Original research

Epidemiology of myasthenia gravis in Denmark, Finland and Sweden: a population-based observational study

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ABSTRACT

Background Incidence and prevalence rates of myasthenia gravis (MG) vary considerably across studies, and mortality risk is rarely addressed. We examined the prevalence and incidence rates, mortality and factors associated with mortality with MG.

Method This was a registry linkage study based on nationwide health and administrative registries of Denmark, Finland and Sweden (populations of 5.9, 5.6 and 10.5 million, respectively). Patients with MG were identified based on International Classification of Diseases codes from inpatient and outpatient specialised care registries. Yearly prevalence, incidence and mortality rates in relation to the total background population were calculated from 2000 to 2020 (study period). The causes of death and factors associated with mortality were addressed separately.

Results The overall incidence of MG was 1.34 (95% CI 1.27 to 1.41), 1.68 (95% CI 1.60 to 1.75) and 1.62 (95% CI 1.56 to 1.68) per 100 000, and the overall prevalence per 100 000 was 18.56 (95% CI 18.31 to 18.81), 20.89 (95% CI 20.62 to 21.16) and 23.42 (95% CI 23.21 to 23.64) in Denmark, Finland and Sweden, respectively. The overall standardised mortality ratio (SMR) was 1.32 (95% CI 1.23 to 1.42) among patients with MG in Denmark, 1.23 (95% CI 1.15 to 1.33) in Finland, and 1.20 (95% CI 1.14 to 1.26) in Sweden, with higher SMR observed in women than men. Annual incidence and prevalence increased over time, whereas the SMR remained stable. The most common causes of death were MG, chronic ischaemic heart disease and acute myocardial infarction.

Conclusions This population-based study from three Nordic countries highlights the need for improved care of patients with MG, especially young women.

INTRODUCTION

Myasthenia gravis (MG) is a rare, chronic, autoimmune disease characterised by variable degrees of abnormal muscle fatigue in ocular, bulbar, axial and extremity skeletal muscle groups, sometimes leading to life-threatening respiratory insufficiency.1 Symptoms of MG are caused by autoantibodies recognising receptors of the postsynaptic neuromuscular junction, interfering with their function and leading to deteriorated synaptic signalling and, subsequently, strength of skeletal muscles.2

The acetylcholine receptor is by far the most common target (approximately 85%) of patients,3 with smaller proportions of patients being positive for autoantibodies for the muscle-specific kinase protein, while 10%–15% of patients are seronegative for any of the known target proteins.4–6

MG is diagnosed based on clinical findings, presence of autoantibodies, neurophysiological tests showing disturbed neuromuscular transmission and treatment response to cholinesterase inhibitors, which increase the concentration of neurotransmitter acetylcholine at the neuromuscular junction.7 Patients with MG can be further subgrouped based on the age of onset, antibody status, presence of thymus pathology and clinical presentation (ie, ocular myasthenia vs generalised myasthenia), all of which impact prognosis and treatment strategy.8–10

In epidemiological studies of MG, the incidence rate has varied with age, sex and ethnic group.11 However, differences in study population composition and criteria for case definitions likely partly explain the substantial variability among previous studies. Hence, the reported incidence ranges from 0.4 (Norway and Denmark) to as high as 2.9 (Sweden) and 4.6 (Germany) per 100 000.3–11
Similarly, a review of 24 studies from 1990 to 2014 found that MG prevalence ranged from 5.4 to 35.0 per 100,000. Only a few comprised larger population-based materials, but nationwide studies conducted in Sweden and Finland reported MG prevalence as 24.8 and 29 per 100,000, respectively.12 13 Similar to other autoimmune conditions, the incidence and prevalence of MG reportedly increase over time, though it is unclear to what degree this is due to improved awareness and detection.14

Improved therapeutic management has contributed to increased life expectancy in MG.15 Nonetheless, mortality remains elevated in patients with MG. An overall mortality rate ratio of 1.41 with higher mortality among women was reported in Denmark and a mortality ratio of 1.28 in patients with MG compared with the general population was reported in Sweden.17

Collectively, the literature does not provide consistent information on the epidemiology of MG in contemporary populations over time, and few studies have examined, for example, factors associated with mortality. The Nordic countries, with universal access to publicly funded healthcare and high-quality health registries, offer excellent opportunities for population-based studies exploring the lifetime MG disease course. However, no study to date has leveraged data from more than one country. The objective of this study was to establish and cross-compare MG incidence, prevalence and mortality rates in Denmark, Finland and Sweden. In addition, causes of death and factors associated with the risk of death were examined.

METHODS

Study setting and data sources

This was an observational, population-based cohort study using data from the nationwide health and administrative registries of Denmark, Finland and Sweden, with total populations of 5.9, 5.6 and 10.5 million, respectively. All three countries have a tax-funded healthcare system with universal access to healthcare for all citizens, as well as digital population, health and social care registries with complete population-wide coverage. The standard of care of MG has largely followed international consensus guidelines in all three countries during the last two decades.21

The identification of patients with MG and the comorbidity data was based on the national patient registries (The Danish National Patient Register, The Finnish Care Register for Health Care, and The Swedish National Patient Registry). Basic demographic information and data on migration were collected from The Danish Civil Registration System, Statistics Finland and The Swedish Population Registry. Cause of death information was collected from the causes of death registries of each country. In Finland and Sweden, the cause of death registries also includes information on the time of death, while in Denmark this information was collected from the Civil Registration System. Data from each registry can be extracted and linked through a unique personal identification number assigned to all individuals at birth or immigration, allowing follow-up of all study participants until death, emigration or end of data collection. In addition, all Nordic countries have central statistical agencies collecting and providing valid historical demographic data which served as the source of information on background population size and composition for epidemiological analyses. The diagnosis information was based on the International Classification of Diseases (ICD) codes.

Study cohorts

All patients with at least one diagnostic code for MG (ICD-10 codes G70.0*, ICD-9 codes 358.0*, ICD-8 code 73 309 and/or ICD-7 code 74400) in the national patient registries between 1 January 2000 (start of the study period) and 31 December 2020 (end of the study period) were included in the study.

Three cohorts were formed for the analyses. The full primary cohort (FPC) included all patients with at least one MG diagnosis and the prevalent subcohort (PSC) included all patients with at least two MG diagnoses in the study period. The incident subcohort (ISC) included all patients with at least two MG diagnoses during the study period, and no MG diagnoses before 1 January 2000. A minimum of 12 months without an MG diagnosis before the date of diagnosis was required for a patient to be included in the incident cohort (prior MG diagnosis was screened from all available registry data, starting from the start of the patient register in each country; year 1977 in Denmark, 1969 in Finland, and 1964 in Sweden). The last incident cohort date was 2019 in Finland and Sweden and 2020 in Denmark, due to the availability of data. The analyses of prevalence and incidence required at least two diagnoses of MG (initial and confirmatory) and were therefore based on the PSC and ISC. The mortality analysis was based on the PSC and was compared with the FPC. For all cohorts, the date of the first inpatient or outpatient specialist visit with an MG diagnosis was designated as the patient’s index date (MG diagnosis date). The baseline period was 12 months prior to the index date.

Statistical analyses

Descriptive statistics were used to calculate numbers and proportions for categorical variables; and means, medians, SD and first and third quartiles (Q1, Q3) for continuous variables. The incidence of MG was estimated in the ISC as the number of incident cases divided by the size of the total population in each country and expressed as the number of incident cases per 100,000 persons. The prevalence of MG was estimated in the PSC as of 31 December (the prevalence date) for each calendar year across the study period (2000–2020). Patients alive on the prevalence date and with the date of MG diagnosis any time before the prevalence date were included in the numerator, and the total background population alive on the prevalence date in the denominator. The expected annual number of deaths was estimated from the sex, age and calendar year-specific national mortality rates and standardised mortality ratios (SMR) were estimated. Furthermore, we examined the number and the proportion (with 95% CIs) of the 10 most common causes of death among patients with MG in each country. Only primary causes of death were analysed. The diseases as cause of death were analysed separately at category level (at the level of three characters in the ICD-10 medical coding system).

A Cox proportional hazards model was used to estimate the HR and 95% CI of death among patients with MG in relation to age, sex, country, calendar year, disease duration and comorbidity. Calendar year and disease duration were evaluated as continuous variables, while comorbidity was included as a time-varying covariate. The listed variables were prespecified. Both univariable models and multivariable models were used in the analyses. In univariable models, each prespecified variable was individually present in the model. In the multivariable model, all the prespecified variables were included.

A sensitivity analysis was conducted examining the survival among patients with MG when using the PSC in comparison to the FPC.
To comply with the General Data Protection Regulation legislation, a minimum of five persons was required for separate reporting in the descriptive analyses. The final assessment of sufficient data volume was based on the estimation of the parameters, for example, the width of the CI or convergence of the estimation algorithm.

All analyses were performed using R (V.4.2.2).

RESULTS

Patient characteristics

Altogether, 11 136 patients with MG were identified during the study period (FPC; Denmark n=2984, Finland n=2653, Sweden n=5499). When restricting this to ≥2 diagnoses of MG during the study period, the study population was reduced to 9054 patients (PSC; Denmark n=2248, Finland n=2306, Sweden n=4500) and when further restricting to ≥2 new diagnoses of MG during the study period, the study population was reduced to 6415 patients (ISC; Denmark n=1559, Finland n=1797, Sweden n=3059) (online supplemental figure 1).

In the ISC, a slightly higher proportion of patients were male (51% in Denmark and Finland and 52% in Sweden), the median age at index date was 64.9 years (Q1, Q3: 49.0, 73.0) in Denmark, 64.9 years (Q1, Q3: 51.2, 74.1) in Finland and 67.5 years (Q1, Q3: 51.5, 76.8) in Sweden (table 1). Most patients were diagnosed at an advanced age (≥65 years) (50% were very late onset MG in Denmark and Finland, and 55% in Sweden).

Men had a higher median age at diagnosis (67.4 years; Q1, Q3: 57.9, 75.5) than women (62.6 years; Q1, Q3: 41.2, 75.6). The median follow-up time was 5.9 years (Q1, Q3: 2.4, 10.6) in Denmark, 7.3 years (Q1, Q3: 3.7, 12.6) in Finland and 7.0 years (Q1, Q3: 3.5, 11.8) in Sweden (table 1).

Incidence (ISC)

The overall incidence of MG was 1.34 (95% CI 1.27 to 1.41), 1.68 (95% CI 1.60 to 1.75), and 1.62 (95% CI 1.56 to 1.68) per 100 000 during the study period in Denmark, Finland, and Sweden, respectively. The incidence of MG (per 100 000 persons) increased over time in all three countries: in Denmark from 0.86 (95% CI 0.64 to 1.14) in 2000 to 1.92 (95% CI 1.59 to 2.30) in 2020, in Finland from 1.58 (95% CI 1.26 to 1.95) in 2000 to 2.15 (95% CI 1.79 to 2.56) in 2019 and in Sweden from 0.95 (95% CI 0.76 to 1.16) in 2000 to 1.74 (95% CI 1.50 to 2.01) in 2019 (figure 1A).

The overall incidence was higher in men than in women in all three countries. In Denmark, it was 1.38 in men (95% CI 1.28 to 1.48) and 1.30 in women (95% CI 1.21 to 1.39). In Finland, the incidence was 1.74 in men (95% CI 1.63 to 1.86) and 1.61 in women (95% CI 1.51 to 1.72). In Sweden, the incidence was 1.70 in men (95% CI 1.62 to 1.78) and 1.54 in women (95% CI 1.46 to 1.62). The age-specific incidence of MG differed in men and women: in women, a higher incidence was seen in the younger age groups (patients <50 years) with a moderate increase with age, whereas a steeper increase in the incidence of MG was observed in men from 50 years onwards (online supplemental figure 2).

Table 1 Baseline characteristics of patients with myasthenia gravis (MG) in Denmark, Finland and Sweden in 2000–2020 (incident subcohort)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Denmark n=1559</th>
<th>Finland n=1797</th>
<th>Sweden n=3059</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>796 (51%)</td>
<td>916 (51%)</td>
<td>1600 (52%)</td>
</tr>
<tr>
<td>Women</td>
<td>763 (49%)</td>
<td>881 (49%)</td>
<td>1459 (48%)</td>
</tr>
<tr>
<td>Age at index date (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>60.5</td>
<td>60.9</td>
<td>62.3</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>64.9 (49.0, 75.0)</td>
<td>64.9 (51.2, 74.1)</td>
<td>67.5 (51.5, 76.8)</td>
</tr>
<tr>
<td>Age group at index date (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 (juvenile MG)</td>
<td>33 (2%)</td>
<td>51 (3%)</td>
<td>80 (3%)</td>
</tr>
<tr>
<td>18–29 (early-onset MG)</td>
<td>116 (7%)</td>
<td>104 (6%)</td>
<td>193 (6%)</td>
</tr>
<tr>
<td>30–49 (early-onset MG)</td>
<td>257 (16%)</td>
<td>278 (15%)</td>
<td>449 (15%)</td>
</tr>
<tr>
<td>50–64 (late-onset MG)</td>
<td>374 (24%)</td>
<td>469 (26%)</td>
<td>645 (21%)</td>
</tr>
<tr>
<td>≥65 (very late onset MG)</td>
<td>779 (50%)</td>
<td>895 (50%)</td>
<td>1692 (55%)</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.0</td>
<td>8.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>5.9 (2.4–10.6)</td>
<td>7.3 (3.7–12.6)</td>
<td>7.0 (3.5–11.8)</td>
</tr>
<tr>
<td>Range</td>
<td>0.0–21.0</td>
<td>0.0–21.0</td>
<td>0.0–20.9</td>
</tr>
<tr>
<td>Immortal time (months)*</td>
<td>8.5</td>
<td>3.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>1.4 (0.4, 6.4)</td>
<td>1.1 (0.5, 2.4)</td>
<td>1.4 (0.6, 3.5)</td>
</tr>
<tr>
<td>Range</td>
<td>0.0–210.0</td>
<td>0.0–203.8</td>
<td>0.0–218.1</td>
</tr>
</tbody>
</table>

*Immortal time, the time between first and second diagnosis of MG.

Figure 1 Incidence (A) and prevalence (B) of myasthenia gravis per 100 000 persons in the incident subcohort in Denmark (DK), Finland (FI) and Sweden (SE) in years 2000–2020.
Neuromuscular

Prevalence (PSC)
The overall prevalence of MG during the study period was 18.56 (95% CI 18.31 to 18.81) per 100,000 in Denmark, 20.89 (95% CI 20.62 to 21.16) in Finland, and 23.42 (95% CI 23.21 to 23.64) in Sweden. The prevalence of MG (per 100,000 persons) increased steadily over time in all three countries: in Denmark from 13.32 (95% CI 12.36 to 14.32) in 2000 to 25.14 (95% CI 23.88 to 26.45) in 2020, in Finland from 11.08 (95% CI 10.20 to 12.01) in 2000 to 28.52 (95% CI 27.13 to 29.95) in 2020, and in Sweden from 16.58 (95% CI 15.75 to 17.44) in 2000 to 27.18 (95% CI 26.19 to 28.19) in 2020 (figure 1B).

The overall prevalence of MG was higher in women than men in all three countries. In Denmark, it was 21.40 in women (95% CI 21.03 to 21.78) and 15.67 in men (95% CI 15.35 to 16.00). In Finland, the prevalence was 23.80 in women (95% CI 23.40 to 24.20) and 17.87 in men (95% CI 17.52 to 18.23). In Sweden, the prevalence was 27.27 in women (95% CI 26.94 to 27.59) and 19.56 in men (95% CI 19.28 to 19.83). The age-specific prevalence of MG increased gradually with age in both men and women (online supplemental figure 3). In patient groups between 20 and 60 years of age, the prevalence was higher in women than men. In patients aged >60 years, a higher prevalence was observed in men.

Mortality (PSC)
The overall survival among patients with MG was 0.84 (95% CI 0.84 to 0.85) at 5-year follow-up, 0.70 (95% CI 0.68 to 0.71) at 10-year follow-up, 0.58 (95% CI 0.56 to 0.59) at 15-year follow-up and 0.49 (95% CI 0.48 to 0.51) at end-of-follow-up. The survival was similar in the FPC and the PSC (data not shown).

The overall SMR was 1.32 (95% CI 1.23 to 1.42) among patients with MG in Denmark, 1.23 (95% CI 1.15 to 1.33) in Finland and 1.20 (95% CI 1.14 to 1.26) in Sweden, compared with the background population. The SMR was rather stable over time in all three countries: in Denmark 1.25 (95% CI 0.82 to 1.82) in 2000 and 1.32 (95% CI 0.99 to 1.71) in 2020, in Finland 1.40 (95% CI 0.83 to 2.17) in 2000 and 1.20 (95% CI 0.90 to 1.55) in 2020 and in Sweden 1.31 (95% CI 0.99 to 1.70) in 2000 and 1.28 (95% CI 1.06 to 1.52) in 2020 (figure 2).

The overall SMR was higher in women than in men in all three countries. In Denmark, it was 1.56 in women (95% CI 1.41 to 1.71) and 1.14 in men (95% CI 1.03 to 1.26). In Finland, SMR was 1.41 in women (95% CI 1.26 to 1.56) and 1.11 in men (95% CI 1.01 to 1.23). In Sweden, SMR was 1.39 in women (95% CI 1.30 to 1.49) and 1.06 in men (95% CI 0.99 to 1.13). In patients over 60 years of age, the SMR was relatively stable in men. In women over 60 years, the SMR decreased with increasing age (online supplemental figure 4).

Cause of death (PSC)
In Denmark, the three most common causes of death were MG (18.10%; 95% CI 15.44% to 21.09%), chronic obstructive pulmonary disease (5.23%; 95% CI 3.79% to 7.14%) and malignant neoplasm of bronchus and lung (4.16%; 95% CI 2.89% to 5.92%) (table 2). In Finland, the three most common causes of death were MG (16.87%; 95% CI 14.26% to 19.85%), chronic ischaemic heart disease (13.14%; 95% CI 10.81% to 15.87%) and acute myocardial infarction (8.58%; 95% CI 6.69% to 10.92%). Similarly, in Sweden, the three most common causes of death among patients with MG were MG (13.46%; 95% CI 11.88% to 15.22%), acute myocardial infarction (6.55%; 95% CI 5.43% to 7.87%) and chronic ischaemic heart disease (5.89%; 95% CI 4.83% to 7.16%). When combined, the most common causes of death among patients with MG in the three countries were MG (15.35%; 95% CI 14.12% to 16.67%), chronic ischaemic heart disease (6.80%; 95% CI 5.95% to 7.75%) and acute myocardial infarction (6.35%; 95% CI 5.54% to 7.28%).
Factors associated with mortality (PSC)

When examining explanatory variables associated with the HR of death among patients with MG, the HR was found to increase with increasing age, to be similar in men and women, and to be lower in Finland (HR=0.70; 95%CI 0.63 to 0.78) and Sweden (HR=0.92; 95%CI 0.84 to 1.00) compared with Denmark (table 3). Moreover, the HR of death decreased slightly over time (HR=0.97; 95%CI 0.96 to 0.98), whereas the HR of death increased with increasing duration of disease (HR=1.07; 95%CI 1.07 to 1.08). Furthermore, patients with diseases of the blood and blood-forming organs (HR=1.65; 95%CI 1.49 to 1.82), metabolic diseases (HR=1.65; 95%CI 1.51 to 1.79), thymoma (HR=1.65; 95%CI 1.65 to 2.12), respiratory diseases (HR=1.59; 95%CI 1.40 to 1.80), cancer (except thymoma) (HR=1.33; 95%CI 1.19 to 1.48), mental and behavioural disorders (HR=1.28; 95%CI 1.14 to 1.45)

Table 2  Ten most common causes of death (ICD-10) among patients with myasthenia gravis in Denmark, Finland and Sweden in 2000–2020 (prevalent subcohort)
**Neuromuscular**

**Table 3** Cox proportional hazards model examining the HR of death and 95% CIs among patients with myasthenia gravis in Denmark, Finland and Sweden in relation to explanatory variables in 2000–2020 (prevalent subcohort)

<table>
<thead>
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<th>Variable</th>
<th>Univariable model</th>
<th>Multivariable model*</th>
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<td>HR</td>
<td>Lower 95% CI</td>
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<tr>
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<td>&lt;18 years</td>
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<td>0.09</td>
</tr>
<tr>
<td>18–29 years</td>
<td>0.35</td>
<td>0.26</td>
</tr>
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<td>30–49 years</td>
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<td>≥65 years</td>
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<tr>
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</tr>
<tr>
<td>Women</td>
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<td>Finland</td>
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<td>Sweden</td>
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<tr>
<td><strong>Disease duration (per year)</strong></td>
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<td><strong>Comorbidities†‡</strong></td>
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<td>Diseases of the blood and blood-forming organs</td>
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<td>Diseases of the circulatory system</td>
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<td>Diseases of the eye and adnexa</td>
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<tr>
<td>Diseases of the musculoskeletal system and connective tissue</td>
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<td>Diseases of the respiratory system</td>
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<td>Endocrine, nutritional and metabolic diseases</td>
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<td>Neoplasms—except thymoma</td>
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<td>Severe infections</td>
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</table>

*Mutually adjusted.
†Comorbidities included as a time-varying covariate.
‡Comorbidities were grouped into: autoimmune disease (hypothyroidism, rheumatoid arthritis, type 1 diabetes mellitus, hyperthyroidism, psoriasis, polymyalgia rheumatica, ulcerative colitis, psoriatic arthritis, multiple sclerosis, Crohn’s disease, coeliac disease, systemic lupus erythematosus, Henoch-Schoenlein purpura (IgA vasculitis), primary sclerosing cholangitis and ankylosing spondylitis); diseases of the blood and blood-forming organs (anaemia, thrombocytopenia and lymphopenia); diseases of the circulatory system (hypertension, stroke, myocardial infarction, cardiac arrhythmia and pulmonary embolism); diseases of the eye and adnexa (cataract and glaucoma); diseases of the musculoskeletal system and connective tissue (osteoarthritis); diseases of the respiratory system (asthma and chronic obstructive lung disease); endocrine, nutritional and metabolic diseases (type 2 diabetes mellitus, dyslipidaemia, obesity and diabetes—other than types 1 and 2); mental and behavioural disorders (depression, anxiety disorders and mood disorders); neoplasms—except thymoma; neoplasms—thymoma; and severe infections (systemic infections and aseptic meningitis).
and diseases of the circulatory system (HR = 1.25; 95% CI 1.15 to 1.36) had an increased HR of death compared with patients without these comorbidities. In contrast, there was no increased risk of death among patients with MG with other autoimmune diseases, ophthalmological diseases, musculoskeletal diseases or severe infections.

**DISCUSSION**

In this large population-based cohort study, we identified more than 9000 patients with ≥2 diagnoses of MG in Denmark, Finland and Sweden over a 20-year study period. The incidence of MG increased over time in all three countries. In younger age groups, a higher incidence was observed in women than men, which increased moderately with age. While in men, a steeper increase with age was observed from age 50 years onwards. The prevalence of MG increased steadily over time in all three countries. A higher prevalence was found in women than in men in the younger age groups. In women, the prevalence increased moderately with age, while in men a steep increase was seen from age 50 years. The SMR was increased in patients with MG in all three countries, especially in women.

Our study showed an overall incidence of MG of 1.34 in Denmark, 1.68 in Finland and 1.62 per 100 000 in Sweden. These estimates are higher than earlier reports from Norway and Denmark (0.4 per 100 000), but slightly lower than those previously reported in Sweden (2.9 per 100 000) and more recently in Germany (4.6 per 100 000). Worldwide, the mean incidence of MG has been reported as 1.0 (range: 0.3–2.8) per 100 000. We found that the incidence of MG increased over time, similarly to a Swedish study but in contrast to a Danish study. The overall prevalence of MG in this study was 18.56 in Denmark, 20.89 in Finland and 23.42 per 100 000 in Sweden. These estimates align with previous studies, in particular from Finland and Sweden. However, the estimates diverge from the findings of an earlier Swedish study (36.1/100 000), a German study (39.3/100 000) and a literature review (10/100,000). In line with our findings, an earlier study from Denmark found an increasing prevalence of MG over time. The observed discrepancies in incidence and prevalence could result from differences in study periods, data sources or definitions of MG, but in general, the increasing incidence and prevalence could be the result of, for example, the rise in the incidence of autoimmune diseases, ageing of the population, increased life expectancy, improved diagnostics and access to testing, improvement of the quality of register data over time, and to a more minor extent, reduced mortality over time.

The observed mortality of MG is largely in line with two Danish studies, which reported overall survival of 81% and 69% at 5 and 10 years of follow-up, respectively, and an overall SMR of 1.41. Similarly, a Swedish study reported a mortality ratio of 1.28 in patients with MG compared with the general population. The most common causes of death among patients with MG in the three countries were MG, chronic ischaemic heart disease and acute myocardial infarction, supporting the findings of previous studies and aligning also with the general population in the three studied countries. Additionally, this study analysed information about the underlying cause of death rather than the immediate cause. Moreover, due to limitations in data capture within the registry, it is not possible to further substantiate the underlying pathology attributing MG as the cause of death. This likely encompasses MG-related causes such as respiratory failure, pneumonia or treatment-related comorbidities like diabetes and cardiovascular disease.

The overall SMR was markedly higher in women than men in all three countries, as reported previously in a Danish study. This could reflect the earlier age at diagnosis in women or possibly suboptimal management of MG in women. Further reasons for the higher risk of death in women could include the more severe and early onset forms of the disease, which are more common in women and women being more prone to autoimmune diseases in general. In addition, the early-onset form of MG results in a longer period of treatment over lifetime and, thus, accumulation of the long-term consequences of the treatments. Comorbidity patterns specific to early-onset MG could play a role too, especially other autoimmune diseases. As opposed to the SMR which is a relative measure, the absolute overall HR of death was however similar in men and women.

When examining factors associated with the risk of death among patients with MG, we observed that the risk of death increased with increasing age and duration of disease but decreased slightly over calendar time. Moreover, patients with MG with diseases of the blood and blood-forming organs, respiratory diseases, metabolic diseases and thymoma had an increased risk of death. Patients with cancer (except thymoma), diseases of the circulatory system and mental disorders also had a moderately increased risk of death. Nevertheless, and in contrast to the general population, there was no difference in the risk of death among men and women with MG, which may reflect the adjustment for important predictors of death among patients with MG. Severe infections can be common in undertreated MG, but in this study, they were not associated with the risk of death, potentially indicating the level of public healthcare with universal coverage in the three studied countries.

The main strength of this study is the real-world setting with complete nationwide coverage in three Nordic countries with minimal loss to follow-up. As this was a register study, it was not possible to compare the results to, for example, data from clinical centres treating patients with MG, but the Nordic registries have been shown to be of great validity regarding data coverage and accuracy. All citizens are included in the health and population registries regardless of social status, income or insurance. Therefore, the data are representative of the entire population with a negligible selection bias, offering a major benefit compared with cohorts that rely on clinical, insurance or survey data. Furthermore, all Nordic countries have publicly funded, universal and high-quality healthcare available to all citizens. Accessing data from more than one country allows the evaluation of broader trends and cross-country differences. However, study limitations include the country-specific differences in the registry structures and data recording practices. For transparency, we report results separately for the three countries. Additionally, case identification was based on ICD codes from specialised inpatient and outpatient care, thus not including primary healthcare. Given that MG is not typically diagnosed or managed by general practitioners, we deem the risk of missing true cases small. To increase the specificity of MG diagnosis, we required ≥2 separate diagnoses from the registries. Due to data constraints, specifically the absence of primary healthcare data and confirmatory MG diagnoses, we are unable to ascertain the age at onset and diagnostic delay. Nevertheless, our findings align with the established age distribution at diagnosis between men and women. Finally, the observational nature of the study design implies that causality cannot be readily inferred from this study.

In conclusion, this population-based study from three Nordic countries showed that the incidence and prevalence of MG increased from 2000 to 2020, whereas the mortality was stable.
over time in Denmark, Finland and Sweden. The findings of this study highlight the importance of careful management of patients with MG and the need for further improved care, especially in the younger age groups of women.

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Contributors
Substantial contributions to the conception and design of the work: JV, SA, MS, JM, Ty-o, IL-S, FB and FP. Substantial contributions to the analysis and interpretation of the data: all authors. Drafting and reviewing the manuscript critically for important intellectual content: all authors. Final approval of the version to be published: all authors. Agree to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors. TY is the guarantor.

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Competing interests
JV: Roche, Sanofi Genzyme, Sarepta Therapeutics, Novartis Pharma AG, Fulcrum Therapeutics, Biogen, Lupin, Amicus, Regeneron, Argenx, BVBA, UCB Biopharma SPRi, Arvinas, ML Biopharma, Atamyo Therapeutics, Horizon Therapeutics, Dyne Therapeutics, Alexion Pharmaceuticals, Edgewise Therapeutics, Genethon, Reneo Pharma, Pharmex, Janssen Pharmaceutical, Kikonron, Dynacure SAS, SA-Merk, Roche, Biogen, Novartis, UCB Pharma, Lundbeck. MS was previously an employee of UCB Pharma, Espoo, Finland. JM is an employee of MedEngine Oy, Finland. LM was previously an employee of MedEngine DK ApS, Denmark. TBO is an employee of MedEngine DK ApS, Denmark. Ty-o is the owner of MedEngine Oy and MedEngine DK ApS. IL-S is an employee of UCB Pharma, Stockholm, Sweden. FB is an employee and stockholder of UCB Pharma, Copenhagen, Denmark. FP: Janssen, Merck KGaA, UCB, Chugai, Lundbeck, Roche, Novartis.

Patient consent for publication
Not applicable.

Ethics approval
This study was approved by Statistics Denmark (708396), the Finnish Data Permit Authority, Findata (THL/1010/14.02.00/2021), Statistics Finland (TK:2457/07.03.00/2021), and the Swedish National Board of Health & Welfare (Socialstyrelsen; Dnr 16836/2021). Ethical approval was obtained by the Swedish Ethics Review Authority (Dnr 2021-00858). Ethical approval was not required according to Finnish and Danish legislation, given that the study was observational and based solely on pseudonymised registry data.

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Data availability statement
Data may be obtained from a third party and are not publicly available. This is a registry study. Data may be obtained from a third party and are not publicly available.

Supplemental material
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REFERENCES
Supplementary material for the following manuscript:

Title
The Epidemiology of Myasthenia Gravis in Denmark, Finland, and Sweden: A Population-Based Observational Study

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SUPPLEMENTARY FIGURES

Supplementary Figure 1. Flow-chart of the study population.

FPC, Full primary cohort; PSC, Prevalent Sub-Cohort; ISC, Incident Sub-Cohort; DK, Denmark; FI, Finland; SE, Sweden.

* A minimum of 12 months without an MG diagnosis before the date of diagnosis was required for a patient to be included in the incident cohort (prior MG diagnosis was screened from all available registry data).
Supplementary Figure 2. Incidence of myasthenia gravis per 100,000 in the Incident Sub-Cohort in Denmark, Finland, and Sweden in year 2000–2020, as stratified by age and sex.

DK, Denmark; FI, Finland; SE, Sweden.
Supplementary Figure 3. Prevalence of myasthenia gravis in the Prevalent Sub-Cohort in Denmark, Finland, and Sweden in year 2000–2020, as stratified by age and sex.

DK, Denmark; FI, Finland; SE, Sweden.
Supplementary Figure 4. Standardised mortality ratio of myasthenia gravis in the Prevalent Sub-Cohort in Denmark, Finland, and Sweden in 2000–2020 compared to the background population, as stratified by age and sex.

DK, Denmark; Fl, Finland; SE, Sweden.