Spirito
7 giugno 2023, 9:00-17:00

Stato dell'arte

TABLE 1. Weighted mean prevalence by decade

	1950–1959	1960–1969	1970–1979	1980–1989	1990–present
Prevalence[a]	22.2	25.1	58.2	58.2	93.9
CI[b]	18.7–26.3	22.7–27.7	54.6–61.9	54.6–61.9	88.2–99.9
Relative rate	1.0	1.1	2.6	2.6	4.2

[a]Rate expressed per million population.
[b]Confidence interval (95%).

Phillips LH 2nd. The epidemiology of myasthenia gravis. Ann N Y Acad Sci. 2003 Sep;998:407-12.

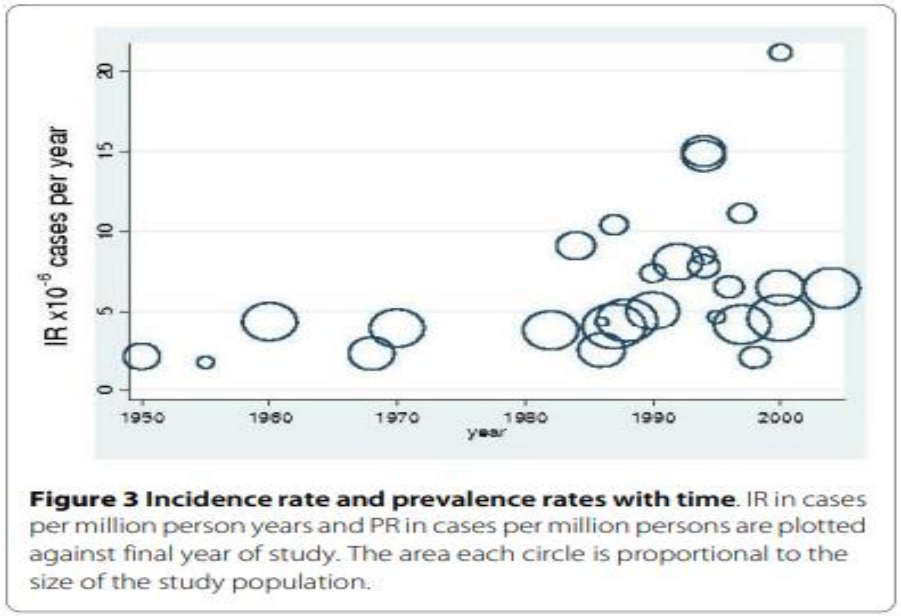


Figure 3 Incidence rate and prevalence rates with time. IR in cases per million person years and PR in cases per million persons are plotted against final year of study. The area each circle is proportional to the size of the study population.

Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. BMC Neurol. 2010 Jun 18;10:46.

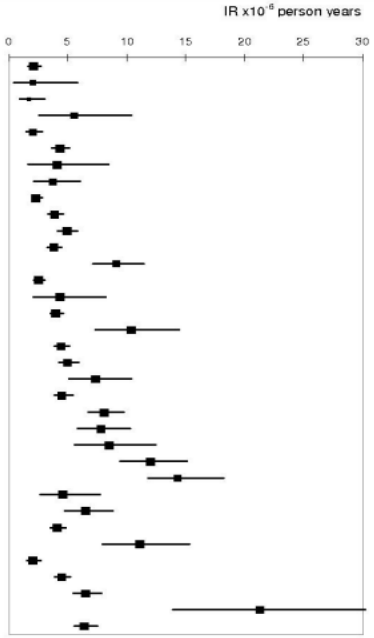
Una patologia con tassi epidemiologici crescenti negli anni

Carr et al. 2010

55 studi population-based inclusi (1950-2007)

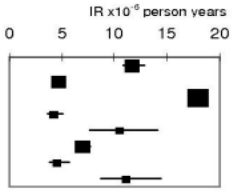
Figure 2a Incidence of MG from ALL MG studies

YEAR	COUNTRY	Years studied	Incident cases
1951	Norway [9]	31,000,000	65
1954	Halifax, Canada [4]	1,500,000	3
1955	Leeds, UK [11]	7,500,000	13
1956	Charleston, USA [12]	1,636,364	9
1958	Merseyside, UK [13]	16,500,000	33
1961	Norway [9]	34,634,146	149
1963	Iceland [14]	1,724,138	7
1965	Amsterdam, Holland [15]	4,300,000	16
1968	Finland [17]	44,933,920	102
1971	Norway [9]	37,948,717	148
1975	Uruguay [18]	27,000,000	132
1981	Norway [9]	41,079,630	155
1984	Virginia, USA [20]	8,021,985	73
1986	Sardinia, Italy [23]	43,999,989	110
1986	Benghazi, Libya [24]	2,076,000	9
1987	Hong Kong, China [26]	50,160,000	202
1987	Viborg, Denmark [27]	3,461,400	36
1988	Eastern Demark [28]	41,363,636	182
1990	Western Denmark [29]	28,011,150	140
1990	Trento, Italy [30]	4,469,140	33
1991	Cuba [32]	28,911,545	131
1992	Belgrade, Yugoslavia [34]	15,308,640	124
1994	Reggio Emilia, Italy [36]	6,260,390	49
1994	Northwestern Sardinia, Italy [35]	3,179,472	27
1994	Cyprus [38]	6,000,000	72
1994	Emilia Romagna, Italy [37]	5,849,420	86
1995	Dutch Antilles [40]	3,232,815	15
1996	Gorski kotar, Croatia [42]	6,585,579	43
1997	Estonia [45]	39,214,890	162
1997	Cambridgeshire, England [43]	3,420,000	38
1998	Dar Es Salaam, Tanzania [47]	23,000,000	47
2000	Nagano, Japan [50]	47,000,000	213
2000	Southern Holland [49]	17,253,170	112
2000	Barcelona, Spain [51]	1,229,230	26
2004	Southern Holland [54]	23926703	154



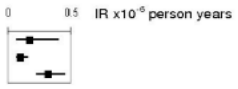
Incidence of MG from AChR MG studies

YEAR	COUNTRY	Years studied	Incident cases
1990	British Colombia [56]	52,000,000	614
1997	Greece [57]	152,713,695	733
1998	UK [58]	176,166,666	3171
2000	Nagano, Japan [50]	41,400,000	178
2001	Tayside, Scotland [59]	4,200,000	44
2001	Norway [60]	64,714,284	453
2004	Southern Holland [54]	23926703	111
2005	Cape Town, South Africa [61]	5,786,502	65



Incidence of MG from MuSK MG studies

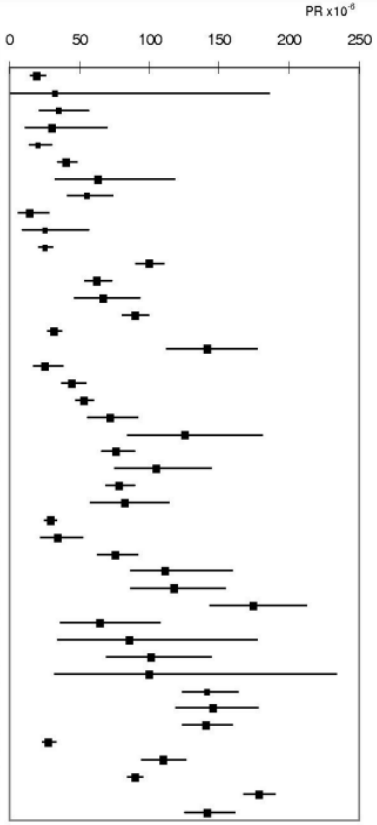
YEAR	COUNTRY	Years studied	Incident cases
2004	Southern Holland [54]	23,926,703	4
2004	Holland [54]	218,054,242	22
2006	Greece [62]	107286179	33



Incidence Rate (IR) medio: 5.3 cases per million person-years (range: 1.7-21.3)

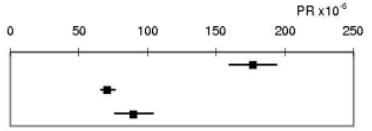
Figure 5 Prevalence of MG from ALL MG studies

YEAR	COUNTRY	Prevalent population	Prevalent cases
1951	Norway [9]	3,100,000	62
1954	Rochester, USA [10]	30000	1
1955	Leeds, UK [11]	500,000	18
1956	Charleston, USA [12]	188,000	6
1958	Merseyside, UK [13]	1500000	32
1961	Norway [9]	3,463,415	142
1963	Iceland [14]	187,000	12
1965	Amsterdam, Holland [15]	860,000	48
1966	Fukuoka, Japan [16]	608,000	9
1966	Niigata, Japan [16]	230,000	6
1968	Finland [17]	4,493,392	115
1971	Norway [9]	3,794,872	379
1975	Uruguay [18]	2,700,000	170
1982	Kumamoto, Japan [19]	537,313	36
1981	Norway [9]	4,107,063	369
1984	Georgia, Russia [20]	5,000,000	161
1984	Virginia, USA [21]	555,851	79
1985	Karachi, Pakistan [22]	1,038,462	27
1986	Sardinia, Italy [23]	2,444,444	110
1987	Hong Kong, China [26]	4,860,000	260
1987	Bologna, Italy [25]	914,463	66
1987	Viborg, Denmark[27]	230,760	29
1988	Eastern Demark [28]	2,298,701	406
1988	Ferrara, Italy [25]	370,374	39
1990	Western Denmark [29]	2,800,000	220
1990	Trento, Italy [30]	446,914	37
1991	Cuba [32]	5,782,309	169
1991	Krasnodar, Russia [33]	655,738	23
1992	Belgrade, Yugoslavia [34]	1,530,864	117
1994	N.W. Sardinia, Italy [35]	268,926	30
1994	Reggio Emilia, Italy [36]	427,493	50
1994	Cyprus [38]	600,000	105
1995	Dutch Antilles [40]	229,800	15
1996	La Palma, Spain [41]	81,507	7
1996	Gorski kotar, Croatia [42]	313,599	32
1997	Assuit, Egypt [44]	50,000	5
1997	Estonia [45]	1,462,130	208
1997	Cambridgeshire,England[43]	684,000	100
1998	Stockholm, Sweden [46]	1,783,428	251
2000	Antioqua, Columbia [48]	5,300,000	147
2000	Southern Holland [49]	1,725,317	189
2001	Moscow [53]	12,000,000	1076
2001	Denmark [52]	5,472,032	977
2004	Southern Holland [53]	1,778,564	253



Prevalence of MG from AChR MG studies

YEAR	COUNTRY	Prevalent population	Prevalent cases
1999	Eastern Denmark [55]	2,298,701	376
1997	Greece [57]	10,475,873	740
2004	Southern Holland [54]	1,778,564	160



Prevalence of MG from MuSK MG studies

YEAR	COUNTRY	Prevalent population	Prevalent cases
2004	Southern Holland [54]	1778564	5
2006	Greece [62]	11293282	33

Prevalence rate (PR) medio: 77.7 cases per million (range: 15-179)

La nostra revisione sistematica

- Prospero Code: CRD42023415272
- Database: Medline, Embase, ISI Web of Science, CINAHL
- Stringa: **(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 "seronegative MG")**
- Analisi letteratura fino a Settembre 2021 ⟹ ultimo aggiornamento ad Aprile 2023

Criteri di inclusione ed esclusione

Criteri inclusione:

i) Studi di soggetti con diagnosi di MG o di sindromi miasteniche (Lambert-Eaton);

ii) Studi con tassi di prevalenza, incidenza o mortalità;

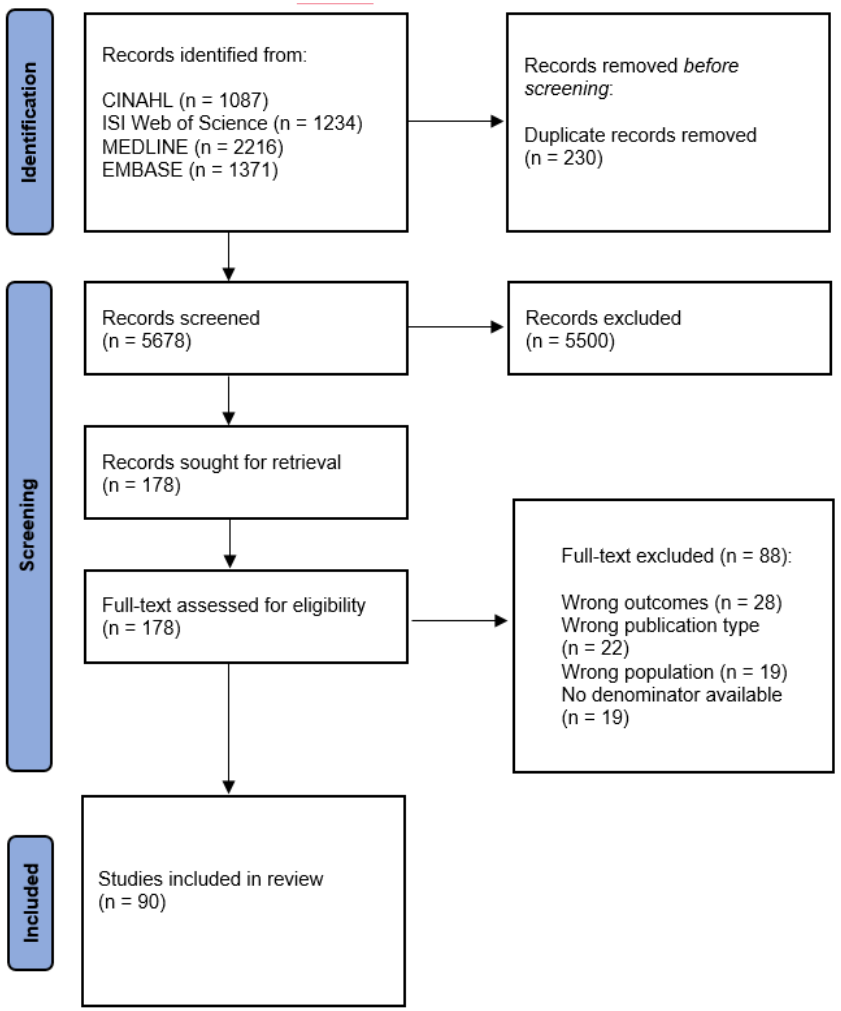
iii) Studi con un definito denominatore di popolazione;

iv) Studi con dati quantificabili ed estraibili per la raccolta.

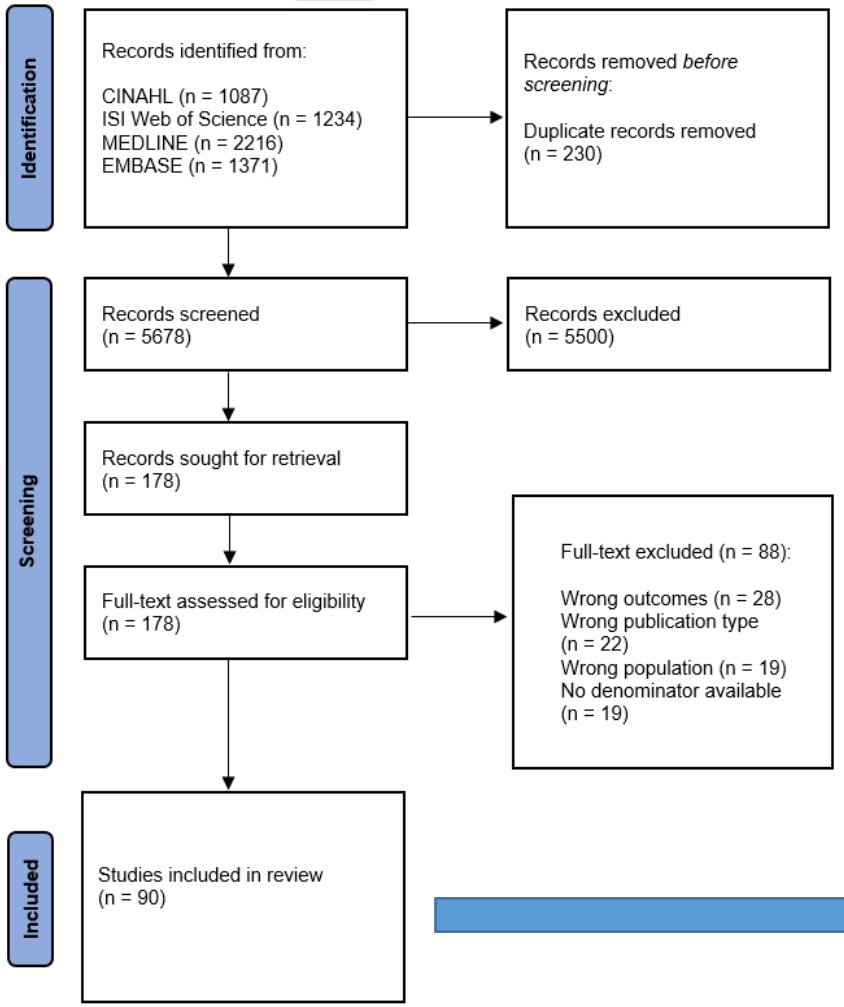
Criteri esclusione:

case report, case series, revisioni, lettere, abstract, editoriali e articoli non pubblicati in lingua inglese.

PRISMA Flow-chart



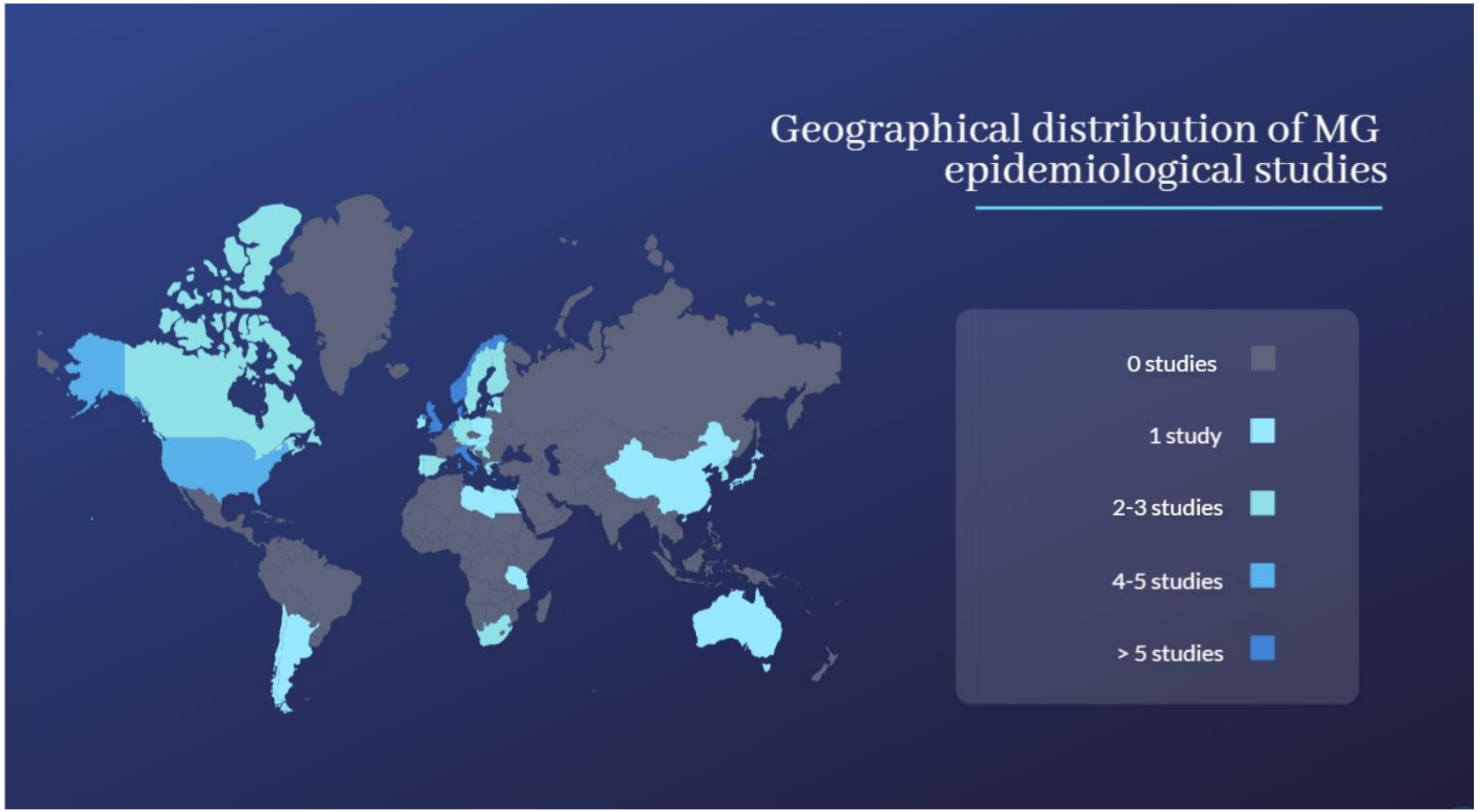
Studi divisi per sottotipi di MG



All MG: Myasthenia Gravis generica, comprendente tutti i tipi di MG.

All MG: 57 studi con PRs, 48 con IRs, 14 studi con Mortality Rates (MRs)
AChR-MG: 2 studi con PRs, 10 studi con IRs, 1 studio con MR
MuSK-MG: PRs e IRs analizzati da 2 studi
Juvenile MG: 4 studi con PRs, 2 studi con IRs
Lambert-Eaton (LEMS): 5 studi con PRs, 3 studi con IRs

Distribuzione geografica degli studi



61/90 studi condotti in Europa.

Italia è risultato il Paese con il maggior numero di studi: 11.

Periodo degli studi: 1952-2020.

Qualità degli studi

Methodological Evaluation of Observational REsearch (MORE)—Observational Studies of Incidence or Prevalence of Chronic Diseases

Valutata attraverso la Methodological Evaluation of Observational REsearch (MORE) checklist[1]

70.3% degli studi ⟹ qualità media

Studi con numero significativo di NR

per quanto riguarda soprattutto la validità esterna.

⇓

Poca qualità in termini di generalizzabilità risultati.

Validità interna: 56% studi non ha riportato validazione dell'

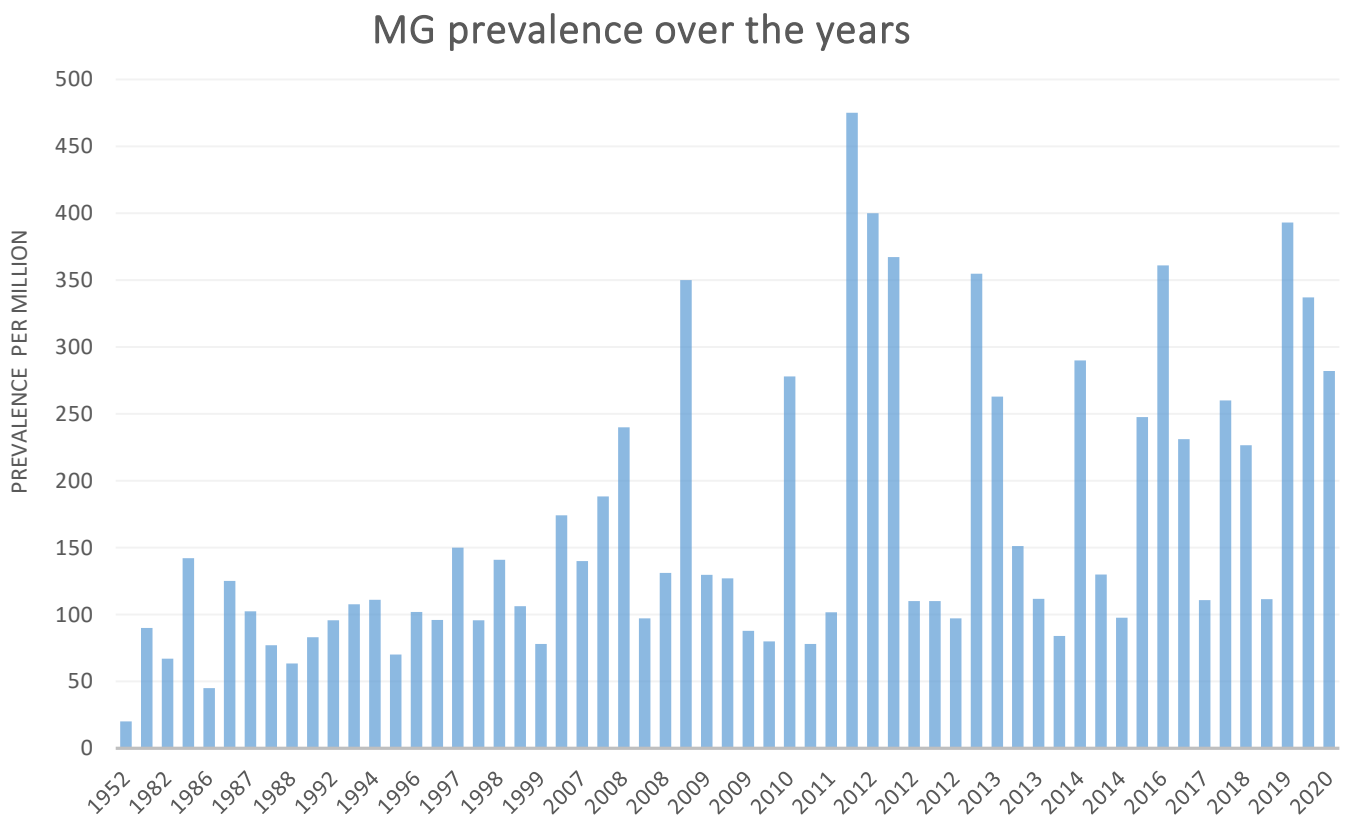
outcome, 64.8% non ha riportato la reliability.

48.4% degli studi ha riportato solo tassi grezzi.

Foldvari 2015	NA	NA	2	NR	NA	NA	NR	NR	0	0	**2**
Garcia-Estevez2023	0	NA	NA	NR	NA	NA	0	NR	0	0	**0**
Gattellari 2012	0	NA	NA	0	0	NA	0	NR	NR	0	**0**
Giagheddu 1989	0	NA	NA	0	0	NA	NR	NR	NR	NR	**0**
Guidetti 1998	0	NA	NA	0	0	NR	0	NR	NR	0	**0**
Heldal 2012	0	NA	NA	0	0	NA	0	0	0	0	**0**
Hendricks 2019	0	NA	NA	NR	NA	NA	NR	NA	NR	NR	**0**
Hokkanen 1969	0	NA	NA	NR	NA	NA	NR	NA	NR	NR	**0**
Holtsema 2000	0	NA	NA	NR	NA	NA	NR	NA	NR	NR	**0**
Joensen 2014	0	NA	NA	NR	NA	NA	NR	NA	NR	NR	**0**
Kalb 2002	0	NA	NA	NR	0	NA	0	NA	NR	NR	**0**
Lai 2010	0	NA	NA	0	NA	NA	0	NA	NR	NR	**0**
Lavrnic 1999	0	NA	NA	NR	NA	NA	0	NA	NR	0	**0**
Lavrnic 2013	0	NA	NA	NR	NA	NA	NR	NA	NR	0	**0**
Lee 2016	0	NA	NA	1	NA	NA	NR	NA	NR	0	**1**
Lefter 2014	0	NA	NA	0	0	NR	0	NR	NR	0	**0**
Lotan 2020	0	NA	NA	1	NA	NA	NR	NA	1	0	**2**
Maddison 2019	1	NA	NA	0	0	NR	0	NR	0	0	**1**
Maharaj 2013	1	NA	NA	1	NA	NA	0	NA	1	0	**3**
Mariaol 2013	1	NA	NA	NR	0	NR	NR	NR	1	0	**2**
Marcinka 2018	0	NA	NA	1	NA	NA	NA	NA	1	0	**2**
Matsuda 2005	1	NA	NA	1	0	NA	NA	NA	1	0	**3**
Matsui 2009	NA	NA	2	NR	NA	NA	NA	NA	NR	0	**2**
Matuta 2001	NA	NA	2	NR	NA	NA	NA	NA	NR	0	**2**
Meyius 2023	1	NA	NA	NR	NR	NA	NR	NA	NR	1	**2**
Mombaur 2014	0	NA	NA	1	NA	NA	NA	NA	0	0	**1**
Montomoli 2012	0	NA	NA	0	0	NR	0	NR	NR	0	**0**
Nemet 2014	NR	NR	NR	1	0	NR	0	NR	1	0	**2**
Niks 2007	0	NA	NA	0	0	NR	0	NR	NR	0	**0**
Oopik 2003	0	NA	NA	1	NA	NA	NA	NA	0	0	**1**
Oopik 2008	0	NA	NA	NA	0	0	NA	NA	NA	0	**0**
Pallaver 2011	1	NA	NA	NR	NR	NA	NR	NA	NR	1	**2**
Park 2022	1	NA	NA	NR	NR	NA	NR	NA	NR	1	**2**
Park 2016	1	NA	NA	NR	NR	NA	NR	NA	NR	1	**2**
Parr 2014	0	NA	NA	1	NR	NA	0	NA	NR	1	**2**
Phillips 1992	1	NA	NA	0	NR	NA	2	NA	NR	1	**4**
Popperud 2017	1	NA	NA	NR	0	NA	2	NA	NR	0	**3**
Poulas 2001	1	NA	NA	NR	NR	NA	0	NA	NR	1	**2**
Radhakrishnan 1988	NA	NA	2	NR	NR	NA	NR	NA	NR	NR	**2**

1. Shamliyan TA, Kane RL, Ansari MT, Raman G, Berkman ND, Grant M, et al. Development quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: pilot study of new checklists. J Clin Epidemiol. 2011;64(6):637-657

Prevalenza All MG

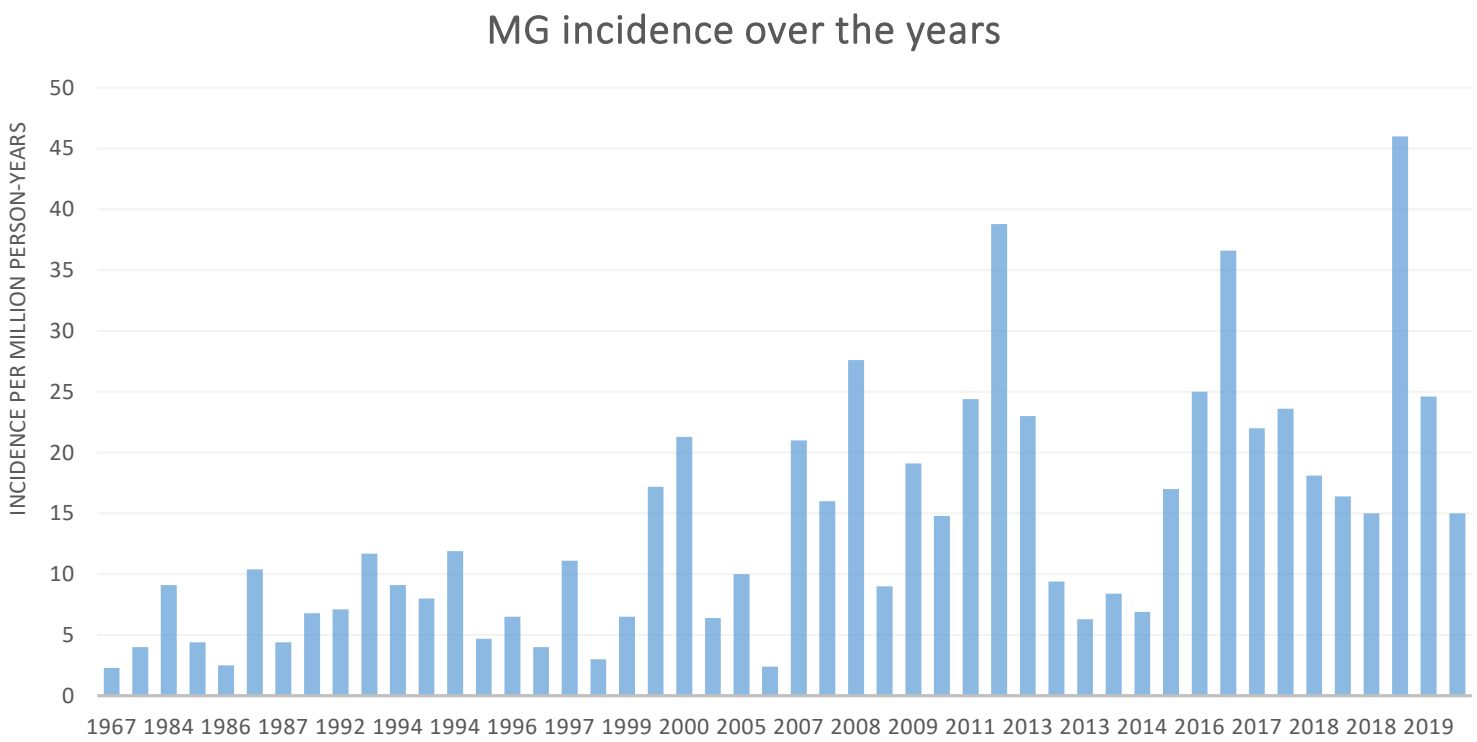


PR medio (1952-2020): 165.6 cases per million (range: 20-475)

PR medio (1952-2007): 99.2 cases per million (range: 20-174.2)

PR medio (2008-2020):
208 cases per million
(range: 78-475)

Incidenza All MG

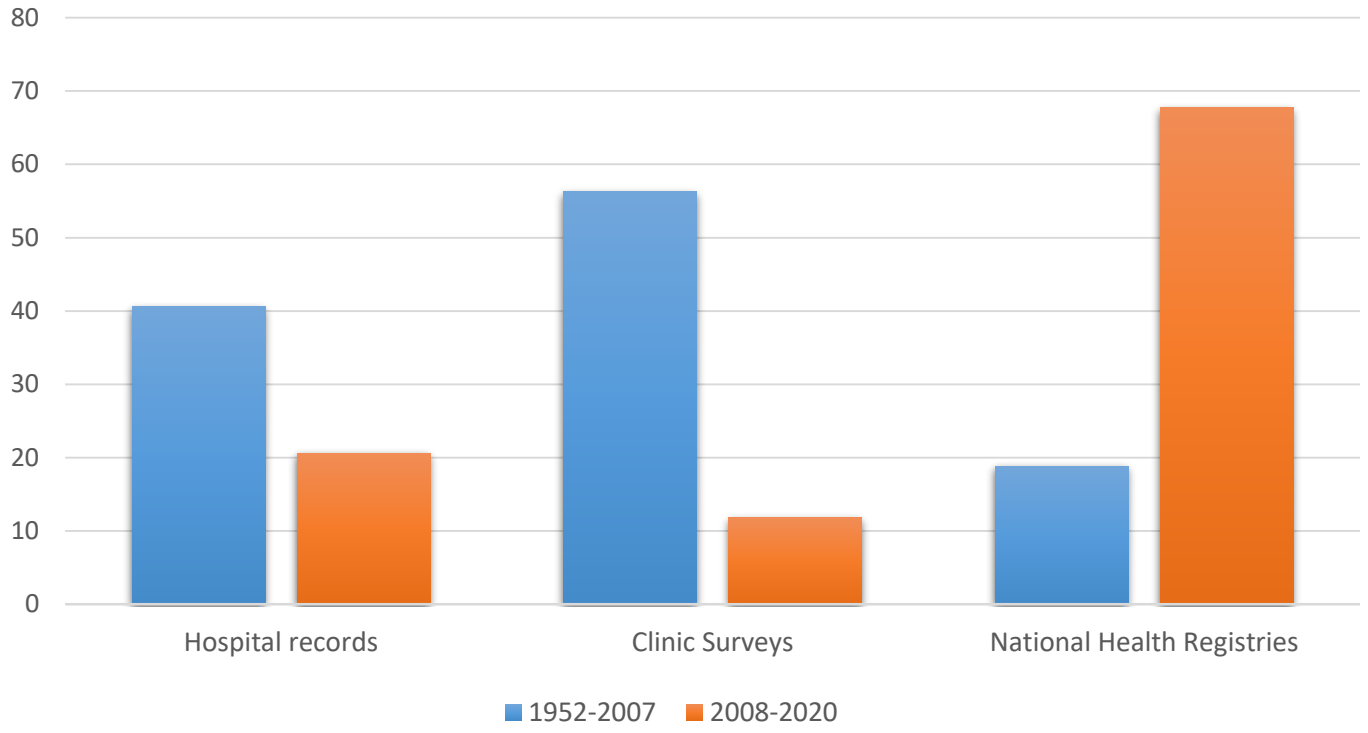


IR medio (1967-2020): 13.9 cases per million person-years (range: 2.3-46)

IR medio (1967-2007): 8.5 cases per million person-years (range: 2.3-21.3)

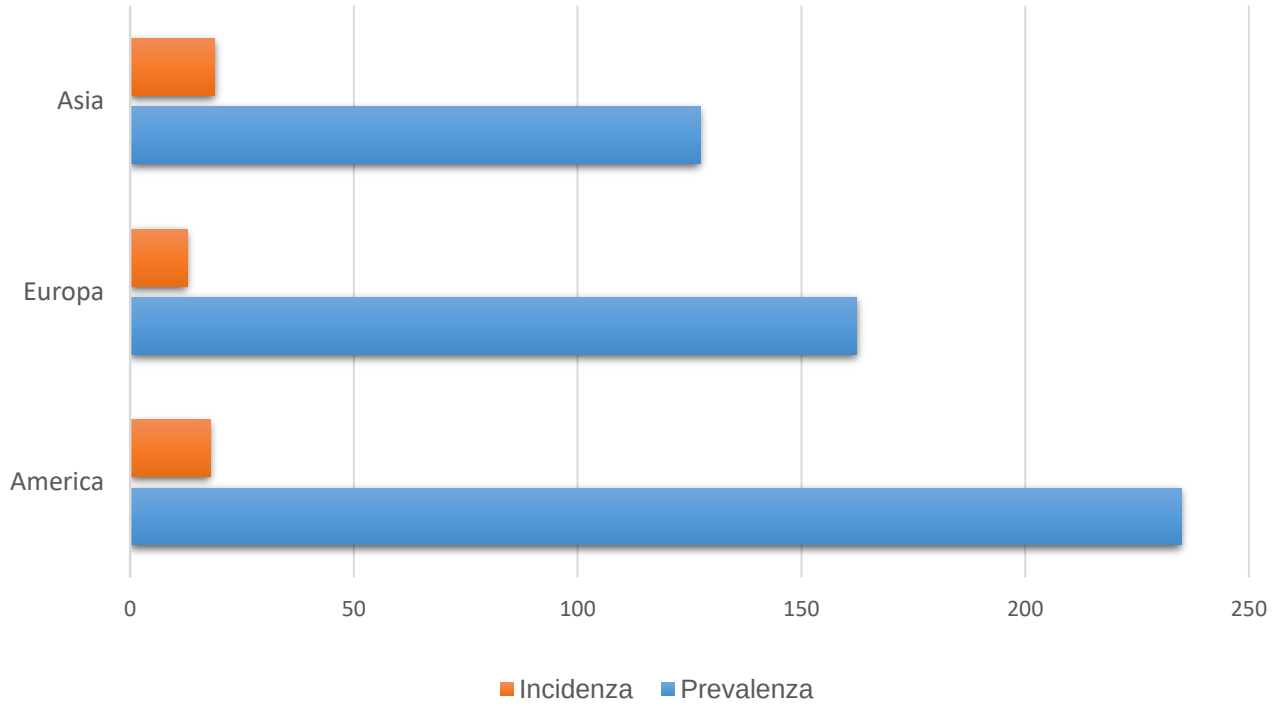
IR medio (2008-2020): 20.3 cases per million person-years (range: 6.3-46)

Fonti All MG



L'utilizzo di registri/database è aumentato da una media del 18.8% a una del 67.7%.

Differenze tra continenti (All MG)



PR in Nord America è risultato il maggiore: 320 cases per million (range: 142-475).

In Oceania e Africa è stato individuato un totale di soli 2 studi.

Influenze etniche nell'epidemiologia della MG?

Table 2. Myasthenia gravis: Average annual incidence rates (per million population)

Years	WM		WW		BM		BW		Total	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
1970-1974	8	8.0	7	6.5	2	12.3	2	11.1	19	7.9
1975-1979	8	7.5	15	13.1	2	11.5	1	5.1	26	10.0
1980-1984	12	10.7	11	9.0	2	11.0	3	14.3	28	10.3
Total	28	8.4	33	9.2	6	11.1	6	9.7	73	9.1

WM White men.
WW White women.
BM Black men.
BW Black women.

Phillips LH 2nd, Torner JC, Anderson MS, Cox GM. The epidemiology of myasthenia gravis in central and western Virginia. Neurology. 1992 Oct;42(10):1888-93.

Troppi pochi dati in letteratura per stabilire una maggiore correlazione tra popolazione afroamericana e MG rispetto ad altre popolazioni.

JAMA Neurology | Review

Health Disparities, Inequities, and Social Determinants of Health in Multiple Sclerosis and Related Disorders in the US
A Review

Lilyana Amezcua, MD, MS; Victor M. Rivera, MD; Teresa Corona Vazquez, MD; Lourdes Baezconde-Garbanati, PhD; Annette Langer-Gould, MD, PhD

IMPORTANCE There is empirical evidence that social determinants of health (SDOH) impact health outcomes in Black and Hispanic and Latinx individuals in the US. Recently, SDOH have risen to the top as essential intervention targets that could help alleviate racial and ethnic disparities. Neuromyelitis optica spectrum disorder (NMOSD) disproportionately affects Black individuals, and multiple sclerosis (MS) has seen a recent shift in select racial groups. It is unclear to what degree SDOH have been investigated and contribute to racial and ethnic health disparities and inequities.

OBSERVATIONS This narrative review provides a contemporary synthesis of SDOH associated with racial and ethnic health disparities and inequities in MS, NMOSD, and other autoimmune disorders, such as myelin oligodendrocyte glycoprotein antibody (MOG-Ab)–associated disease. These immune-mediated neurological diseases were chosen for their capacity to be a high burden to society and because of complementary SDOH-associated challenges among minority populations. A paucity of research addressing inequities and the role of SDOH in MS and NMOSD was noted despite findings that Black individuals have a higher risk of developing MS or NMOSD and associated mortality compared with White individuals. Greater health disparities were also found for those with lower income and education, lower health literacy, and negative illness perceptions in MS. No studies in MOG-Ab disorders were found.

CONCLUSIONS AND RELEVANCE Increased efforts are needed to better understand the role of SDOH in racial and ethnic health disparities and inequities in MS, NMOSD, and emerging autoimmune disorders. This includes developing research frameworks aimed at understanding the magnitude and interrelationships of SDOH to better develop system-based multilevel interventions across the spectrum of care for these neurological conditions.

JAMA Neurol. 2021;78(12):1515-1524. doi:10.1001/jamaneurol.2021.3416
Published online October 4, 2021.

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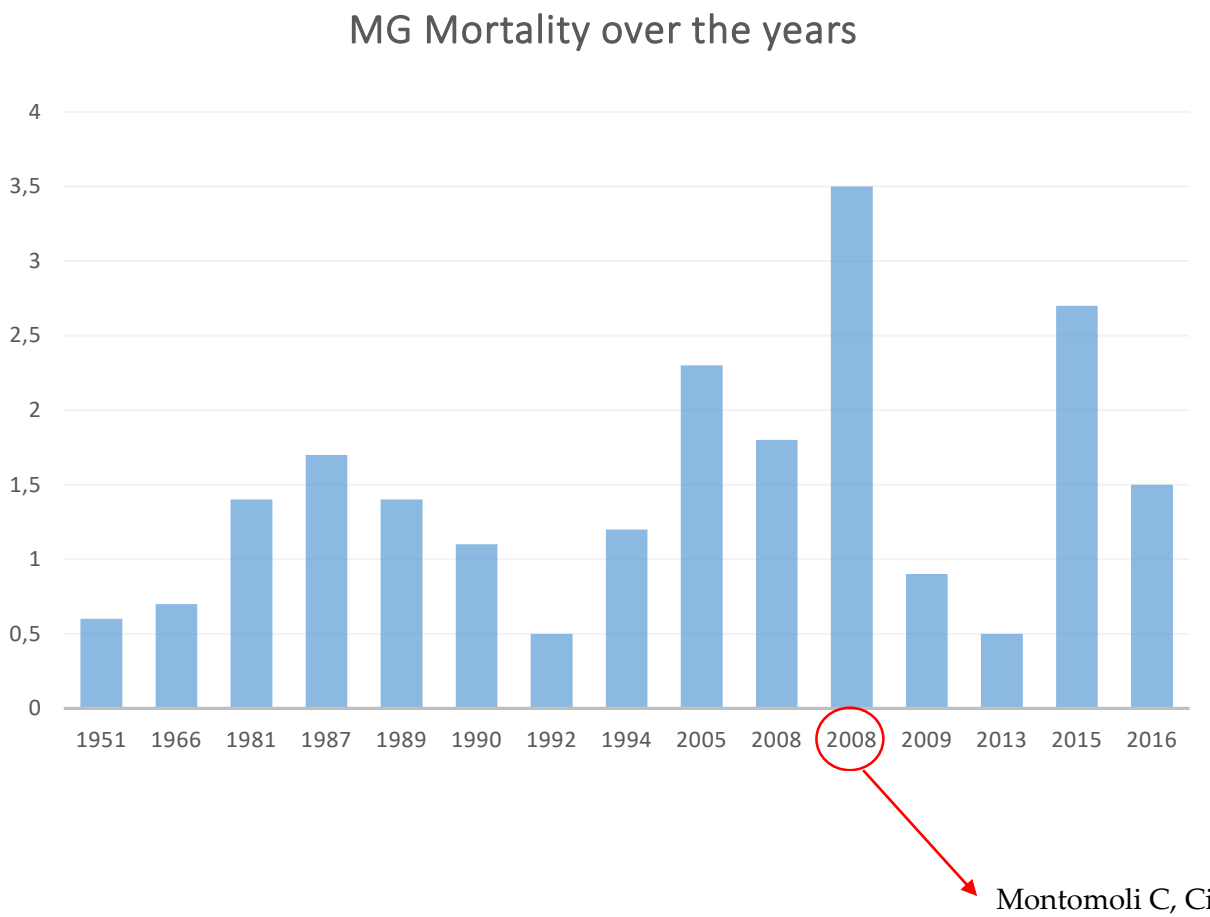
Corresponding Author: Lilyana Amezcua, MD, MS, Keck School of Medicine, Department of Neurology, University of Southern California, 1520 San Pablo St, Ste 3000, Los Angeles, CA 90033 (lamezcua@usc.edu).

Amezcua L, Rivera VM, Vazquez TC, Baezconde-Garbanati L, Langer-Gould A. Health Disparities, Inequities, and Social Determinants of Health in Multiple Sclerosis and Related Disorders in the US: A Review. JAMA Neurol. 2021 Dec 1;78(12):1515-1524.

Mortalità All MG



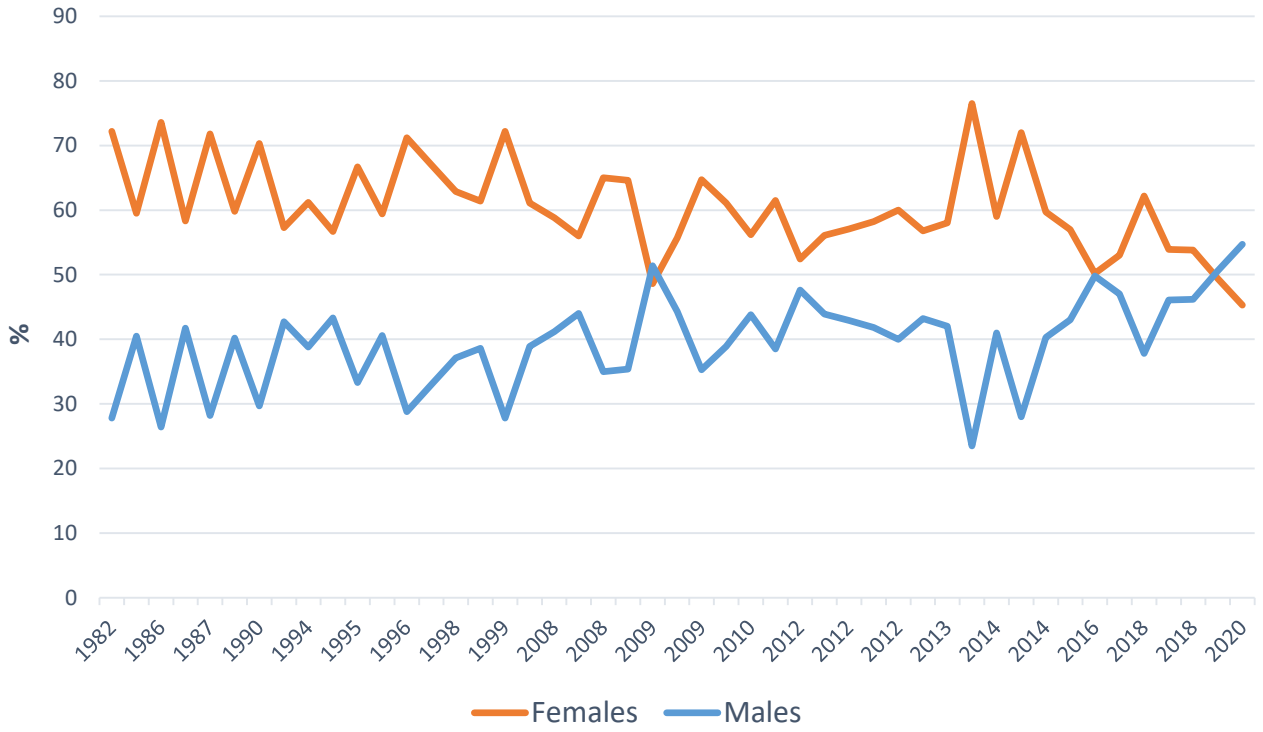
MR medio (1951-2016): 1.5 cases per million person-years (range: 0.5-3.5).

Non è stato individuato alcun trend temporale significativo, né differenze tra continenti.

Montomoli C, Citterio A, Piccolo G, Cioccale R, Ferretti VV, Fratti C, Bergamaschi R, Cosi VE. Epidemiology and geographical variation of myasthenia gravis in the province of Pavia, Italy. Neuroepidemiology. 2012;38(2):100-5.

Età e sesso studi MG (1)

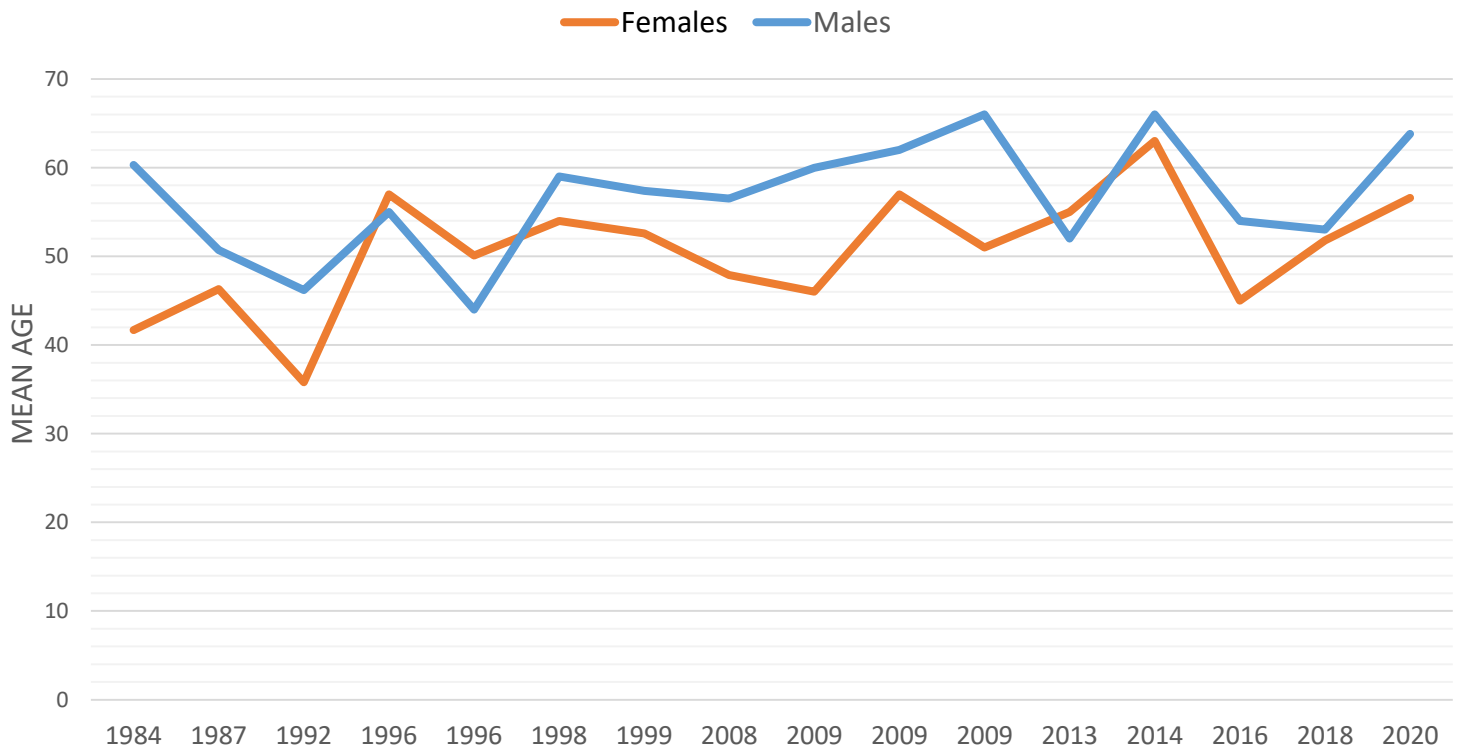
Percentuali di maschi e femmine



Rapporto F/M=1.5/1

Età e sesso studi MG (2)

Età media stratificata per sesso



Età media: 53.2 anni (range: 25-74.9).

Età media uomini: 56.6 anni, range: 44-66;
Età media donne: 50.7 anni, range: 35.8-63.

Prevalenza e incidenza sottotipi di MG

Prevalenza

Year	Cases per million	Country
AChR-MG		
1997	70.7	Greece
2004	90	The Netherlands
MuSK-MG		
2004	1.9	The Netherlands
2006	2.9	Greece
Juvenile/Congenital MG		
2001	45.6	Hong Kong
2007	9.2	The UK
2013	3.6	Norway
2018	22.2	Slovenia
LEMS		
1999	2.3	South Netherlands
2003	2.5	The Netherlands
2013	2.6	USA
2013	2.9	Ireland
2017	2.7	Japan

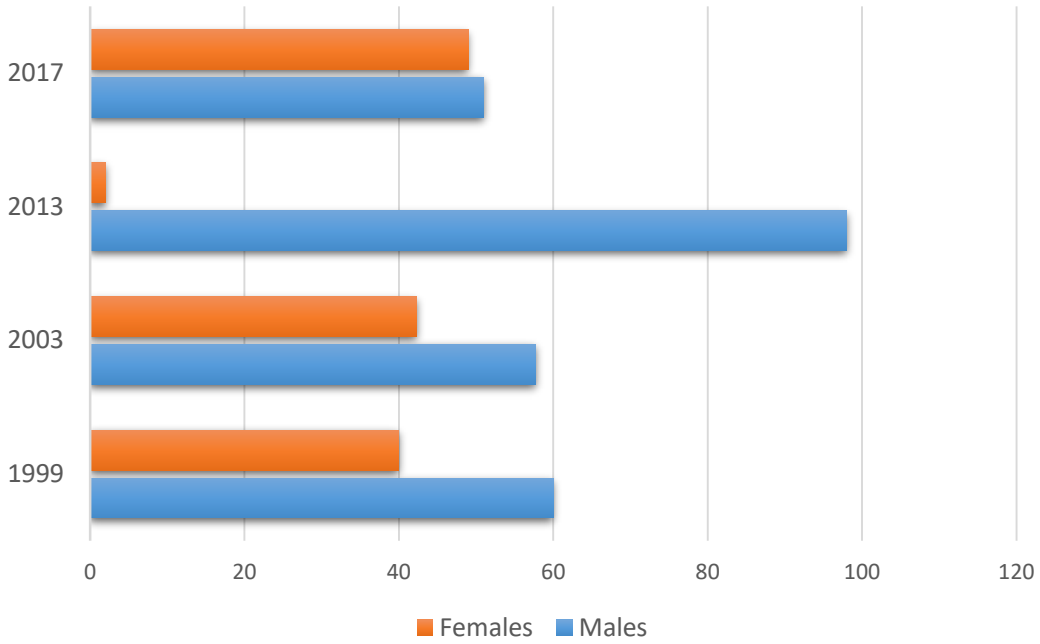
Human Leukocyte Antigen (HLA)?

Maggiore omogenità rispetto a MG

Incidenza

Year	Cases per million person-years	Country
AChR-MG		
1997	7.4	Greece
1999	20.8	Eastern Denmark
1999	18	The UK
2001	10.5	Tayside, Scotland
2004	4.6	Netherlands
2005	11.2	Cape Town, South Africa
2005	2.6	South Africa
2007	7	Norway
2012	15.2	Argentina
2012	7.5	South Africa
2013	18.5	Israel
MuSK-MG		
2004	0.1	The Netherlands
2006	0.3	Greece
Juvenile MG		
2007	1.6	The UK
2013	1.6	Norway
LEMS		
1999	0.5	South Netherlands
2003	0.4	The Netherlands
2013	0.6	USA

Età e sesso studi LEMS



Età media: 58.8 anni
(range 55-62.2).

Tumour association

50–60% of patients with LEMS have a tumour.[3] SCLC, a smoking-related lung carcinoma with neuroendocrine characteristics, is almost always the tumour type that occurs in patients with LEMS, although there have been a few reports of non-small-cell and mixed lung carcinomas.[5,13–17] Several papers describe associations o

Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol. 2011 Dec;10(12):1098-107.

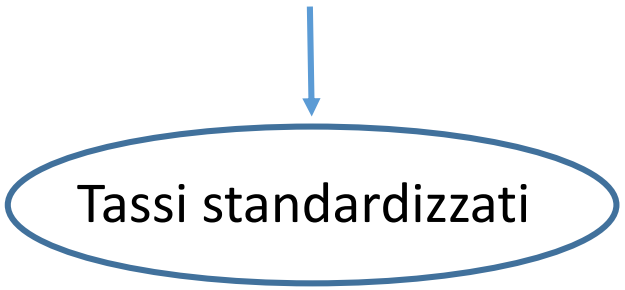
LEMS con tumore più frequente in uomini. LEMS senza tumore più frequente in donne.

The prevalence of LEMS in Japan is estimated at 2.7 in 1 000 000. Of 46.7% of patients had tumours. About 33.3% of Japanese LEMS had SCLC. There were predominances of men in the LEMS with tumours (paraneoplastic LEMS, P-LEMS) (78.6%) and women in the LEMS without tumours (primary autoimmune form of LEMS, AI-LEMS) (68.8%). AI-LEMS

Yoshikawa H, Adachi Y, Nakamura Y, et al. Nationwide survey of Lambert-Eaton myasthenic syndrome in Japan. BMJ Neurology Open 2022;4:e000291

Prospettive future

- Migliorare qualità studi → Maggiore comprensione su eventuali pattern genetici/ambientali



- Espandere studi in Africa e Oceania per avere visione più globale del fenomeno

- Aumentare il numero di studi riguardanti i sottotipi di MG

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