**EPIDEMIOLOGY OF MYASTHENIA GRAVIS**

MG is an uncommon disease involving the striated muscles and characterized by weakness and fatigue caused by defective nerve impulse transmission. An autoimmune pathogenesis has been established for MG. The disease is attributable to different immunological mechanisms mediated by anti-acetylcholine receptor (AchR) antibodies, and it is due to antibodies binding to AchRs on the muscle membrane. All ages are affected and incidence is higher in females than in males. Association with thymic hyperplasia or thymoma and other autoimmune diseases are known. Clinical diagnosis is not always simple and MG presentation is polymorphic. Failure to diagnosis MG in the early stages is frequent and this condition is known for remaining undiagnosed for a long time.

Searches were conducted in Pubmed, a database which includes Medline, the most frequently used medical database. We selected all articles with the objectives of estimating epidemiological indices of prevalence and/or incidence during the last twenty years only in NEPHIRD partner countries. The overall prevalence was calculated as the median of prevalence of each of the selected studies when the 95% CI of the selected studies were overlapping.

The following information was collected and summarised for each of the studies. (The summary table is provided in Appendix 1)

- Design of the study (case reports, cross-sectional surveys);
- Target (total population; specific group population; unknown);
- Availability of case definition;
- Date of diagnosis;
- Date of manifestation of first symptoms;
- Prevalence and incidence estimate (point prevalence and mean annual incidence rate per 10,000. For each rate were calculated 95% CI by considering it to be the mean of a Poisson distribution);
- Data source (medical record; special survey; multiple source).

The exclusion criteria follow:

- description of the rare diseases it self, like symptoms or diagnosis;
- description of treatment;
- description concerning genetic structure;
- health care policy;
- study conducted before 1980;

Medline was consulted using the search algorithm:

“Myasthenia Gravis” AND
“name of European country” AND
Results

We found a total of 13 available studies on the epidemiology of MG during the last twenty years in the European Countries (England, Sweden, Yugoslavia, Italy: Emilia Romagna, Italy: Sardinia, Holland, Italy: Ferrara, Croatia, Norway, Denmark, Greece, Spain and Italy).

A summary of the results are reported in Table 1:

<table>
<thead>
<tr>
<th>Country</th>
<th>Authors</th>
<th>Population</th>
<th>Year</th>
<th>Prevalence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>/10.000 (95%IC)</td>
<td>/10.000 (95%IC)</td>
</tr>
<tr>
<td>England</td>
<td>Robertson NP</td>
<td>684,000</td>
<td>1992</td>
<td>1.5 (1.2-1.8)</td>
<td>0.1 (0.07-0.15)</td>
</tr>
<tr>
<td>Sweden</td>
<td>Kalb B</td>
<td>1,783,428</td>
<td>1998</td>
<td>1.4 (1.2-1.5)</td>
<td>nd</td>
</tr>
<tr>
<td>Yugoslavia</td>
<td>Lavrnic D</td>
<td>1,531,232</td>
<td>1983</td>
<td>1.2 (1.0-1.5)</td>
<td>0.07 (0.06-0.09)</td>
</tr>
<tr>
<td>Italy: Emilia Romagna</td>
<td>Guidetti D</td>
<td>2,924,710</td>
<td>1993</td>
<td>1.17 (0.87-1.55)</td>
<td>0.15 (0.11-0.18)</td>
</tr>
<tr>
<td>Italy: Sardinia</td>
<td>Aiello I</td>
<td>268,926</td>
<td>1958</td>
<td>1.11 (0.75-1.59)</td>
<td>0.08 (0.05-0.12)</td>
</tr>
<tr>
<td>Holland</td>
<td>Wirtz PW</td>
<td>1,725,317</td>
<td>1990</td>
<td>1.06 (0.91-1.24)</td>
<td>0.06 (0.05-0.07)</td>
</tr>
<tr>
<td>Italy: Ferrara</td>
<td>Tola MR</td>
<td>370,374</td>
<td>1987</td>
<td>1.05 (0.75-1.44)</td>
<td>nd</td>
</tr>
<tr>
<td>Croatia</td>
<td>Zivadinov R</td>
<td>313,599</td>
<td>1976</td>
<td>0.99 (0.68-1.40)</td>
<td>0.06 (0.03-0.09)</td>
</tr>
<tr>
<td>Norway</td>
<td>Storm-Mathisen A</td>
<td>4,107,063</td>
<td>1952</td>
<td>0.9 (0.80-0.90)</td>
<td>0.04 (0.04-0.05)</td>
</tr>
<tr>
<td>Denmark</td>
<td>Christensen PB</td>
<td>2,800,000</td>
<td>1985</td>
<td>0.78 (0.60-0.80)</td>
<td>0.05 (0.04-0.06)</td>
</tr>
<tr>
<td>Greece</td>
<td>Poulas K</td>
<td>10,180,913</td>
<td>1983</td>
<td>0.7 (0.62-0.79)</td>
<td>0.07 (0.06-0.08)</td>
</tr>
<tr>
<td>Spain</td>
<td>Aragones JM</td>
<td>122,923</td>
<td>1992</td>
<td>nd</td>
<td>0.15 (0.17-0.25)</td>
</tr>
<tr>
<td>Italy</td>
<td>Casetta I</td>
<td>36,0950</td>
<td>1985</td>
<td>nd</td>
<td>0.21 (0.13-0.31)</td>
</tr>
</tbody>
</table>

The overall prevalence, calculated as the median of prevalence of each of the selected studies when the 95% CI of the selected studies were overlapping, was 1.2/10,000.

The point prevalence rate ranged from 0.7 (Greece) to 1.5 (England) per 10,000.
The highest prevalence was in England and Sweden.

- In England eight sources were used to identify patients with MG: general practices, hospital data bases, departmental notes, myasthenia associations, immunology, thoracic surgery, ophthalmology, paediatric neurology and other specialities. The largest source of ascertainment was from general practitioner referrals, which also provided the largest number of patients identified from a single source. In this study the highest reported prevalence for myasthenia, is likely to be the result of optimum case ascertainment, increase disease duration, application of complex diagnostic tests, and the impact of an aging population leading to a relative increase in the prevalence of MG.

- In Sweden a regional database of MG patients was used to estimate the prevalence of the disease.

- MG prevalence of 1/10,000 reported in the province of Ferrara probably reflects a more complete ascertainment, owing to wide access to sources of study material and full cooperation from medical practitioners. The following sources were used for case identification: archives of hospitals, archives of neurological centres, records of thoracic surgery clinics and the list of anticholinesterase drug prescription. The prevalence obtained in this study is the result of a community with high standards of medical services and also reflects improved training of the neurologist in epidemiology, the long life of the patients due to progressive improvement in MG management.

The annual incidence was reported to range from 0.04 (Norway) to 0.21 (Italy) (Table 1) per 10,000. Considering that the study in Belgrade was based on the whole population, the incidence rate is close to the true one.

Age-standardized rate to European population were reported only in Norway and Denmark.
Bibliography on epidemiology of Myasthenia Gravis

1. Epidemiology of seropositive myasthenia gravis in Greece

   OBJECTIVES: To study the epidemiological characteristics of myasthenia gravis in Greece. METHODS: A population based study was carried out of seropositive myasthenia gravis in Greece for the period from 1 January 1983 to 30 June 1997; 843 patients were studied. RESULTS: The average annual incidence for the period 1992-7, for which the database is complete, was 7.40/million population/year (women 7.14; men 7.66). On 1 July 1997, there were 740 prevalent cases. The point prevalence rate was 70.63/million (women 81.58; men 59.39). The average overall annual mortality rate in the patients was 0.67/million population (women 0.53; men 0.82), and the mortality rate attributed to myasthenia gravis was 0.43/million population (women 0.41; men 0.45). The average age at onset was 46.50 years (women 40.16; men 54.46), and the mean age of the prevalent patients was 52.58 (women 47.65; men 59.48). The women: men incidence ratio was 1:1.04, and the prevalence ratio was 1.41:1. It is predicted that the prevalence and women: men prevalence ratio would increase if the patient list included all patients with a date of onset before 1983. CONCLUSIONS: The largest epidemiological study ever performed on myasthenia gravis is presented. The most important epidemiological indexes are provided.

2. Incidence and prevalence of myasthenia gravis in the county of the coast and Gorski kotar, Croatia, 1976 through 1996.
   Zivadinov R, Jurjevic A, Willheim K, Cazzato G, Zorzon M.

   For the period 1976 through 1996, we carried out an incidence and prevalence study of myasthenia gravis in the County of the Coast and Gorski kotar, Croatia. This was the first epidemiological study of myasthenia gravis in Croatia. A total of 43 incident cases were identified. Overall the average crude annual incidence rate was 6.52 per 1,000,000 person-years; 5.59 per 1,000,000 person-years for men and 7.41 per 1,000,000 person-years for women. The incidence rate was 6.30 (95% confidence intervals 4.56-8.51), age-adjusted to the European population and 5.17 (95% confidence intervals 3.74-6.98), age-adjusted to the world population. On 31 December 1996, there were 32 prevalent cases. The crude prevalence was 99 per 1,000,000 population (95% confidence intervals 67.7-139.6). The prevalence adjusted to the European and world populations was 101.9 (95% confidence intervals 69.7-143.7) and 75.9 (95% confidence intervals 51.9-107) per 1,000,000 population, respectively. Our incidence findings are similar to those reported in North-East Italy but lower than those in the United States. Our prevalence findings were generally higher.
than those in Northern European Countries but lower than those in the United States. Standardization of rates to the European or world population could facilitate comparison between different populations.

3. Myasthenia gravis: a higher than expected incidence in the elderly.

This 10-year (1991 to 2000) prospective study of MG in the county of Osona (Barcelona, Spain) reveals an annual incidence rate of 21.27 cases per million inhabitants (95% CI 13.89 to 31.16). Incidence increased from 5.03 x 10(6) in the age group of 0 to 14 years to 14.68 x 10(6) in the age group of 15 to 64 years and to 63.38 x 10(6) in the older population. These results, the highest reported to date, may be explained by the population aging.

Robertson NP, Deans J, Compston DA.

OBJECTIVES: To perform a comprehensive survey of myasthenia gravis in the county of Cambridgeshire, England, establishing contemporary epidemiological data. METHODS: Cases were ascertained from multiple sources. Prevalent patients were visited and assessed by means of a standardised questionnaire and examination complemented by review of medical case notes. RESULTS: One hundred cases were identified in a population of 684000 (prevalence 15 per 100000 population, 95% confidence intervals (95% CIs) 12-18). Thirty eight new diagnoses were made overall five year period providing an incidence of 1.1/100000 population/year. The sex ratio was 2:1 F:M. After a mean follow up of 11.7 years, symptomatic disease was still restricted to ocular muscles in 25 patients. Thirty four of 100 patients underwent thymectomy a mean of 0.8 years after presentation, and a thymoma was present in 12. Highest remission rates were seen in patients presenting with generalised disease who underwent thymectomy but did not have a thymoma (27%). Co-segregation of an additional autoimmune disease occurred in 27 patients and in 24/49 (49%) women with onset<50 years of age. CONCLUSIONS: This, the second highest reported prevalence for myasthenia, is likely to be the result of optimum case ascertainment, increased disease duration, application of complex diagnostic tests, and the impact of an aging population leading to a relative increase in the prevalence of ocular myasthenia.

This is the first epidemiological study of myasthenia gravis (MG) in the area of Belgrade. During the survey period (1983-1992), 124 incidental cases of MG were observed, producing an average annual incidence rate of 7.1 per million population (women, 8.3; men, 5.8). Age and sex-specific incidence rates for females demonstrated a bimodal pattern, with the first peak in the age group between 20 and 40, and the second peak in the age group 70-80. The age-specific rates for males showed unimodal pattern, reaching a maximum in the age group between 60 and 80. There was a tendency of more frequent disease appearance in the urban opposed to the suburban districts. On the prevalence day, December 31, 1992, the point prevalence rate was 121.5 per million (women, 142.5; men, 98.8). Only for incidental cases, the point prevalence rate was 77.1 (women, 83.2; men, 70.4). The average annual mortality rate was 0.47 per million (females, 0.52; males, 0.42), while cumulative lethality was 5.6 (women, 5.6; men, 5.7). Most frequently initial symptoms were ocular, occurring in 58% of patients. Through the period of investigation ocular symptoms were generalized in 68%, most frequently in the first 2 years (62.5%). Thymoma was confirmed in 11.3% of patients. In this group there was equal presence of both sexes, older median age at onset, and more severe clinical course of MG. Associated autoimmune disease was found in 17 out of 124 incidental cases (13.7%). The most common were thyroid diseases (7.3%). Family history of MG was recorded in 2 cases belonging to 1 family (1.6%).

6. Epidemiological study of myasthenia gravis in the province of Ferrara, Italy.
Tola MR, Granieri E, Paolino E, Caniatti L, Quatrale R, Mazzanti B, D'Alessandro R.

The only prevalence rate of myasthenia gravis (MG) so far estimated in Italy by an epidemiological study carried out in Pavia, North Italy, indicates a prevalence quite similar to that observed in other countries. The purpose of the survey was to verify the frequency of the disease in a geographically well-defined and previously surveyed community. On the basis of 39 cases, on December 31, 1987 the prevalence per million was 105.3 (102.3 if standardized for the Italian population). This is the highest prevalence figure yet found, indicating a value similar to that established in Northern Europe. According to Kurtzke this high prevalence rate reflects the high standard of the local public health service, which permitted a more intensive search for affected subjects.

7. Epidemiological study of myasthenia gravis in the province of Reggio Emilia, Italy.
Guidetti D, Sabadini R, Bondavalli M, Cavalletti S, Lodesani M, Mantegazza R,
Cosi V, e Solime F.
We carried out a retrospective incidence, prevalence and mortality survey of myasthenia gravis in the province of Reggio Emilia in Northern Italy. Based on 49 patients, the mean incidence per year for the period 1980 through 1994 was 7.8 per 1,000,000. On 31 December 1994 the prevalence rate was 117.5 per 1,000,000 for all patients, either active or recovered (50 cases in a population of 427,493) and 103.4 per 1,000,000 for the active disease. In the 15-year period 1980-1994 the average mortality rate was 1.0 per 1,000,000 per year. The average age at onset was 44.6 +/- 21.0, and the average age at the time of prevalence determination was 51.1 +/- 19.6 for the active disease. At the time of diagnosis, 21 patients (36.8%) were classed in group I according to Osserman's criteria, 31 in group II (54.4%), (19 in group II-A and 12 in group II-B), and the other 5 (8.8%) in group III. Of all the prevalence cases, 6 (12%) were in remission without therapy and 6 with therapy, while most of the others 16 (32%) were classed in group I, 15 (30%) in group II, and 1 (2%) in group III. Thymectomy was performed in 20 patients (35.1%), 12 (21%) had thymoma (malignant in 4 cases), 6 had thymic hyperplasia while in two patients thymic histology was normal. The relation the grade of Osserman's scale at the time of incidence and the presence of thymoma were significant. Higher grades of Osserman's scale were associated were malignant thymoma. Furthermore the relationship between thymectomy and the grade of Osserman's scale at the date of prevalence was significant for the presence of lower grades of Osserman's scale in the patients submitted to thymectomy.

8. Epidemiology of myasthenia gravis in northwestern Sardinia.
Aiello I, Pastorino M, Sotgiu S, Piras M, Sau GF, Sanna G, Rosati G.

A previous epidemiological study on myasthenia gravis (MG) in Sardinia indicate da prevalence rate of 4.5 per 100,000 population and an incidence of 0.25 per100,000 population in the period 1958-1986. This study, however, investigated the entire Sardinian population (about 1,500,000) and the reported rates are likely to be underestimated. Because the use of a very large population has been found to cause major bias in case finding, the present study was designed to overcome this bias by determining the prevalence and incidence of MG in a well-defined area of Northwestern Sardinia, with a population of about 270,000(1991 census). Potential MG cases were ascertained using all possible medical sources. The diagnosis of MG was based on the clinical, neurophysiological andconventional pharmacological findings (Tensilon test, response toanticholinesterases). On prevalence day (December 31, 1994) 29 MG patients wereliving in the study area (17 women and 12 men). Since the total population onprevalence day was 268,926 (137,284 women and 131,642 men), the calculated prevalence was 11.1 per 100,000 population (12.4 women and 9.9 men). The present study shows that the risk of MG in Sardinia is higher than previously suggested. The risk, however, is not significantly different from that found in other comparable Italian and European areas. It contrasts with what has been found for other autoimmune diseases such as multiple sclerosis and insulin-dependent diabetes mellitus in Sardinians, both showing frequencies up to 3-5 times higher than in the rest of Italy.
9. The epidemiology of myasthenia gravis, Lambert-Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland.


J Neurol. 2003 Jun;250(6):698-701

We studied the epidemiology of myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS), and their association with small cell lung carcinoma (SCLC) and thymoma, in a well defined region of the Netherlands. Available data on all the patients with MG, LEMS, thymoma or SCLC living between 1 January 1990 and 31 December 1999 in the northern region of South Holland, with a population of 1.7 million inhabitants, were evaluated. A total of 202 patients with MG (20 with thymoma) and ten patients with LEMS (seven with SCLC) were identified. LEMS was 46 times less prevalent (2.32 x 10(-6)) than MG (106.1 x 10(-6)), whereas the annual incidence rate of LEMS was 14 times lower (0.48 x 10(-6)) than of MG (6.48 x 10(-6)), reflecting the poor survival of LEMS patients with SCLC. SCLC was diagnosed in 1593 patients, seven (0.44 %) of whom developed LEMS. Mean age at diagnosis of SCLC was significantly lower in SCLC patients with LEMS (p =0.006). A thymoma was diagnosed in 32 patients, of whom the ten patients with MG (31 %) had a younger age at diagnosis of thymoma than the patients without MG (p= 0.27). This study confirms the increasing prevalence of MG over the last few decades as reported by others, and underscores the relative rarity of LEMS. The frequency of LEMS in our patients with SCLC was lower than reported in previous studies. In patients with a SCLC or thymoma, the tumour was diagnosed at younger age in those who had the associated myasthenic syndrome.


Christensen PB, Jensen TS, Tsiropoulos I, Sorensen T, Kjaer M, Hojer-Pedersen E, Rasmussen MJ, Lehelde E, de Fine Olivarius B.

Neurology. 1993 Sep;43(9):1779-83.

We studied the epidemiology of myasthenia gravis (MG) in western Denmark from 1975 to 1989, basing case identification on records from all hospitals in the survey area. The population surveyed was 2.80 million in 1985. The average annual incidence rate was 5.0 per million population (women, 5.9; men, 4.2). The point-prevalence rate (January 1, 1990) was 78 per million population (women, 102; men, 53). In men, the incidence increased after 40 years. In women, the incidence rates showed a bimodal pattern with a peak of 7.0 in the age group 20 to 29 years and a second peak of 11.7 in the age group 70 to 79 years. The differences in sex- and age-specific incidence rates suggest that younger women are more susceptible to MG than younger men. Old men and postmenopausal women had similar rates. When last examined, 21% of the 220 prevalent cases were in remission and 18% were moderately or severely disabled.
The number of patients with myasthenia gravis diagnosed and registered in Norway from 1912-1981 has been collected, representing essentially all diagnosed cases during these 70 years. Until 1948, Oslo University Hospital, the National Hospital, had the only neurological department in Norway. Since then, neurological departments have been established throughout our country. All these departments and all practising neurologists in Norway responded to the appeal for the necessary information on their diagnosed patients up to the end of 1981. The majority of the results are based on the period 1951-1981. The National Bureau of Statistics has registered the deaths of myasthenia gravis cases since 1951, and since 1956 where it has constituted an underlying or contributory cause. The incidence rate by diagnosis per million population 1951-1981 is 2.6 for males, 5.3 for females and 4 for both sexes. The prevalence per million population is 52 for males, 127 for females and 90 for both sexes. The mortality in males is 144% and in females 155% of the mortality in the population. The excess mortality is much greater in patients below 60 years of age, especially in females where a value of 483% if found.

A regional database of myasthenia gravis (MG) patients was used to estimate the prevalence and selected characteristics of the disease in the county of Stockholm, Sweden. The prevalence of MG was 14.1/100,000 (17.1 for women and 10.8 for men). The mean age at onset for women and men was 34.9 and 48.5 years, respectively. About 60% of patients were diagnosed within the first year after initial symptoms. Generalized MG was found in 79% of patients, and 10% had severe symptoms. Almost two thirds of the patients had undergone thymectomy, and 30% needed immunosuppressive treatment. The increase in the prevalence of MG since the 1960s probably reflects an improvement in prognosis and higher detection rates of patients with milder symptoms. A delay in diagnosis indicates that early signs and symptoms of MG are still not well known by all doctors.
BACKGROUND: The reported annual incidence of myasthenia gravis (MG) ranges from 0.25 to 15 per million. The sex- and age-related pattern of disease incidence is still debated. METHODS: An intensive descriptive study was performed in the province of Ferrara (mean population 360,950 people) over the period 1985 through 2000. RESULTS: The average crude annual incidence rate was 2 per 100,000. We confirm a female preponderance in the total population, particularly in the youngest age groups. CONCLUSIONS: We observed an early increase in incidence in females, partly due to thymoma-associated MG, while MG without thymoma showed increasing incidence with age nonsignificantly different in the two sexes. 2004 S. Karger AG, Basel
## Appendix 1. The summary table of studies related to epidemiology of Myasthenia Gravis in European Countries.

<table>
<thead>
<tr>
<th>Authors/ Publication date</th>
<th>Study Population</th>
<th>Study Period</th>
<th>Epidemiological indices</th>
<th>Age at Diagnosis/Onset</th>
<th>Study Design</th>
<th>Source</th>
<th>Case Definition</th>
</tr>
</thead>
</table>
| Zivadinov R, et. al. 1998 | County of the Coast and Gorski Kotar, Croatia General population (≅ 313,599) | 1 Jan 1976 – 31 Dec 1996 | Incidence: 0.06/10^4 person years crude rate (0.03 – 0.08) 0.06/10^4 adjusted to European population (0.04 –0.08) | Median age at onset 56yr. (19 – 82 yr. Range) | Cohort study with case referral | In patients/ outpatients records of all health facilities with possibility of case visit Code 773.0 ICD-8 Code 358.0 ICD-9 | • Clinical history of  
• Lab findings  
• And when possible (in 95.5%) ascertainment by neurologist |
| Aiello I, et. al. 1997 | North Western Sardinia General population (≅ 268,926) | 1958-1986 | Incidence: 0.08/10^4 (0.05 – 0.12) for 1982 -1994 Prevalence: 1.11/10^4 (0.75 – 1.59) on 31 Dec 1994 | Mean at onset 42.9 ± 19.07 | Cross sectional with record review of health services’ files from 1965 to 1995 | Health institutions’ records | |
| Robertson MP, et. al. 1998 | Cambridgeshire County General population (684,000(by mid 1995) | 30 Jun 92 – 1Jul 97 | Incidence: 0.11/10^4 (1.2 – 1.8) on 1 July 1997. Prevalence: 1.5 /10^4 | Mean age at onset 46 yr. Mean age at diagnosis 47.8 yr. | Cross section with record review starting from 1965 Active case registration since 1992 | All possible health units which might see patients of myasthenia gravis | Record review with the help of standard questionnaire  
Diagnostic criteria: if three of the following are present  
• typical history  
• clinical evidence of fatigability with recover on rest  
• clinical response ACH esterase administration  
• detection of ACH receptor antibody  
• decrement on electrical activity on repetitive stimulation  
• exclusion of alternative relevant diagnosis |
| Christensen PB, et. al. 1993 | Western Denmark (≅ 2,8 * 10^6) on 1July, 1985 | | Incidence: 0.05/10^4 (0.044 – 0.057) Prevalence: 0.78/10^4 on 1 Jan, 1990 | Median age at diagnosis 54 yr. (3 – 85 range) | Cross sectional medical records retrieval Code 733.0 ICD-8 | All hospital records (from 100 different departments) from the region with check up on the state university | Diagnostic criteria  
• muscle weakness & rapid fatigue in one or more muscle groups  
• muscle weakness aggravated by exercise and relieved by rest |
<table>
<thead>
<tr>
<th>Region / Country</th>
<th>Population</th>
<th>Year Range</th>
<th>Incidence Rate</th>
<th>Age at Diagnosis</th>
<th>Study Design</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region of Emilia-Romagna, Italy</td>
<td>2,924,710</td>
<td>1 Jan 1993 – 31 Dec 1994</td>
<td>0.147/10⁴ (0.1176 – 0.182)</td>
<td>Mean age at diagnosis 55.2 ± 19.9 yr.</td>
<td>Prospective study with periodic review of all discharge diagnosis and other possible sources</td>
<td>• a significant response to ACH-esterase drugs</td>
</tr>
<tr>
<td>Southeastern Europe</td>
<td>10,180,913</td>
<td>1 Jan 1983 – 30 Jun 1997</td>
<td>0.1/10⁴</td>
<td>Mean age at diagnosis 46.5</td>
<td>Cross-sectional study of computerised records of patients sero positive from 1983</td>
<td>The diagnosis of Myasthenia Gravis was confirmed by seropositivity for the presence of antibodies against human ACHR (&gt;1 nmol/l) and supported for many patients by pharmacological test and neurophysiological examination and clinical finding</td>
</tr>
<tr>
<td>Belgrade, Yugoslavia</td>
<td>1,531,232</td>
<td>1983-1992</td>
<td>0.71/10⁴ (0.62-0.79) on 1 July 1997</td>
<td>39.7± 19.6 yr.</td>
<td>Cross-sectional study</td>
<td>Minimal diagnostic criteria were evidence of fluctuating muscle weakness and fatigability and positive response to neostigmin and/or edrophonium</td>
</tr>
<tr>
<td>Stockholm, Sweden</td>
<td>1,783,428</td>
<td>31 Dec 1998</td>
<td>ND</td>
<td>40.2 (6-86)</td>
<td>Cross-sectional study with record review</td>
<td>• neurofisiological studies</td>
</tr>
<tr>
<td>Ferrara, Italy</td>
<td>360,950</td>
<td>1985-2000</td>
<td>0.2/10⁴ (0.17-0.25) - the incidence rate adjusted to European population was ND</td>
<td>52.3</td>
<td>Multicenter prospective study</td>
<td>• Clinical features</td>
</tr>
</tbody>
</table>

- **Guidetti D, et. Al. 1998**
- **Poulas K, et al. 2001**
- **Lavrnic D, et al. 1999**
- **Kalb B, et al. 2002**
- **Casseta I et. Al. 2004**
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Year</th>
<th>Sample Size</th>
<th>Date Range</th>
<th>Dataset</th>
<th>Diagnostic Criteria</th>
<th>Laboratory Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tola MR 1989</td>
<td>Ferrara, Italy</td>
<td>1987</td>
<td>370,374</td>
<td>31 dic 1987</td>
<td>ND</td>
<td>38.9 (12-76)</td>
<td>Cross-section study</td>
</tr>
<tr>
<td>Wirtz PW 2003</td>
<td>South Holland</td>
<td>1990 to 31 dic 1999</td>
<td>1,725,317</td>
<td>0.06/10⁴ (0.05-0.07)</td>
<td>48 (4-90)</td>
<td>Cross-section study</td>
<td>Hospital database using ICD-9 codes 358.0</td>
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<td>Stor Matihisen 1984</td>
<td>Norway</td>
<td>1912-1981</td>
<td>4,107,063</td>
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<td>ND</td>
<td>Cross-section study</td>
<td>Clinical database of Public and private neurological department</td>
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<td>Aragones JM et al. 2003</td>
<td>Barcelona, Spain</td>
<td>1991-2001</td>
<td>1,252,923</td>
<td>Prospective population-based study</td>
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