BMJ Open

# Patient-reported burden of myasthenia gravis: baseline results of the international prospective, observational, longitudinal real-world digital study MyRealWorld-MG

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**To cite:** Dewilde S, Philips G, Paci S, *et al*. Patient-reported burden of myasthenia gravis: baseline results of the international prospective, observational, longitudinal real-world digital study MyRealWorld-MG. *BMJ Open* 2023;**13**:e066445. doi:10.1136/bmjopen-2022-066445

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-066445).

Received 08 July 2022
Accepted 18 January 2023



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## ABSTRACT

**Objectives** Myasthenia gravis (MG) is a rare, chronic, autoimmune neuromuscular disease which can affect functional and mental aspects of health and health-related quality of life (HRQoL). This study aims to obtain detailed knowledge of the impact of MG on HRQoL in a broad population from the perspective of the patient.

**Design** Prospective, observational, digital, longitudinal real-world study.

**Setting** Adult patients with MG from seven countries (USA, Japan, Germany, UK, Italy, Spain and Canada) downloaded a mobile application onto their phones and entered data about themselves and their MG.

**Outcome measures** Data was collected using the following general and disease-specific patient-reported outcome measurements: EuroQol 5 Domains Health-Related Quality of Life Questionnaire (EQ-5D-5L), Myasthenia Gravis Activities of Daily Living (MG-ADL), Myasthenia Gravis Quality of Life 15-item revised scale (MG-QoL-15r), Hospital Anxiety and Depression Scale (HADS) and Health Utilities Index III (HUI3). Patients were categorised by their self-assessed Myasthenia Gravis Foundation of America (MGFA) class (I–V).

**Results** Baseline results of 841 participants (mean age 47 years, 70% women) are reported . The distribution across the MGFA classes was: 13.9%, 31.0%, 38.1%, 15.5% and 1.6% for classes I–V. The MGFA class was a strong predictor of all aspects of HRQoL, measured with disease-specific and with generic instruments. The domains in which patients with MG most frequently mentioned problems were usual activities, anxiety and depression, tiredness, breathing and vision. The mean total MG-ADL Score was positively associated with increasing MGFA classes: 2.7, 4.4, 6.3 and 8.4 for MGFA classes I–IV. Mean baseline EQ-5D-5L utility was also associated with MGFA classes and was 0.817, 0.766, 0.648 and 0.530 for MGFA class I–IV.

**Conclusions** MG has a large impact on key aspects of health and HRQoL. The impact of this disease increases substantially with increasing disease severity.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A new digital platform that integrated several generic and disease-specific tools enabled people with myasthenia gravis (MG) to share their daily life experience of living with the condition.
⇒ Self-enrolment after invitation through neurologists, patient advocacy groups and community networks in seven countries resulted in a large and diverse group of patients with MG.
⇒ The utilisation of an app for data entry makes data entry less accessible to people with vision impairment (a common symptom of MG), or those with a severe form of MG.
⇒ The lack of direct contact with a clinician or member of the research team may have led to the inclusion of ineligible individuals, a higher rate of inaccurate or missing data and a lower follow-up rate.
⇒ The use of self-assessed instead of clinician assessed Myasthenia Gravis Foundation of America classes to subdivide participants in most analysis, caused inconsistencies impacting the validity and data quality.

## INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease caused by impaired transmission at the neuromuscular junction.[1] Patients with MG suffer from fatigable muscle weakness ranging from a purely ocular form to severe weakness of the limb, bulbar or respiratory muscles, which is called generalised MG.[1–3] An MG crisis can be life-threatening, and patients may need assistance with breathing. MG is a rare disease with an estimated prevalence of 1.5–2 per 100 000 inhabitants and most neurologists would only have a few cases simultaneously in their practice.[3 4] Incidence

rates have a bimodal distribution with two peaks: early-onset MG in the third decade, mostly in women, and late-onset MG in the elderly, mostly in men. Around 10% of cases have an onset before the age of 18 years.[3]

It has been shown that generalised MG has a negative impact on several aspects of health-related quality of life (HRQoL) such as physical function, physical role, bodily pain, vitality and social function. The negative impact of MG increases with increased disease severity.[5 6] However, even with a mild clinical picture, mental health is impaired, and depression has been reported in up to one-third of patients with MG.[6 7] More detailed data from both generic and MG-specific patient-reported outcome measures (PROMs) measured in a large and diverse group of patients with MG are needed to fully understand the impact of MG on HRQoL, ranging from mild ocular MG to the severe MG crisis: a complication of MG characterised by worsening of muscle weakness resulting in respiratory failure. HRQoL data can help to improve clinical patient management and are an integral part of health technology assessments to inform public decision-making.

In recent years, disease-specific and generic PROMs have been used in randomised clinical trials (RCTs) to objectively measure the effect of new treatments on patients' HRQoL, in addition to evaluating the efficacy of treatment on the course of the disease. However, most recent RCTs focus on medically severe and refractory patients, whereas a large proportion of patients are mildly to moderately affected.[8] Although mild and moderate patients have been included in some RCTs, there are no publications exploring the HRQoL impact of MG on a wide variety of patients from all severity levels. Furthermore, the controlled conditions of RCTs may also have an impact on the reported HRQoL measurements.

The objective of this prospective study is therefore to provide a detailed real-world, longitudinal view of the impact of MG from the perspective of the patients in a large and diverse population of patients with MG.

## METHODS

### Study design and setting

We conducted a prospective, observational, longitudinal, real-world, PRO study using a digital data collection platform. A mobile application (app) called MyRealWorld-MG was developed for this study by Vitaccess (London, UK), a digital healthcare consultancy specialised in real-world evidence. Potential participants could download the app from the Google Play or Apple App Store onto their phone or tablet. Participants enter monthly data about their MG, comorbidities, the disease management and the impact of MG on their lives, over a period of approximately 2 years. The period of recruitment for the current interim analysis was from 12 December 2019 to 1 April 2020, and the data used in this publication concern the data entered at baseline only. The rationale and methods of the broader MyRealWorld-MG study have been published elsewhere.[9]

### Patient and public involvement

The study was designed in close collaboration with the study scientific advisory board (SAB), which included at least 1 patient with MG affiliated with a patient advocacy group (PAG) in each study country. PAG members of the SAB were consulted to make sure that the suggested design and outcomes were relevant to persons with MG. They also evaluated key study materials such as the protocol, and suggested content for the MyRealWorld MG smartphone app, which they tested in its early iterations. In addition, they have provided input into the publication and communication plan of the study and are offered the opportunity to coauthor resulting academic papers.[9]

### Participants

Adults diagnosed with MG and resident in one of the participating countries: The USA, Japan, Germany, the UK, Italy, Spain and Canada were invited to participate in the study via their neurologist and via communication from PAGs such as AFM-Téléthon, Association A.M.I.S., European Association of Myasthenia Gravis Patients. In addition, patients were recruited via word of mouth, via community networks such as the Myasthenia Gravis Foundation of America (MGFA) and through Vitaccess's social media accounts. All patients were treated by a neurologist. There were no physical study sites, and there were no other exclusion criteria other than the diagnosis of MG and being an adult.

### Data collection

At study enrolment, participants completed questionnaires in their native language concerning demographics, diagnosis, past treatments, living situation, current medical resource use and sick leave in the past month and several PROMs to assess their HRQoL. Validated translations of all PROMs were used in all countries and remaining study materials were professionally translated. The complete schedule of PROMs that was presented to the participants during the study has been described by Berrih-Aknin *et al*.[9] In this interim analysis, the baseline results of the PROMs described below are reported.

#### Myasthenia Gravis Foundation of America

The MGFA classification was used to identify subgroups of patients with MG with similar clinical characteristics or disease severity. This classification divides MG into five main classes and several subclasses, making a gradual differentiation from patients with exclusively ocular myasthenia gravis (MGFA class I) to patients with a myasthenic crisis.[10] In this study, patients were instructed to enter their MGFA class preferably as determined by their neurologist, and otherwise to indicate which of the five detailed descriptions of MGFA classes that were given best describes their symptoms (self-assessment).

#### EuroQol 5 Domains Health-Related Quality of Life Questionnaire (EQ-5D-5L)

The EQ-5D-5L is a generic instrument to measure HRQoL.[11] It consists of a descriptive system and a visual

analogue scale (EQ-VAS). The descriptive system defines health in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with five severity levels for each dimension. The EQ-VAS records the self-rated health on a scale with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status). The results of the EQ-5D-5L can be converted into a utility score ranging from states considered to be worse than dead (<0) to 1 for full health, anchoring dead at 0. Multiple country-specific value sets are available that allow for the conversion into utility scores.[12] The interim 'crosswalk' value set for the UK was used in the current study.[13]

#### EQ-5D-5L bolt-on items

There are several additional (exploratory) dimensions to the five EQ-5D-5L dimensions available, so-called 'bolt-ons'.[14] These single-item dimensions concerning vision, breathing, tiredness, sleep, social relationships and self-confidence are relevant to describe common HRQoL impairments in MG. Each bolt-on dimension has five severity levels,[15–20] similar to the five levels of the core dimensions of the EQ-5D.

#### Myasthenia Gravis Activities of Daily Living (MG-ADL)

The MG-ADL is an MG-specific questionnaire, which assesses the severity of the following eight symptoms across four domains: bulbar domain (talking, chewing, swallowing); respiratory domain (breathing); limb weakness (impairment of ability to brush teeth or comb hair, impairment of ability to rise from a chair); and ocular domain (double vision, eyelid droop). For each symptom, there are four response options scored from 0 to 3. The total score is a sum of the eight symptom scores and ranges therefore from 0 (no impact) to 24 (severe impact) on daily living.[21 22]

#### Myasthenia Gravis Quality of Life 15-item revised scale (MG-QoL15r)

The MG-QoL15r is an MG-specific HRQoL questionnaire, which assesses the impact of MG on the following domains: emotions, physical health, self-care, social life and role.[23 24] The MG-QoL15r questionnaire consists of 15 items, with each three response options scored from 0 to 2. The maximum score of 30 represents the largest impact on HRQoL and is calculated by taking the sum of the item scores.

#### Hospital Anxiety and Depression Scale (HADS)

The HADS is a generic instrument developed to assess psychological distress in non-psychiatric patients.[25 26] It consists of two subscales: anxiety and depression, with seven items each. Scoring for each item ranges from 0 to 3, with 3 denoting the highest anxiety or depression level. The total subscale score ranges from 0 to 21. Scores from 8 to 10 indicate mild anxiety or depression, scores from 11 to 14 moderate anxiety or depression and scores≥15 severe anxiety or depression.[27]

### Statistical analysis

The aim of the study was to enrol approximately 2000 patients with MG across the 7 countries and recruitment is on-going. There was no formal sample size calculation for this observational study, nor was there any stratified enrolment by disease severity. No hypotheses were tested in this exploratory observational study. Aggregated and deidentified data were summarised. For continuous variables, sample size, mean, SD and IQR (Q1, Q3) or 95% CI are presented. For categorical variables sample size and proportion are reported. A regression analysis on the utility complement (=1-utility value) and the different items of the MG-ADL instrument was estimated using a normal distribution and an identity link to assess which items of the MG-ADL had the largest impact on utility values. The transformation from the utility value into the utility complement was done to avoid negative values and to make the dependent variable right skewed, which makes it more amenable to statistical modelling.

## RESULTS

### Demographic and clinical characteristics of the participants

At the time of data cut-off for this interim analysis, a total of 834 participants downloaded the app and responded to at least one PROM. The participant flow is presented in figure 1. Self-reported demographic and clinical characteristics of the participants in MyRealWorld-MG are provided in table 1. Of 770 (92.5%) participants in MyRealWorld-MG with known or self-reported MFGA class,[10] two-thirds suffered from mild generalised MG class II (31%) or moderate generalised MG class III (38.1%), whereas the proportions of ocular MGFA class I (13.9%) and severe MGFA class V (1.6%) disease were small (table 1). As the sample of MGFA class V patients was too small to present robust outcomes, these results are not shown but only sporadically mentioned in the text. Overall, 70% of participants were women, and all patients received treatment. Three quarters of patients were taking pyridostigmine, and almost half the patients were receiving daily doses of steroids. Furthermore, about one in five patients were taking azathioprine, an immunosuppressant, and another 20% received either intravenous immunoglobulin or plasma exchange.

### Results by instrument

#### Myasthenia Gravis Activities of Daily Living

In each of the eight MG symptoms, the proportion of participants reporting problems increased sharply with increasing disease severity (table 2). More than half of participants with generalised MG indicated problems with breathing, double vision and eyelid droop. Problems with bulbar symptoms were mentioned in about 45% of participants; this included talking, chewing and swallowing. About half of patients mentioned problems due to muscle fatigue characterised by the ability to rise from a chair, brushing teeth or combing hair. The mean total MG-ADL score increased by about two points for each

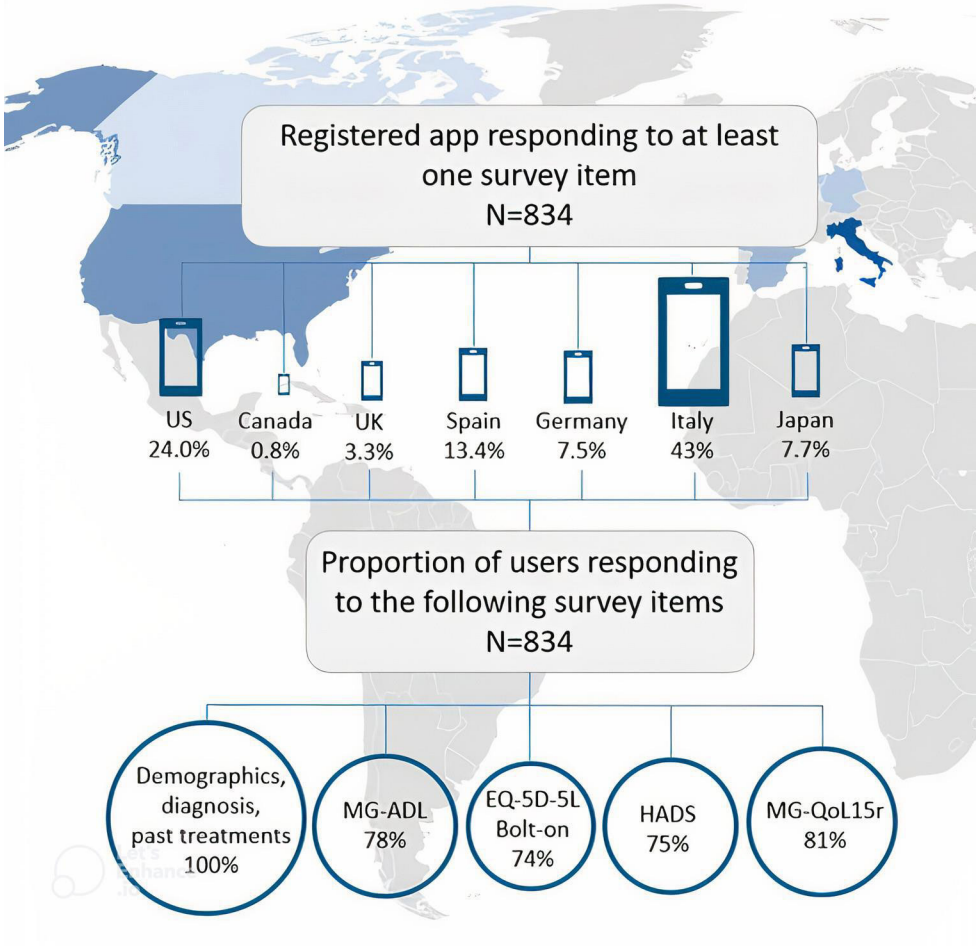


**Figure 1** Participant flow. The flowchart shows the distribution of the total number of patients at baseline by country who responded to at least one item, followed by the percentage of respondents for each PROM/survey section. Abbreviations: App, smartphone application; EQ-5D-5L, EuroQol 5 Domains Health-Related Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL15r, Myasthenia Gravis Quality of Life 15-item revised scale.

increase in MGFA class. This increasing trend was also noted in MGFA class V.

### EuroQol 5 Domains Health-Related Quality of Life Questionnaire

For all the dimensions of the EQ-5D-5L, the proportion of participants experiencing problems increased with increasing severity of MG (table 3). Usual activities and pain/discomfort were the dimensions that were most frequently mentioned by the participants as being problematic, followed by anxiety/depression. Moderate-to-extreme pain/discomfort was experienced by 12.0% in MGFA class I to 52.9% in MGFA class IV and moderate-to-extreme problems with usual activities by 8.4% in MGFA class I to 58.8% in MGFA class IV.

The increasing proportion of participants with problems in higher MGFA classes was reflected in the lower mean EQ-VAS scores for self-rated health. The mean EQ-VAS for all MG patients had considerable heterogeneity, as the EQ-VAS mean score decreased from 72 in MGFA class I to 49 for MGFA class IV.

### Bolt-ons

A high proportion of participants indicated problems on the different bolt-on dimensions. The dimensions with the highest proportion of participants mentioning moderate-to-extreme problems were tiredness (49.2%), sleep (30.2%) and vision (32.6%) (table 3). Self-confidence and social relationship were also problematic in a quarter and a fifth of the patients, respectively.

### EQ-5D utilities (UK value set)

A negative association was found between the mean utility and disease severity from 0.817 for MGFA class I to 0.53 for MGFA class IV (table 4). Women had lower utilities than men; however, no linear association was found with age. Patients needing a caregiver had a lower utility of 0.30 compared with patients who lived independently. Several definitions of an MG crisis were tested to measure its impact on the utilities of patients: patients who had to take rescue medication, who needed an emergency room visit or a hospital admission, or who had to take sick leave because of an MG crisis had lower utilities (0.627) than

**Table 1** Patient characteristics and representativeness of the patients included in the MyRealWorld-MG digital data collection, in comparison to national registries

| | | Registries | | | | | |
|---|---|---|---|---|---|---|---|
| | MyRealWorld-MG sample | Explore-MG (USA)[28] | Clicon (Italy)[29] | Myasthenia association members (Germany)[6] | Population-based cohort (Norway/The Netherlands)[30] | Single-centre study (Poland)[31] | Cross-sectional analysis of patient with MG registry (USA)[32] |
| | N=834 | N=232 | N=4397 | N=1518 | N=837 | N=339 | N=1140 |
| MGFA | | | | | | | |
| I: Ocular | 14% | 30%* | n/a | n/a | 12% | 16%† | n/a |
| II: Mild generalised | 31% | 30%* | n/a | n/a | n/a | 53% | n/a |
| III: Moderate generalised | 38% | 16%* | n/a | n/a | n/a | 12% | n/a |
| IV: Severe generalised | 15% | 8%* | n/a | n/a | n/a | 3% | n/a |
| V: Intubation/myasthenic crisis | 2% | 12%* | n/a | n/a | n/a | 0% | n/a |
| Age | | | | | | | |
| Mean (SD) | 47.4 (14.3) | 60.1 (18.5) | 61.7 (16.8) | 56.7 (16.9) | 60.3 (17.6) | 51.6 (18.3) | 54.6 (14.8) |
| Sex | | | | | | | |
| Male | 30% | 49% | 47% | 41% | 41% | 35% | 34% |
| Female | 70% | 51% | 53% | 59% | 59% | 65% | 66% |
| Current treatment | | | | | | | |
| Pyridostigmine, neostigmine | 76% | 49% | 34% | n/a | 67% | n/a | 71% |
| Mycophenolate mofetil | 14% | 7% | 0% | n/a | n/a | n/a | 24% |
| Azathioprine | 19% | 17% | 9% | n/a | n/a | n/a | 19% |
| Prednisone, prednisolone | 46% | 34% | 55% | n/a | 33% | n/a | 42% |
| Methotrexate | 2% | 1% | 1% | n/a | n/a | n/a | 2% |
| Ciclosporin | 4% | 0% | 1% | n/a | n/a | n/a | 1% |
| Cyclophosphamide | 0% | 12% | 0% | n/a | n/a | n/a | 0% |
| Tacrolimus | 9% | 0% | 0% | n/a | n/a | n/a | 1% |
| Rituximab | 4% | 12% | 0% | n/a | n/a | n/a | 3% |
| Eculizumab | 4% | 0% | 0% | n/a | n/a | n/a | n/a |
| Intravenous IG | 17% | 20% | 2% | n/a | n/a | n/a | 19% |
| Plasma exchange | 3% | | 1% | n/a | n/a | n/a | 4% |
| Had thymectomy | 12% | 28% | 4% | 58% | n/a | n/a | 40% |

*Worst MG class ever.
†16.5% in remission.
IG, immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; n/a, not available.

Table 2 Distribution of MG patients across the MG-ADL items

| Items | All patients N=645 | MGFA I N=87 | MGFA II N=181 | MGFA III N=235 | MGFA IV N=89 |
|---|---|---|---|---|---|
| Talking | | | | | |
| Normal | 58.5% | 81.6% | 72.4% | 48.1% | 34.8% |
| Intermittent slurry or nasal speech | 36.3% | 17.2% | 26.5% | 47.2% | 52.8% |
| Constant slurring or nasal, but can be understood | 3.3% | 1.1% | 0.6% | 4.3% | 6.7% |
| Difficult to understand speech | 2.0% | 0.0% | 0.6% | 0.4% | 5.6% |
| Chewing | | | | | |
| Normal | 56.9% | 90.8% | 68.5% | 41.7% | 37.1% |
| Fatigue with solid food | 38.1% | 9.2% | 29.3% | 53.6% | 50.6% |
| Fatigue with soft food | 3.7% | 0.0% | 1.1% | 4.3% | 10.1% |
| Gastric tube | 1.2% | 0.0% | 1.1% | 0.4% | 2.2% |
| Swallowing | | | | | |
| Normal | 55.4% | 86.2% | 63.5% | 46.0% | 37.1% |
| Rare episode of choking | 39.2% | 13.8% | 32.6% | 49.8% | 49.4% |
| Frequent choking necessitating changes in diet | 4.2% | 0.0% | 2.2% | 4.3% | 11.2% |
| Gastric tube | 1.2% | 0.0% | 1.7% | 0.0% | 2.2% |
| Breathing | | | | | |
| Normal | 40.5% | 71.3% | 47.5% | 29.8% | 22.5% |
| Shortness of breath with exertion | 48.1% | 27.6% | 48.1% | 54.5% | 55.1% |
| Shortness of breath at rest | 10.4% | 1.1% | 4.4% | 15.3% | 19.1% |
| Ventilator dependence | 1.1% | 0.0% | 0.0% | 0.4% | 3.4% |
| Brush teeth or comb hair | | | | | |
| None | 51.6% | 87.4% | 61.3% | 39.6% | 23.6% |
| Extra effort but no rest periods needed | 29.3% | 11.5% | 26.5% | 38.7% | 32.6% |
| Rest periods needed | 18.1% | 1.1% | 12.2% | 21.7% | 40.4% |
| Cannot do one of these functions | 0.9% | 0.0% | 0.0% | 0.0% | 3.4% |
| Rise from a chair | | | | | |
| None | 47.0% | 87.4% | 58.0% | 32.3% | 20.2% |
| Mild, sometimes uses arms | 33.8% | 11.5% | 34.8% | 41.7% | 36.0% |
| Moderate, always use arms | 18.0% | 1.1% | 7.2% | 25.5% | 39.3% |
| Severe, requires assistance | 1.2% | 0.0% | 0.0% | 0.4% | 4.5% |
| Double vision | | | | | |
| None | 40.6% | 43.7% | 44.8% | 37.9% | 29.2% |
| Occurs, but not daily | 32.4% | 26.4% | 27.6% | 35.7% | 41.6% |
| Daily, but not constant | 18.1% | 16.1% | 18.8% | 20.0% | 16.9% |
| Constant | 8.8% | 13.8% | 8.8% | 6.4% | 12.4% |
| Eyelid droop | | | | | |
| None | 38.6% | 50.6% | 40.9% | 37.4% | 23.6% |
| Occurs, but not daily | 35.5% | 33.3% | 36.5% | 34.0% | 39.3% |
| Daily, but not constant | 17.1% | 6.9% | 14.9% | 22.1% | 19.1% |
| Constant | 8.8% | 9.2% | 7.7% | 6.4% | 18.0% |
| MG-ADL total score | | | | | |
| Mean | 5.7 | 2.7 | 4.4 | 6.3 | 8.4 |
| SD | 4.0 | 2.6 | 3.3 | 3.5 | 4.1 |

MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America.;

Table 3 Distribution across the domains of the EQ-5D-5L (A) and six bolt-on domains (B)

| | A: EQ-5D-5L | | | | | B: Bolt-ons 5L | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All patients N=610 | MGFA I N=83 | MGFA II N=162 | MGFA III N=226 | MGFA IV N=85 | All patients N=610 | MGFA I N=83 | MGFA II N=162 | MGFA III N=226 | MGFA IV N=85 |
| | **Mobility** | | | | | **Vision** | | | | |
| No problems | 47.7% | 84.3% | 59.3% | 35.4% | 20.0% | 32.1% | 37.3% | 35.2% | 30.1% | 17.6% |
| Mild problems | 32.0% | 10.8% | 30.2% | 42% | 29.4% | 35.3% | 27.7% | 35.8% | 37.6% | 37.6% |
| Moderate problems | 15.9% | 4.8% | 10.5% | 19% | 32.9% | 24.9% | 20.5% | 22.8% | 27% | 35.3% |
| Severe problems | 3.3% | 0.0% | 0.0% | 2.7% | 15.3% | 6.7% | 14.5% | 6.2% | 4.4% | 5.9% |
| Extreme problems | 1.2% | 0.0% | 0.0% | 0.9% | 2.4% | 1.0% | 0.0% | 0.0% | 0.9% | 3.5% |
| | **Self-care** | | | | | **Breathing** | | | | |
| No problems | 66.4% | 95.2% | 78.4% | 54.9% | 41.2% | 60.3% | 85.5% | 69.1% | 52.7% | 36.5% |
| Mild problems | 22.8% | 4.8% | 17.9% | 33.6% | 27.1% | 27.1% | 14.5% | 26.5% | 29.6% | 37.6% |
| Moderate problems | 8.9% | 0.0% | 3.7% | 10.2% | 24.7% | 9.8% | 0.0% | 4.3% | 15.5% | 16.5% |
| Severe problems | 1.5% | 0.0% | 0.0% | 1.3% | 5.9% | 2.3% | 0.0% | 0.0% | 2.2% | 8.2% |
| Extreme problems | 0.5% | 0.0% | 0.0% | 0.0% | 1.2% | 0.5% | 0.0% | 0.0% | 0.0% | 1.2% |
| | **Usual activities** | | | | | **Sleep** | | | | |
| No problems | 31.2% | 63.9% | 41.4% | 18.1% | 9.4% | 37.2% | 49.4% | 43.2% | 30.5% | 27.1% |
| Mild problems | 38.5% | 27.7% | 42.0% | 43.4% | 31.8% | 32.6% | 34.9% | 35.8% | 32.3% | 28.2% |
| Moderate problems | 22.6% | 6.0% | 14.8% | 31.0% | 34.1% | 22.5% | 12.0% | 17.3% | 28.3% | 28.2% |
| Severe problems | 5.9% | 1.2% | 1.9% | 6.2% | 18.8% | 5.9% | 3.6% | 2.5% | 7.1% | 12.9% |
| Extreme problems | 1.8% | 1.2% | 0.0% | 1.3% | 5.9% | 1.8% | 0.0% | 1.2% | 1.8% | 3.5% |
| | **Pain/discomfort** | | | | | **Tiredness** | | | | |
| No problems | 30.3% | 49.4% | 35.8% | 24.8% | 15.3% | 16.4% | 38.6% | 21.0% | 8.0% | 8.2% |
| Mild problems | 40.7% | 38.6% | 45.1% | 42.5% | 31.8% | 34.4% | 43.4% | 38.3% | 31.9% | 20.0% |
| Moderate problems | 22.6% | 8.4% | 17.9% | 25.7% | 35.3% | 35.4% | 14.5% | 33.3% | 42.9% | 42.4% |
| Severe problems | 4.9% | 2.4% | 1.2% | 5.8% | 12.9% | 10.3% | 2.4% | 6.8% | 12.8% | 22.4% |
| Extreme problems | 1.5% | 1.2% | 0.0% | 1.3% | 4.7% | 3.4% | 1.2% | 0.6% | 4.4% | 7.1% |
| | **Anxiety/depression** | | | | | **Self-confidence** | | | | |
| No problems | 42.6% | 56.6% | 47.5% | 38.9% | 34.1% | 45.4% | 68.7% | 48.8% | 39.8% | 28.2% |
| Mild problems | 35.1% | 31.3% | 36.4% | 36.3% | 28.2% | 30.8% | 19.3% | 28.4% | 33.2% | 41.2% |
| Moderate problems | 17.5% | 9.6% | 14.8% | 17.3% | 29.4% | 16.1% | 6.0% | 19.1% | 16.4% | 20.0% |
| Severe problems | 3.6% | 1.2% | 1.2% | 6.2% | 4.7% | 5.6% | 6.0% | 3.7% | 7.5% | 5.9% |
| Extreme problems | 1.2% | 1.2% | 0.0% | 1.3% | 3.5% | 2.1% | 0.0% | 0.0% | 3.1% | 4.7% |
| | | | | | | **Social relationships** | | | | |
| No problems | | | | | | 57.4% | 83.1% | 58.6% | 50.4% | 44.7% |
| Mild problems | | | | | | 23.6% | 12% | 27.8% | 26.1% | 21.2% |
| Moderate problems | | | | | | 13.1% | 3.6% | 11.1% | 16.4% | 21.2% |
| Severe problems | | | | | | 4.1% | 1.2% | 1.9% | 5.3% | 9.4% |
| Extreme problems | | | | | | 1.8% | 0.0% | 0.6% | 1.8% | 3.5% |

EQ-5D-5L, EuroQol 5 Domains Health-Related Quality of Life Questionnaire; MGFA, Myasthenia Gravis Foundation of America.

participants who did not experience an MG crisis (0.725). Finally, comorbidities also affected the MG patients' utility values.

A first regression analysis with the utility complement (1-utility) as dependent variable and the domains of the MG-ADL as independent variables, indicated that the MG-ADL domains muscle weakness (rising from a chair p<0.0001, ability to brush teeth or comb hair p<0.0001), followed by breathing (p<0.0001) and double vision (p=0.021) had the largest impact on utility values (table 5). Furthermore, utilities decreased with higher total MG-ADL scores. The distribution of utilities for each

**Table 4** EQ-5D-5L utilities in patient subgroups

| | Mean, std (Q1 ; Q3) |
|---|---|
| Overall all patients (N=610) | 0.689, 0.222 (0.602 ; 0.837) |
| Gender (N=586) | |
| Males (N=174) | 0.722, 0.232 (0.639 ; 0.848) |
| Females (N=412) | 0.677, 0.220 (0.586 ; 0.836) |
| Age (N=589) | |
| 18–29 (N=79) | 0.669, 0.263 (0.567 ; 0.837) |
| 30–39 (N=131) | 0.690, 0.199 (0.599 ; 0.819) |
| 40–49 (N=129) | 0.676, 0.246 (0.587 ; 0.837) |
| 50–59 (N=136) | 0.674, 0.225 (0.604 ; 0.811) |
| 60–69 (N=85) | 0.705, 0.162 (0.647 ; 0.837) |
| 70+ (N=29) | 0.686, 0.257 (0.572 ; 0.837) |
| MGFA (N=562) | |
| I: Ocular (N=83) | 0.817, 0.171 (0.739 ; 1.000) |
| II: Mild generalised (N=162) | 0.766, 0.146 (0.664 ; 0.837) |
| III: Moderate generalised (N=226) | 0.648, 0.202 (0.570 ; 0.768) |
| IV: Severe generalised (N=85) | 0.530, 0.272 (0.409 ; 0.691) |
| V: Intubation/myasthenic crisis (N=6) | 0.360, 0.508 (-0.140 ; 0.681) |
| Living situation | |
| At home without the need of help from a caregiver (N=337) | 0.747, 0.198 (0.659 ; 0.877) |
| With a family member (N=190) | 0.622, 0.204 (0.550 ; 0.736) |
| At home and needing the help from a caregiver (N=25) | 0.450, 0.293 (0.166 ; 0.636) |
| Recent MG crisis | |
| No crisis (N=350) | 0.725, 0.190 (0.634 ; 0.837) |
| Hospitalisation or ER visit for any reason in the past month (N=39) | 0.602, 0.275 (0.393 ; 0.778) |
| Use of intravenous IG, Plex or steroids as rescue medication in the past month (N=97) | 0.627, 0.219 (0.548 ; 0.739) |
| Sick leave taken in the past month (N=212) | 0.604, 0.222 (0.547 ; 0.736) |
| Most frequently mentioned comorbidities | |
| None (N=291) | 0.753, 0.196 (0.647 ; 0.879) |
| Thyroid problems, thyroid disorder (N=177) | 0.657, 0.211 (0.560 ; 0.816) |
| Anxiety (N=130) | 0.544, 0.242 (0.409 ; 0.725) |
| Depression (N=117) | 0.546, 0.225 (0.434 ; 0.715) |
| Respiratory disease (eg, asthma, COPD) (N=110) | 0.579, 0.244 (0.453 ; 0.728) |
| Osteoporosis (N=92) | 0.567, 0.266 (0.381 ; 0.747) |
| Diabetes with(out) chronic complications (N=53) | 0.627, 0.214 (0.548 ; 0.767) |
| Cardiovascular disease (N=38) | 0.562, 0.275 (0.531 ; 0.735) |
| Rheumatoid arthritis, psoriatic arthritis (N=37) | 0.557, 0.263 (0.336 ; 0.728) |
| Cancer (N=26) | 0.667, 0.233 (0.595 ; 0.751) |

Based on the UK crosswalk value set.
COPD, chronic obstructive pulmonary disease; EQ-5D-5L, EuroQol 5 Domains Health-Related Quality of Life Questionnaire; ER, emergency room; IG, immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; Plex, plasma exchange; Q1, first quartile; Q3, third quartile.

MG-ADL score is shown in a bubble plot (figure 2A) where the size of the bubbles represents the number of observations. A negative trend can be observed in the bubble plot, which is made explicit in figure 2B, where a second regression analysis is presented with the utility complement (1-utility) as dependent variable and MG-ADL total score as an independent variable, showing the graphical and numerical association between the MG-ADL and utility values. The equation shows that each additional score of the MG-ADL was associated with a reduction of 0.02 (rounded) in utility value.

### Myasthenia Gravis Quality of Life 15-item revised scale

The mean total MG-QoL15r Score increased for each additional MGFA class by about 3 points: from 5.5 in class I, 9.2 in class II, 13.7 in class III to 16.4 in class IV. The impact of the disease on the different MGQoL15r domain scores was important. For 11 out of 15 questions, more than half of the participants experienced problems. The domain with the highest proportion of participants mentioning moderate-to-severe problems was usual activities: hobbies, making plans and limitations in performing work, closely followed by feelings of frustration (online supplemental table 1).

### Hospital Anxiety and Depression Scale

The mean score on the depression subscale increased with increasing disease severity, from 4.6 in MGFA class I to 7.7 in class III and 8.3 in class IV. The proportion of participants with scores indicative for moderate-to-severe depression increased from 5.9% in MGFA class I to 27.3% in MGFA class IV. The mean score on the anxiety subscale was similar in MGFA classes I to III and increased somewhat in class IV. The proportion of participants with scores indicative of moderate-to-severe anxiety was 21.2% in MGFA class I to 41.4% in class IV (online supplemental table 2).

Table 5 Impact of the MG-ADL individual items on the EQ-5D-5L utilities

| Independent variables | Parameter estimate | SE | 95% lower CI | 95% upper CI | Type 3 p value |
|---|---|---|---|---|---|
| Intercept | 0.103 | 0.013 | 0.079 | 0.128 | n/a |
| Talking | 0.010 | 0.013 | −0.015 | 0.035 | 0.445 |
| Chewing | 0.018 | 0.015 | −0.012 | 0.048 | 0.249 |
| Swallowing | 0.026 | 0.014 | −0.002 | 0.054 | 0.071 |
| Breathing | 0.064 | 0.012 | 0.040 | 0.088 | <0.0001 |
| Brush teeth and hair | 0.067 | 0.011 | 0.045 | 0.088 | <0.0001 |
| Rise from a chair | 0.080 | 0.011 | 0.058 | 0.103 | <0.0001 |
| Double vision | 0.018 | 0.008 | 0.003 | 0.034 | 0.021 |
| Eyelid droop | 0.010 | 0.008 | −0.007 | 0.026 | 0.250 |

The dependent variable is the EQ-5D-5L utility value, based on N=532 simultaneous measurements of EQ-5D-5L and MG-ADL.
EQ-5D-5L, EuroQol 5 Domains Health-Related Quality of Life Questionnaire; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; n/a, not applicable;

## DISCUSSION

In this international real-world study of adults with MG, the digitally collected data with different disease-specific and generic PROMs indicated a considerable impact across all aspects of HRQoL in all five MGFA severity classes. Furthermore, the impact of MG on HRQoL was robust and consistent between PROMs. Findings on impaired HRQoL were similar across comparable dimensions and items, and the impact was considerable given patients were on active treatment.

### Representativeness of the sample

The baseline characteristics of the MyRealWorld-MG participants were compared with the populations of large cohorts from the USA, Italy, Germany, Poland, Norway and the Netherlands (table 1).[6 28–31] The EXPLORE-MG registry collected data from 232 patients with MG in the USA, including asymptomatic patients and only reported patient's worst MGFA class since diagnosis at baseline. Consequently, the US study reported higher patient numbers at both ends of the spectrum .[28] Compared with all aforementioned cohorts, participants in MyReal-World-MG were younger, and there was a higher proportion of women .[6 28–31]

### Comparison of domains across PROMs

The reporting of problems in daily activities, mental health, breathing and vision overlapped across several instruments and although questions were framed differently, results were surprisingly close.

Problems in performing usual activities were mentioned by one-third of all participants on the EQ-5D-5L (30%) and MG-QoL15r (20% for shopping and errands, 36% for performing work) questionnaires.

About a quarter of the participants mentioned moderate-to-severe feelings of anxiety and depression on

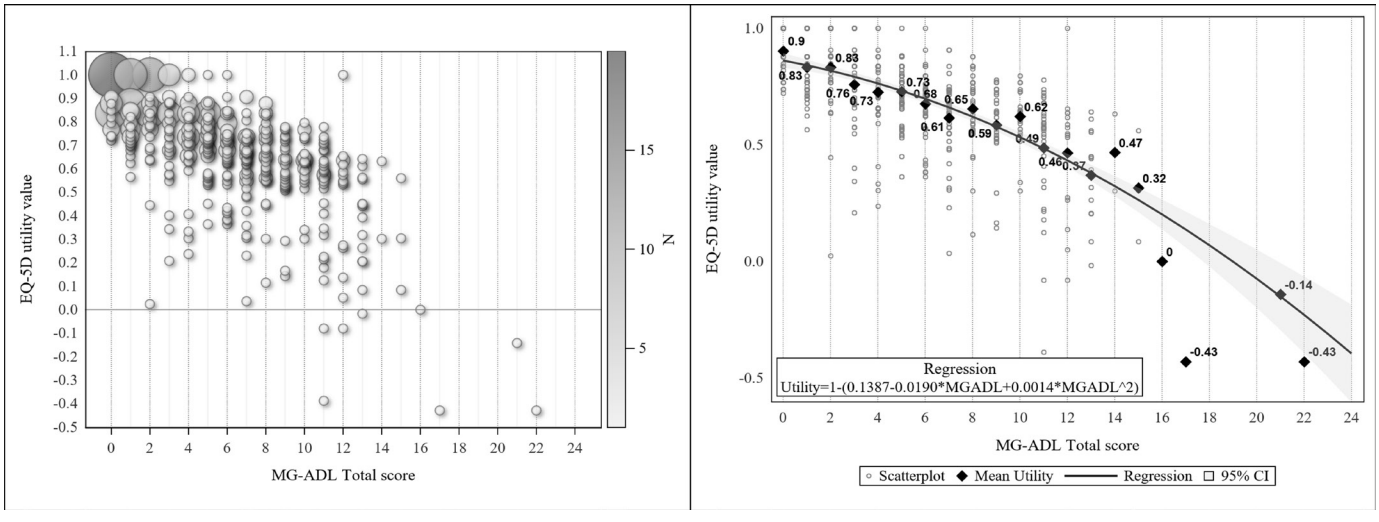


Figure 2 Bubble plot of the utility value by MG-ADL (A) and plot of utility regression in function of the MG-ADL (B). (A) The distribution of utilities for each MG-ADL Score with the size of the bubbles representing the number of observations. (B) This regression analysis shows the graphical and numerical association between the MG-ADL and the utility values, with the utility as dependent and MG-ADL total scores as independent variable. MG-ADL: Myasthenia Gravis Activities of Daily Living; EQ-5D-5L: EuroQol 5 Domains Health-Related Quality of Life Questionnaire.

the EQ-5D-5L (22%) and the MG-QoL15r (10% depressed and 12% overwhelmed), whereas the proportion of patients with problems in mental health obtained with the HADS were higher (29% anxiety, 18% depressed). Taking the latter as the more precise measurement, about one-third of patients have moderate-to-severe anxiety problems and one fifth moderate-to-severe depression.

Problems with breathing were frequently mentioned in generalised patients with MG in the MG-ADL (11%) and the EQ-5D-5L breathing bolt-on question (13%). The proportions of patients with MG in this sample reporting breathing problems was therefore around one in eight patients and was remarkably close in both instruments even though the descriptive system of both instruments differed substantially.

Unsurprisingly, a high proportion of participants with ocular problems was observed in all MGFA classes with the EQ-5D-5L vision bolt-on question (33%), the MG-ADL (27% having daily or constant double vision and 26% daily or constant eyelid droop) and the MGQoL-15r (a lot of problems with using my eyes, 19%).

### Self-assessment of the MGFA

In clinical practice, it is usually the neurologist who—periodically—assesses the patient's MGFA class. In this study, patients filled in the questionnaires without the proximity of their neurologist, and therefore transcribed their MGFA class from their medical file (if known) or else self-assessed their MGFA class based on detailed descriptions. While this method is not validated and no study to date has confirmed the concordance between the neurologist's and the patient's MGFA assessments, we have found in this study that the MGFA correlated remarkably well with all PROMs. Even if on the patient level some mistakes were made, overall, this self-assessment was feasible and produced sensible and reliable results at the population level. Some seeming inconsistencies may be noted between the (self-assessed) MFGA class and the responses to MG-ADL domains (eg, patients with MGFA class II reporting a gastric tube, or patients with MGFA class IV scoring very low on total MG-ADL). It is, however, important to note that while the MGFA class does not vary much over time as it is not used as an outcome measure but as a disease severity classification, the MG-ADL is a symptom scale and varies considerably on a weekly basis. It is possible that an MGFA II patient who is relatively stable most of the time, has an occasional exacerbation. Equally, it is not out of the ordinary that an MGFA I patients with predominantly ocular problems has occasional (temporary) problems in other domains, resulting in the seemingly conflicting numbers seen in table 2.

### Comparison with published literature

The observed impact of MG on HRQoL was also in accordance with previous studies. Recent studies confirm that the HRQoL is lower in patients with MG compared with the general population despite active treatment, with patients with MG suffering from inferior physical capacity and poorer mental health.[5 29 32–34] One study concluded that patients with ocular symptoms had a HRQoL similar to the healthy controls.[5 30] This contrasts with our study, which demonstrates a clear impact of MG also in MGFA class I using the different PROMs. In a single-centre, cross-sectional study with 339 patients with MG, higher MGFA class was related to worse mean scores on the Short-Form 36-item questionnaire for health survey for general health, physical composite score and mental composite score domains. As in our study, patients with MGFA I-II class had significantly better HRQoL than patients with more severe MG. However, in this single-centre study, no difference was found between MGFA classes I and II and between MGFA classes III and IV,[31] whereas our study demonstrates that each additional MGFA class brings an additional burden to the patient in terms of physical functioning, activities, social functioning, and symptoms such as fatigue and difficulty breathing.

Results from a mailed questionnaire among 1518 members of the German Myasthenia Association[6] found that participants suffered from muscle weakness after physical strain (75.4%), walking problems (69.6%), chewing problems (39.1%), eyelid droop (37.8%) and double vision (37.1%) in similar proportion to the patients in our sample. Differences with our study were reporting of vision problems, which were much more frequently reported in MyRealWorld-MG; and depression which was mentioned as a comorbidity by 38.6% of participants in the German study[6]; whereas in our sample only 23% mentioned having depression as a comorbidity and 18.1% were found to be moderately-to-severely depressed when assessed with the HADS. In this study, lower utilities among women were observed, which is a frequent finding in population norms studies conducted among the general population. The difference between male and female patients with MG (0.045) in this study was higher than what is typically found in the general population (eg, 0.021 difference using UK population norms).[35] Finally, a cross-sectional observational study with 200 German participants focused on prevalence of fatigue in patients with MG and its impact on HRQOL, and reported findings consistent with our results on the bolt-on fatigue question. The rate of anxiety and depression in that study, using the cut-off score of ≥8 on the HADS was 27.8% and 19.6%, respectively, which are parallel to our findings.[36]

### Limitations

One limitation of our study is the possible selection bias due to the digital data collection. Only individuals with access to the internet and a telephone or tablet were able to enrol in the study. Therefore, older individuals, less confident with the use of apps on smartphones or individuals with severe ocular or dexterity problems due to their MG might be under-represented. Furthermore, as potential participants were made aware of the study through PAGs and social media, a possible bias to more proactive individuals cannot be excluded. The MyRealWorld-MG study population is considerably younger and with a

higher proportion of female participants compared with other cohorts,[2 6 28–31] which might also affect results. Another limitation is that with the remote app approach, the eligibility of participants and accuracy of data could not be directly verified. The study results are also reported by instrument, with a different sample size and a slightly different composition of patients for each instrument, which may also introduce a bias in the results. Finally, the comparison of our results with data in the available literature is hampered by the different instruments used to evaluate the HRQoL in MG. Only our publication reported HRQoL across the different MGFA classes, whereas other publications reported results by refractory versus non-refractory patients with MG or by MG subtype[2 30] In this baseline analysis, HRQoL in subgroups with different MG treatments was not performed.

The MyRealWorld-MG study will establish a longitudinal data set for the different PROM instruments.[9] Further research to compare results of the MG disease population with a reference population is needed to give more insight in the impact of MG on HRQoL.

## CONCLUSION

In this real-world study with a large and diverse MG population and different PROM instruments,[9] a consistent and large impact of MG on HRQoL aspects such as usual activities, depression, tiredness, breathing and vision was observed despite the best supportive care. The impact of MG is considerable in all MGFA classes and increases substantially with increasing disease severity.

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**Contributors** SD and MFJ contributed to the conception and design of the study, analysed the data and wrote the manuscript. ML, GP, SP, JB and SC designed the study, provided strategic advice and reviewed the manuscript. ML, LD, CQ, JP, SB-A, KGC, SM, RM, FS, AM, GB and HM contributed to conception and design of the study, collected the data and reviewed the manuscript. SD is the guarantor and accepts full responsibility for this work.

**Funding** The study is funded by argenx BV, Ghent, Belgium. No grant or award is applicable.



**Competing interests** SD is the principal investigator of the study, and MFJ has been commissioned by argenx BV and received honoraria to design the study, analyse and report the data. ML is CEO and owner of Vitaccess, who has been commissioned by argenx BV to carry out the data collection. CQ and LD are employees of Vitaccess. GP, SP, JB and SC are employees of argenx BV, the sponsor of the study. SD and MFJ are members of the EuroQol Group. KGC has received advisory board honoraria, speaker fees and funding for research from Alnylam, Biogen, CSL Behring and Sanofi-Genzyme; and travel reimbursement from Sanofi-Genzyme. KGC holds the Emil von Behring Chair in Neuromuscular and Neurodegenerative Disorders, sponsored by CSL Behring. HM has served as a paid consultant for argenx BV, Alexion Pharmaceuticals, Ra Pharmaceuticals and UCB Pharma and has received speaker honoraria from the Japan Blood Products Organisation and research support from the Ministry of Health, Labour and Welfare, Japan. RM has received speaking honoraria from BioMarin, Alexion and UCB, served on advisory boards for Alexion, argenx BV and UCB and received support for congress participation from Merck, Teva and Biogen. FS has received public speaking honoraria from Biogen, Mylan, Novartis, Roche, Sanofi and Teva; and served on advisory boards for Almirall, argenx BV, AveXis, Biogen, Forward Pharma, Merk, Novartis, Novatek, Pomona, Roche and Sanofi.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Consent obtained directly from patient(s)

**Ethics approval** This study involves human participants. Ethics approval in the USA, Germany and the UK was granted by Salus Institutional Review Board (IRB) (protocol number 5105-08-2019). In Canada, ethics approval was granted by Veritas IRB (protocol number ARG-MG-2019-01) excluding the region of Newfoundland and Labrador. For these two regions, ethics approval was granted by the Newfoundland and Labrador Health Research Ethics Board (protocol number 5105-08-2019). The Istituto Neurologica Carlo Besta granted ethics approval for Italy (protocol number 5105-08-2019). In Spain, approval was obtained through the Research Ethics Committees with Medicines Hospital de la Santa Creu i Sant Pau (protocol number ARG-MG-2019-01). Non-Profit Organization MINS IRB granted approval for the MRW-MG study in Japan (protocol number ARG-MG-2019-01). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Anonymised, aggregated study data is available upon reasonable request through the data access request form. All applications will be reviewed by the study's scientific advisory board before access is granted.



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**SUPPLEMENTAL MATERIAL**

**Table S1. Distribution across the domains of the MG-QoL15r**

| Domains | All patients N=679 | MGFA I N=93 | MGFA II N=187 | MGFA III N=244 | MGFA IV N=102 |
|---|---|---|---|---|---|
| **I feel frustrated** | | | | | |
| Not at all | 25% | 54.9% | 29.4% | 15.4% | 9.9% |
| Somewhat | 54% | 38.5% | 60.4% | 55.4% | 55.4% |
| Very Much | 21% | 6.6% | 10.2% | 29.2% | 34.7% |
| **I have trouble using my eyes (e.g. double vision)** | | | | | |
| Not at all | 35% | 41.8% | 37.4% | 31.3% | 23.8% |
| Somewhat | 45.7% | 37.4% | 44.4% | 50% | 52.5% |
| Very Much | 19.4% | 20.9% | 18.2% | 18.8% | 23.8% |
| **I have trouble eating** | | | | | |
| Not at all | 54.5% | 91.2% | 65.8% | 42.1% | 27.7% |
| Somewhat | 41.1% | 8.8% | 32.1% | 54.6% | 59.4% |
| Very Much | 4.5% | 0% | 2.1% | 3.3% | 12.9% |
| **I have limited my social activity** | | | | | |
| Not at all | 34.1% | 62.6% | 41.2% | 22.9% | 17.8% |
| Somewhat | 43.5% | 33% | 41.7% | 50% | 42.6% |
| Very Much | 22.5% | 4.4% | 17.1% | 27.1% | 39.6% |
| **I am limited in my ability to enjoy hobbies and fun activities** | | | | | |
| Not at all | 22.5% | 54.9% | 26.7% | 11.7% | 5.9% |
| Somewhat | 48.4% | 35.2% | 51.9% | 53.8% | 44.6% |
| Very Much | 29.2% | 9.9% | 21.4% | 34.6% | 49.5% |
| **I have trouble meeting the needs of my family** | | | | | |
| Not at all | 41.5% | 73.6% | 49.7% | 29.2% | 19.8% |
| Somewhat | 43.2% | 23.1% | 43.9% | 51.3% | 49.5% |
| Very Much | 15.3% | 3.3% | 6.4% | 19.6% | 30.7% |
| **I have to make plans around an illness or condition that I suffer from** | | | | | |
| Not at all | 17.9% | 44% | 23.5% | 7.9% | 4% |
| Somewhat | 47.2% | 46.2% | 50.8% | 48.8% | 40.6% |
| Very Much | 35% | 9.9% | 25.7% | 43.3% | 55.4% |
| **I am bothered by limitations in performing my work (including work at home)** | | | | | |
| Not at all | 19.6% | 49.5% | 22.5% | 8.8% | 6.9% |
| Somewhat | 44.6% | 39.6% | 52.9% | 43.3% | 38.6% |
| Very Much | 35.7% | 11% | 24.6% | 47.9% | 54.5% |

| Domains | All patients N=679 | MGFA I N=93 | MGFA II N=187 | MGFA III N=244 | MGFA IV N=102 |
|---|---|---|---|---|---|
| **I have difficulty speaking** | | | | | |
| Not at all | 58.6% | 81.3% | 71.1% | 50% | 32.7% |
| Somewhat | 37.4% | 17.6% | 28.9% | 46.7% | 54.5% |
| Very Much | 4% | 1.1% | 0% | 3.3% | 12.9% |
| **I have lost some personal independence (e.g. driving, shopping, running errands)** | | | | | |
| Not at all | 42.6% | 69.2% | 55.6% | 29.6% | 20.8% |
| Somewhat | 37.2% | 24.2% | 32.6% | 47.1% | 38.6% |
| Very Much | 20.2% | 6.6% | 11.8% | 23.3% | 40.6% |
| **I am depressed** | | | | | |
| Not at all | 46.4% | 72.5% | 53.5% | 40% | 24.8% |
| Somewhat | 43.9% | 24.2% | 41.2% | 45.4% | 63.4% |
| Very Much | 9.7% | 3.3% | 5.3% | 14.6% | 11.9% |
| **I have trouble walking** | | | | | |
| Not at all | 44.9% | 85.7% | 59.9% | 27.1% | 19.8% |
| Somewhat | 45.7% | 13.2% | 38.5% | 61.7% | 54.5% |
| Very Much | 9.4% | 1.1% | 1.6% | 11.3% | 25.7% |
| **I have trouble getting around public places** | | | | | |
| Not at all | 51% | 83.5% | 68.4% | 35.4% | 27.7% |
| Somewhat | 38% | 14.3% | 28.3% | 52.5% | 43.6% |
| Very Much | 11% | 2.2% | 3.2% | 12.1% | 28.7% |
| **I feel overwhelmed** | | | | | |
| Not at all | 46.3% | 73.6% | 56.1% | 37.9% | 21.8% |
| Somewhat | 42.1% | 20.9% | 37.4% | 46.3% | 64.4% |
| Very Much | 11.6% | 5.5% | 6.4% | 15.8% | 13.9% |
| **I have trouble performing my personal grooming needs** | | | | | |
| Not at all | 64.1% | 92.3% | 75.4% | 52.9% | 41.6% |
| Somewhat | 30.4% | 7.7% | 24.1% | 38.3% | 48.5% |
| Very Much | 5.5% | 0% | 0.5% | 8.8% | 9.9% |
| **MG-QoL-15r total score** | | | | | |
| Mean | 11.7 | 5.5 | 9.2 | 13.7 | 16.4 |
| SD | 7.1 | 5.2 | 6.1 | 6.4 | 6.4 |
| Min | 0 | 0 | 0 | 0 | 2 |
| Q1 | 6 | 1 | 4 | 9 | 11 |
| Q3 | 17 | 8 | 13 | 18 | 22 |
| Max | 29 | 21 | 25 | 29 | 28 |

*MG-QoL15r: Myasthenia Gravis Quality of Life 15-item revised scale; MGFA: Myasthenia Gravis Foundation of America. SD: Standard deviation; Min: minimum; Q1: first quartile; Q3: third quartile; Max: maximum.*

**Table S2: Distribution across the domains of the HADS**

| Domains of the HADS | All patients N=629 | MGFA I N=87 | MGFA II N=184 | MGFA III N=248 | MGFA IV N=100 |
|---|---|---|---|---|---|
| **Total Anxiety score** | | | | | |
| % No anxiety | 46.7% | 66.7% | 57.1% | 39.5% | 30.0% |
| % Mild anxiety | 23.9% | 10.3% | 22.3% | 28.2% | 29.0% |
| % Moderate anxiety | 21.0% | 12.6% | 15.2% | 23.8% | 31.0% |
| % Severe anxiety | 8.4% | 10.3% | 5.4% | 8.5% | 10.0% |
| Mean Anxiety Score (SD) | 8.2 (4.3) | 7.1 (4.4) | 7.2 (4) | 8.6 (4.2) | 9.5 (4.1) |
| **Total Depression score** | | | | | |
| % No depression | 57.1% | 77.0% | 66.9% | 47.6% | 45.0% |
| % Mild depression | 24.6% | 16.1% | 22.3% | 29.4% | 27.0% |
| % Moderate depression | 14.0% | 4.6% | 8.7% | 17.7% | 22.0% |
| % Severe depression | 4.3% | 2.3% | 2.2% | 5.2% | 6.0% |
| Mean Depression Score (SD) | 6.9 (4.2) | 4.8 (4) | 5.8 (3.9) | 7.7 (3.9) | 8.3 (4.2) |

*HADS: Hospital anxiety and depression scale; MGFA: Myasthenia Gravis Foundation of America. SD: Standard deviation*