The Burden Patients with Myasthenia Gravis Experience in Terms of Breathing, Fatigue, Sleep, Mental Health, Discomfort and Usual Activities in Comparison to the General Population

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ABSTRACT

Introduction: Myasthenia gravis (MG) is a rare neuromuscular disorder marked by a variable combination of weakness of eye, bulbar, respiratory, axial, and limb muscles. This study compared the experience of people with MG regarding breathing, fatigue, sleep, pain/discomfort, mental health, and usual activities with the general population.

Methods: The MyRealWorld-MG digital, multinational study enrolled patients with MG and collected demographics, PROMIS-Dyspnea, PROMIS-Sleep Disturbance, FACIT-Fatigue, EQ-5D-5L, Health Utilities Index (HUI-3), Hospital Anxiety and Depression Scale (HADS), MG-Activities of Daily Living (MG-ADL), and MG-Quality-of-Life (MG-QoL-15r). Comparisons with the general population were based on PROMIS population norms, published literature, or on data from a digital, multinational, observational study which enrolled a representative sample of the general population (POPUP).

Results: In MyRealWorld-MG ($N = 2074$), patients experienced higher intensity, frequency, and duration of PROMIS shortness of breath than a US population ($p < 0.0001$). Patients with MG had higher PROMIS-Sleep Disturbance scores than POPUP (53.7 vs 50.0, $p < 0.0001$), and 54.9% of patients had clinically severe FACIT-Fatigue scores vs 6.8% in POPUP ($p < 0.0001$). Among patients with MG, 69.6% and 18.5% had moderate-to-severe HADS-Anxiety and HADS-Depression compared to 20.3% and 6.9% in POPUP ($p < 0.001$). Statistically significant and strong associations were found between fatigue, sleep, dyspnea, usual activities, and emotions. All outcomes worsened with more severe disease.

Conclusion: A considerable burden was observed in this comparison of breathing, sleep, fatigue, mental health, and usual activities between patients with MG and the general population, using data from two international studies and published population norms. Even

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mildly affected patients had significantly worse outcomes than the general population.

Key Summary Points

This study investigated the burden of myasthenia gravis (MG) regarding breathing, fatigue, sleep, pain/discomfort, mental health, and usual activities, and the effect of disease severity.

Validated patient-reported outcome measures were utilized to collect data from both patients with MG and the general population.

Patients with MG experienced significantly more breathing problems, fatigue, sleep disturbances, mental health issues, pain/discomfort, and difficulties in performing usual activities compared to the general population.

The health-related quality of life of patients with MG worsened with increased disease severity, except for mental health, where anxiety was significantly higher across all disease severities.

These findings emphasize the need for a patient-centered approach to MG treatment, addressing not only physical symptoms but also mental health aspects to improve the overall well-being of patients.

INTRODUCTION

Myasthenia gravis (MG) is a rare, chronic autoimmune disease, characterized by extensive muscular weakness [1]. Typical for MG is that a variable combination of ocular, bulbar, limb, and respiratory muscles are affected, causing diverse manifestations of the disease. A systematic review and meta-analysis performed by Salari et al. (2021) estimates the prevalence of MG to be 12.4 (95% CI 10.6–14.5) per 100,000 individuals [2], which is a substantial increase compared to estimations from a previous systematic review conducted by Carr et al. (2010), in which a prevalence of 7.7 per 100,000 individuals was reported [3].

Various medical treatments are available with the aim to alleviate MG symptoms [4]. However, despite treatment options and positive developments in disease management [5, 6], multiple studies demonstrated poor health-related quality of life (HRQoL) among patients with MG. About 15–20% of patients with MG experience a myasthenic crisis, where respiratory failure causes a life-threatening situation that requires emergency treatment, including mechanical ventilation and/or nasogastric tube feeding [7]. Besides physical impairments, a high prevalence of mood disorders such as anxiety and depression [8] has been found in MG.

The present study was co-designed with patient advocacy groups (PAGs) from different countries. Patients highlighted symptoms or functionings that were most affected by the disease, such as breathing, fatigue, sleep, mental health, and self-confidence. The aim of this study was to explore the burden patients with MG experience in terms of physical health, mental health, symptoms, and capabilities, by comparing dimensions of health and HRQoL of people diagnosed with MG with the general population. Furthermore, this study also examines whether problems in these dimensions worsen with increased disease severity. The intention is to elevate the patient voice by providing objective, quantitative self-reported data that can be put into perspective by contrasting outcomes with a representative sample of the general population. This is a tandem paper to a similar study which identified lower utility values and higher need for medical care and caregiver help in patients with MG compared to the general population [9].

METHODS

The data for this comparative analysis are based on two observational studies of which the baseline data have been extracted: one study was conducted among patients with MG (MyRealWorld-MG) and the other study collected data among members of the general population (POPUP).

MyRealWorld-MG

The MyRealWorld-MG (MRW) study is a digital, prospective, observational, multicountry study, conducted among adult patients with MG in nine countries (USA, UK, Canada, Italy, Germany, Spain, France, Denmark, Japan). The objective of MRW was to provide a comprehensive real-world, longitudinal view of the impact of MG in a large and diverse cohort of patients with MG, from their own perspective. More detailed information on the rationale and design of the study is available in the study protocol [10]. The analysis presented here concerns the data entered at baseline. No formal sample size calculations were performed; feasibility was the main driver with the objective of maximizing the sample size and participating countries.

The data collection in MRW covered the following questions: demographics, medical history, EQ-5D-5L, and six additional "bolt-on" dimensions (breathing, vision, sleep, fatigue, self-esteem, and social relationships), the Health Utilities Index (HUI-3), the MG-Activities of Daily Living (MG-ADL), the MG-Quality of Life questionnaire (MG-QoL-15r), the Hospital Anxiety and Depression Scale (HADS), the Patient-Reported Outcomes Measurement Information System (PROMIS)-Dyspnea Characteristics, the PROMIS-Sleep Disturbance, and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue. From this pool of items, the following HRQoL dimensions were selected for further examination in this study: breathing, fatigue, sleep, mental health, pain/discomfort, and usual activities. The investigation into each of these dimensions was based on all available items from all of the above instruments. In MRW, participants filled in the patient-reported outcome measures (PROMs) on their smartphone as and when they were presented to them. The digital application presented different PROMs at varying periods in time, and not all participants chose to fill in all the instruments that were presented to them, resulting in variable sample sizes for each instrument.

Data for Comparison with General Population

A multinational digital study, POPUP, enrolled 9000 general population participants in eight countries (USA, Canada, UK, Italy, Spain, Germany, the Netherlands, and Belgium). The main objective of POPUP was to establish population norms in these countries using multiple HRQoL instruments. National population norms can be used as reference data to assess disease burden by comparing HRQoL in populations with and without any particular disease. Participants were recruited by market research companies in each country. From each national respondent panel, representative samples were drawn for this study based on previously agreed variables (age, gender, education, and region). Selected respondents were invited by email to participate and received a personal link to a website where they could respond to the questions in return for points (that could later be exchanged for gifts). This study provided general population comparison data on the following instruments: EQ-5D-5L and bolt-ons, HUI-3, HADS, MG-ADL, and MG-QoL. National data used in this study were collected between January and March 2021. The POPUP sample size was not based on formal sample size calculation but driven by the aim of representativity for the general population.

The PROMIS-Sleep Disturbance results were compared with the PROMIS US population norms for this instrument. The comparison to the PROMIS-Dyspnea Characteristics was made with a US COVID population and the FACIT-Fatigue results were contrasted with German general population norms, as no published

PROMIS norms were available for these outcomes, and this was the best available and most recent data to compare our results with.

Details of Outcome Measures

EQ-5D-5L

The EQ-5D-5L is a generic HRQoL instrument consisting of a descriptive system adopting five single-item dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item is described in five severity levels ranging from "no problems" to "unable to/extreme problems" [11]. Besides the descriptive system, the questionnaire includes a thermometer-like, visual analogue scale (EQ VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health) on which respondents can rate their overall health. EQ-5D-5L asks respondents to rate their health on the day of completion.

Selected "bolt-on" dimensions were added to the five core EQ-5D-5L dimensions [12] with the same five severity levels varying from "no problems" to "extreme problems". The six bolt-on questions vision, breathing, sleep, tiredness, social relationships, and self-confidence were included in MRW and POPUP.

Health Utilities Index 3 (HUI-3)

The HUI-3 is a generic, preference-based instrument for measuring the health status of participants and their health-related quality of life. Respondents are asked to think about their health and their ability to do activities of daily living during the past week. The HUI-3 classification system distinguishes eight single-item dimensions of health: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each level is described with five or six levels of ability/disability [13].

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item instrument to determine the levels of anxiety and depression that a person is experiencing [14]. Seven of the items relate to anxiety and seven relate to depression. All items have four response options with scores ranging from 0 to 3, allowing for the calculation of two separate total scores for the anxiety and depression subscales, respectively (HADS-A; HADS-D), both ranging from 0 to 21. Scores of 11 or more on either subscale are considered to be a significant case of psychological morbidity, while scores of 8–10 represent "borderline" and 0–7 "normal" [14].

Myasthenia Gravis Activities of Daily Living (MG-ADL)

The MG-ADL scale is one of the most widely used outcomes to assess symptom severity in MG. This scale contains eight items (talking, chewing, swallowing, breathing, brushing teeth and combing hair, rising from a chair, double vision, and eyelid droop) across four dimensions (bulbar, respiratory, limb weakness, and ocular). The severity of each item can be indicated by assigning a score between 0 and 3, after which a total score can be calculated (ranging from 0 to 24) indicating the total symptom burden [15]. No recall period is included in the MG-ADL.

Myasthenia Gravis-Quality of Life questionnaire (MG-QoL-15r)

The MG-QoL-15r is a validated HRQoL measure for patients with MG, including items on well-being and independence [16]. MG-QoL-15r assesses the impact of MG over the previous few weeks on the following dimensions: emotions (e.g., feeling frustrated, depressed, overwhelmed), physical health (e.g., eyes, difficulty speaking, walking, getting around public places), self-care (e.g., eating, loss of personal independence, difficulty with personal grooming), social life (e.g., limited social activity, hobbies), and impact on role (e.g., meeting needs of family, work including work at home). All items have three response options with scores ranging from 0 to 2 and allow for the calculation of a total score by summing the level scores for all 15 items (ranging from 0 to 30). Note that any reference to MG was omitted from this questionnaire for data collection in the POPUP general population respondents.

PROMIS-Dyspnea Characteristics Item Pool

PROMIS is a set of person-centered measures that evaluates physical, mental, and social health in adults and children [17, 18]. It can be used with the general population as well as with individuals living with chronic conditions. PROMIS-Dyspnea Characteristics measure is a generic five-item scale, which assesses frequency, severity, and duration of dyspnea (shortness of breath) over the previous 7 days. All items are scored on a 0–10 scale except for shortness of breath that uses a 0–4 scale. A total score can be obtained by summing the level scores for all items. The MRW data were compared to data from US patients who were admitted to hospital for COVID-19 and for whom pre-COVID scores were reported [19]. The PROMIS item bank did not have T scores available for this *item pool*.

PROMIS-Sleep Disturbance-Short Form 6a

The PROMIS-Sleep Disturbance-Short Form 6a is a six-item short form to assesses overall sleep quality and sleep disturbance over the past 7 days. Each item has five response options. For most PROMIS short forms, T scores are available that are standardized scores with a mean of 50 as the average for the US general population, and a standard deviation of 10 [20]. For PROMIS measures, higher scores equal more of the concept being measured. For PROMIS-Sleep Disturbance, available T scores for the US general population were used to make a comparison with the general population [21].

FACIT: Fatigue

The FACIT-Fatigue measure is a generic 13-item survey, which assesses fatigue levels and impact over the previous 7 days [22]. Items are scored on a 0–4 response scale with anchors ranging from "not at all" to "very much so". A total score can be obtained by summing the level scores for all items (ranging from 0 to 52 with 0 being the worst possible score and 52 being the best possible score indicating no fatigue; for this purpose, each negatively worded item response is recoded). FACIT-Fatigue published population norms for Germany [23] were utilized for the comparison with MRW.

Ethical statement

Ethical approval was obtained in all countries from Salus IRB (USA, UK, Italy, Spain, Germany, France, Netherlands, Denmark), KULeuven and UGent (Belgium), Veritas IRB (Canada), and MINS-IRB (Japan). For a full list of participating IRBs, please see the supplementary material. All participants signed an informed consent form and the study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

Descriptive analyses were presented as mean and standard deviation (SD) for continuous variables, and proportions for categorical variables. For all PROMs, the total scores or subtotal scores by dimension were calculated, if applicable. Statistical comparison between the data from MRW and data from the general population was performed using independent samples T tests for continuous variables and Cochran–Mantel–Haenszel tests for categorical variables. Furthermore, as an exploratory analysis to understand which dimensions of HRQoL are related, correlations between selected HRQoL dimensions were calculated. We expected significant associations between (1) fatigue, sleep, and dyspnea; (2) being fatigued and having problems with performing usual activities; (3) having problems with performing usual activities and emotions of frustration and feeling overwhelmed; (4) experiencing fatigue and emotions; and (5) having mental health problems (anxiety, depression) and having sleeping problems, being fatigued and having problems with performing usual activities. Pearson correlations were used between the dimensions expressed as continuous variables whereas Spearman rank correlations were used to calculate associations between categorical variables and/or non-normal continuos variables. Correlations were considered very strong when their absolute value was 0.80–1.00, strong 0.60–0.80, moderate 0.40–0.60, weak 0.20–0.40, or non-existent < 0.20 [24].

RESULTS

Patient Characteristics

The demographic characteristics of 2074 patients with MG included in MRW were compared with those of a representative sample of the general population from POPUP ($N = 9000$, Table 1). The POPUP population had an almost equal gender distribution (51.2% female) with an average age of 46.9 years. This was in contrast to MRW which enrolled mostly female patients (68.7%), but had a similar average age.

Sample Sizes

Sample sizes differed substantially between instruments for MRW (Table 2). In POPUP on the other hand, all respondents answered all questions and instruments, and therefore a complete sample was obtained.

PROMs: Breathing

Three items or PROMs provided data on breathing problems in patients with MG (Table 3). Regardless of which instrument was used, patients with MG experienced significantly more breathing problems than the general population (all $p < 0.0001$), including a higher frequency, intensity, and duration of being out of breath. More than double the number of MG respondents indicated having "moderate to extreme problems with breathing" and three times the number of patients with MG reported abnormal breathing compared to respondents from the general population.

PROMs: Fatigue

Patients with MG had a mean FACIT-Fatigue score that was substantially lower than the score of the general population (higher scores are better, Table 4, $p < 0.0001$). More than half of patients with MG had clinically significant fatigue, for which 30 is a common cutoff value on this scale, which was eight times more than in the German general population. The finding

Table 1 Respondent characteristics for MRW and POPUP

	MRW $N = 2074$	POPUP $N = 9000$
MG-ADL		
Mild: 0–4	58.7%	95.5%
Moderate: 5–9	40.2%	3.7%
Severe: ≥ 10	1.1%	0.8%
Age		
Mean (SD)	49.8 (14.8)	46.9 (16.2)
Female		
18–34	14.7%	13.6%
35–54	34.7%	18.5%
55+	19.3%	19.1%
Male		
18–34	2.0%	13.9%
35–54	10.0%	18.5%
55+	19.3%	16.4%
Living situation		
At home without help from a caregiver	55.9%	70.5%
At home with help from a caregiver	6.4%	3.1%
With a family member	37.2%	26.0%
In a nursing home	0.1%	0.3%
In a long-term care rehabilitation facility	0.4%	0.1%
EQ VAS		
Mean	61.7	75.7
SD	22.1	17.4
Q1	48	69
Median	65	80

Table 1 continued

	MRW $N = 2074$	POPUP $N = 9000$
Q3	80	90

MG myasthenia gravis, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *VAS* visual analogue scale, *SD* standard deviation, *Q1, Q3* first, third quartile, *N* sample size, *MRW* MyRealWorld-MG Digital study, *POPUP* General Population study

Table 2 Samples for MRW and POPUP per PROM

	Patients with MG from MRW	General population
PROMIS-Dyspnea Characteristics	$N = 325$	US COVID population [19] $N = 126$, pre-COVID scores
FACIT-Fatigue	$N = 324$	German general population [22], $N = 2576$
PROMIS-Sleep Disturbance	$N = 251$	US population
EQ-5D-5L and six bolt-on questions	$N = 1299$	POPUP, $N = 9000$
MG-ADL	$N = 1236$	POPUP, $N = 9000$
MG-QoL-15r	$N = 1177$	POPUP, $N = 9000$
HUI-3	$N = 540$	POPUP, $N = 9000$
HADS	$N = 1159$	POPUP, $N = 9000$

PROMIS Patient-Reported Outcomes Measurement Information System, *FACIT* Functional Assessment of Chronic Illness Therapy, *EQ-5D-5L* EuroQol 5-Dimension 5-Level questionnaire, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *MG-QoL-15r* MG Quality of Life questionnaire, *HUI-3* Health Utilities Index Mark, *HADS* Hospital Anxiety and Depression Scale, *MRW* MyRealWorld-MG Digital study, *POPUP* General Population study, *N* sample size

of more frequent fatigue was confirmed with the EQ-5D-5L tiredness bolt-on, for which double the number of patients with MG scored moderate-to-extreme problems compared to the general population.

PROMs: Sleep

Patients with MG had a mean PROMIS-Sleep Disturbance score which was higher than the standardized score of the US general population ($p < 0.0001$, Table 5), although it was not meaningfully higher. On the other hand, 40% more patients with MG scored moderate-to-extreme problems on the EQ-5D-5L sleep bolt-on in comparison to the general population ($p < 0.0001$).

PROMs: Mental Health

According to the HADS, 69.6% and 18.5% of patients with MG reported having moderate-to-severe anxiety or depression, respectively, strongly contrasting the 20.3% and 6.9% in POPUP (Table 6, $p < 0.0001$). This finding was echoed in the other PROMs items that were asking about self-reported mental health conditions (the anxiety/depression dimension of the EQ-5D-5L, the self-confidence bolt-on, the HUI-3 emotion item, and the frustration, depression, and feeling overwhelmed items of the MG-QoL-15r): all showed significantly worse scores for patients diagnosed with MG (all $p < 0.0001$).

PROMs: Pain/Discomfort

Patients with MG more often scored problems on EQ-5D-5L pain/discomfort and on the HUI-3 pain/discomfort item when compared to POPUP ($p < 0.0001$, Table 7).

PROMs: Usual Activities

Patients with MG encounter a wide range of substantial difficulties in carrying out their usual activities, covering problems working, carrying out home work, taking care of their

Table 3 Comparison of breathing problems between respondents of MRW and the general population

Instrument/domain	MRW	Source		P value
PROMIS-Dyspnea	$N = 325$	US COVID population [19] $N = 126$, pre-COVID scores		
General shortness of breath[a]	3.02 (2.53)	0.0 (0.7)		< 0.0001
Intensity of shortness of breath	2.93 (2.61)	0.0 (0.0)		< 0.0001
Frequency of shortness of breath	3.36 (2.85)	0.0 (0.0)		< 0.0001
Duration of shortness of breath	2.9 (2.57)	0.0 (0.0)		< 0.0001
EQ-5D-5L bolt-on: Breathing	$N = 1299$	POPUP, $N = 9000$		
I have no problems breathing	58.2%	77.6%		< 0.0001
I have slight problems breathing	27.0%	15.5%		
I have moderate problems breathing	12.0%	5.2%		
I have severe problems breathing	2.4%	1.2%		
I have extreme problems breathing	0.4%	0.5%		
Mean (SD)	1.6 (0.8)	1.3 (0.6)		< 0.0001
MG-ADL: Breathing	$N = 1236$	POPUP, $N = 9000$		
Normal	37.5%	77.1%		< 0.0001
Shortness of breath with exertion	51.0%	20.1%		
Shortness of breath at rest	10.7%	2.1%		
Ventilator dependence	0.9%	0.7%		
Mean (SD)	0.8 (0.7)	0.3 (0.5)		< 0.0001

[a]Items use a 0–10 numeric rating scale (where 0 represents no shortness of breath and 10 represents the worst possible shortness of breath). If the participant has no shortness of breath, the instrument stops after the first item and the subsequent three items are assigned a score of 0

families, engaging in hobbies, participating in social activities, and living independently. This is evidenced in Table 8 with the usual activities dimension of the EQ-5D-5L, and with six relevant MG-QoL-15r items (all $p < 0.0001$). The unpredictable, fluctuating nature of MG was evidenced by its impact on the MG-QoL-15r item "having to make plans around an illness", for which almost 40.0% of patients with MG reported having to take this "very much" into account, compared to only 7.6% of the general population. Similarly, losing personal independence in driving, shopping, running errands

was considered "very much" to be the case in about a quarter of patients with MG (23.9%), versus nearly 4.8% in the general population. Likewise, the ability to perform work or house work is "very much" affected in almost 38.4% of people suffering from MG, which is five times higher than in the general population (6.9%). The EQ-5D-5L domain usual activities was considered without problems by less than one-third of people suffering from MG (29.1%) whereas over three-quarters in the general population (76.6%) indicated not having a problem in this domain. In contrast, the social

Table 4 Comparison of problems with fatigue between respondents of MRW and the general population

Instrument/domain	MRW	Source	*P* value
FACIT-Fatigue scale	$N = 324$	German general population, $N = 2576$	
Mean (SD)	28.9 (11.5)	43.5 (8.3) [22]	< 0.0001
% with score below 30	54.9%	6.8%	< 0.0001
(Clinically significant fatigue)			
EQ-5D-5L bolt-on: Tiredness	$N = 1299$	POPUP, $N = 9000$	
I am not tired	14.6%	46.5%	< 0.0001
I am slightly tired	32.3%	29.9%	
I am moderately tired	37.1%	15.4%	
I am severely tired	12.7%	6.0%	
I am extremely tired	3.3%	2.2%	
Mean (SD)	2.6 (1.0)	1.9 (1.0)	< 0.0001

relationship bolt-on was almost identical between the two respondent groups (despite it being statistically significant which is due to the high sample size).

PROMS: Associations Between Problems in Different Dimensions Experienced by Patients with MG

In our study we found that problems in one domain often were associated with problems in other dimensions. For example, patients with dyspnea problems were also more likely to experience fatigue (correlation ρ (PROMIS-Dyspnea, FACIT-Fatigue) = − 0.60, $p < 0.0001$) and to a lesser extent problems with sleeping (ρ(PROMIS-Dyspnea, PROMIS-Sleep Disturbance) = 0.42, $p < 0.0001$). Sleeping problems and fatigue were also strongly associated with each other (ρ(FACIT-Fatigue, PROMIS-Sleep Disturbance) = − 0.53, $p < 0.0001$) (Supplementary Materials Table S1).

Furthermore, strong associations were found between experiencing higher levels of fatigue (FACIT-Fatigue Total score) on the one hand, and problems with EQ-5D-5L usual activities ($\rho = - 0.57$), problems with the EQ-5D-5L bolt-on social relationships ($\rho = - 0.47$), and with the following MG-QoL-15r items: limitations in social activity ($\rho = - 0.59$), limitations in the enjoyment of hobbies and fun activities ($\rho = - 0.58$), being bothered in performing work (also at home) ($\rho = - 0.64$), and losing personal independence (including driving, shopping, errands) ($\rho = - 0.62$) on the other hand (Supplementary Materials Table S2). All these usual activity-related items were also interrelated with each other and significant moderate to strong correlations between 0.53 and 0.69 were observed among all of these items.

Likewise, the *usual activity* items of the EQ-5D-5L and MG-QoL-15r described above have moderate to strong associations with MG-QoL-15r *feelings* of frustration ($\rho = 0.43$ to 0.60), feeling overwhelmed ($\rho = 0.42$ to 0.57), and with the EQ-5D-5L bolt-on social relationships ($\rho = 0.38$ to 0.48) (Supplementary Materials Table S3).

Additionally, *fatigue* was significantly associated with *emotions*. Strong correlations were observed between the FACIT-Fatigue and MG-

Table 5 Comparison of sleep problems between respondents of MRW and the general population

Domain/instrument	MRW	Source	P value
PROMIS-Sleep Disturbance	N = 251	US general population	
Mean (SD)	53.7 (8.1)	50.0 (10.0)[a]	< 0.0001
EQ-5D-5L bolt-on: Sleep	N = 1299	POPUP, N = 9000	
I have no problems sleeping	33.7%	39.6%	< 0.0001
I have slight problems sleeping	32.5%	36.0%	
I have moderate problems sleeping	24.6%	15.9%	
I have severe problems sleeping	8.0%	6.2%	
I have extreme problems sleeping	1.2%	2.3%	
Mean (SD)	2.1 (1.0)	2.0 (1.0)	< 0.0001

[a]Based on PROMIS calibration sample

QoL-15r feelings of frustration ($\rho = -0.58$), MG-QoL-15r feelings of depression ($\rho = -0.56$), and MG-QoL-15r feeling overwhelmed ($\rho = -0.58$); and moderate correlations with the EQ-5D-5L bolt-on item self-confidence ($\rho = -0.41$) (Supplementary Materials Table S4).

Finally, we observed that neither HADS-Anxiety nor HADS-Depression or the EQ-5D-5L anxiety/depression domain was meaningfully associated with PROMIS-Sleep, FACIT-Fatigue, EQ-5D-5L domain usual activities, or any of the MG-QoL-15r items related to usual activities (Supplementary Materials Table S5).

Comparison by Disease Severity

In Table 9, several HRQoL dimensions are contrasted between mild MG (patients with MG-ADL 0–4), moderate MG (patients with MG-ADL 5–9) and severe MG (patients with MG-ADL 10 and above), and these outcomes are also compared with outcomes observed in the general population. The impairment in breathing, sleep disturbance, problems with fatigue, levels of pain/discomfort, loss of independence in daily living, and the (dis)ability to carry out work were all significantly related to the severity of the patient's MG. Furthermore, all outcomes were also significantly worse than those observed in the general population. Patients

suffering from mild MG also had markedly worse HRQoL than members from the general public. No relationship was found between MG severity and anxiety or depression, with similar mean scores across all severity categories, but all markedly higher than the mean score observed in the general population.

DISCUSSION

This direct comparison of physical and mental functioning between patients diagnosed with MG and the general population revealed a statistically significant and large impairment among patients with MG in all dimensions. The observed impairment in these areas is compatible with results from previous studies, which in all cases highlighted a similar magnitude of difficulties in physical functioning, mental health, and social discomfort [25–28].

Comparison with Published Literature

A review conducted by Lehnerer and colleagues on the burden that people diagnosed with MG experience revealed that patients' most bothersome symptoms were blurry/double vision, breathing difficulties, all-over fatigue, and swallowing problems [27]. Furthermore, published literature showed that many of the

Table 6 Comparison of mental health problems between respondents of MRW and the general population

Instrument/subdomain	MRW	POPUP	P value
HADS	N = 1159	N = 9000	
HADS-Anxiety[a]			
Normal	6.7%	63.6%	< 0.0001
Mild	23.6%	16.1%	
Moderate	47.7%	10.9%	
Severe	21.9%	9.4%	
Mean (SD)	11.5 (2.4)	6.4 (4.6)	< 0.0001
HADS-Depression[a]			
Normal	24.2%	84.0%	< 0.0001
Mild	57.3%	9.2%	
Moderate	16.9%	4.2%	
Severe	1.6%	2.7%	
Mean (SD)	8.9 (2.0)	5.0 (4.1)	< 0.0001
EQ-5D-5L	N = 1299	N = 9000	
Anxiety/Depression			
I am not anxious or depressed	42.5%	57.5%	< 0.0001
I am slightly anxious or depressed	34.6%	25.4%	
I am moderately anxious or depressed	18.6%	11.5%	
I am severely anxious or depressed	3.3%	3.8%	
I am extremely anxious or depressed	1.1%	1.9%	
Mean (SD)	1.9 (0.9)	1.7 (0.9)	< 0.0001
EQ-5D-5L: bolt on	N = 1299	N = 9000	
Self-confidence			
I have no problems with self-confidence	44.7%	66.8%	< 0.0001
I have slight problems with self-confidence	30.4%	18.7%	
I have moderate problems with self-confidence	16.7%	9.4%	
I have severe problems with self-confidence	6.6%	3.5%	
I have extreme problems with self-confidence	1.6%	1.6%	
Mean (SD)	1.9 (1)	1.5 (0.9)	< 0.0001

Table 6 continued

Instrument/subdomain	MRW	POPUP	*P* value
HUI-3	*N* = 540	*N* = 9000	
Emotion			
Happy and interested in life	25.0%	41.2%	< 0.0001
Somewhat happy	44.1%	39.1%	
Somewhat unhappy	21.7%	14.4%	
Very unhappy	6.7%	3.7%	
So unhappy that life is not worthwhile	2.6%	1.7%	
Mean (SD)	2.2 (1)	1.9 (0.9)	< 0.0001
MG-QoL-15r	*N* = 1117	*N* = 9000	
I feel frustrated			
Not at all	23.5%	52.5%	< 0.0001
Somewhat	52.3%	38.2%	
Very much	24.2%	9.3%	
Mean (SD)	1.0 (0.7)	0.6 (0.6)	< 0.0001
I am depressed			
Not at all	43.7%	66.6%	< 0.0001
Somewhat	45.0%	25.7%	
Very much	11.3%	7.7%	
Mean (SD)	0.7 (0.7)	0.4 (0.6)	< 0.0001
I feel overwhelmed			
Not at all	44.4%	70.0%	< 0.0001
Somewhat	42.3%	22.4%	
Very much	13.3%	7.6%	
Mean (SD)	0.7 (0.7)	0.4 (0.6)	< 0.0001

[a]Scores of 0–7 represent "normal" levels of anxiety or depression; scores of 8–10 represent "borderline"; and mean total scores of 11 or more on indicate a "significant case of psychological morbidity"

Table 7 Comparison of problems with pain/discomfort between respondents of MRW and the general population

Instrument/domain	MRW	POPUP	*P* value
EQ-5D-5L: Pain/Discomfort	*N* = 1299	*N* = 9000	
I have no pain or discomfort	29.2%	47.5%	< 0.0001
I have slight pain or discomfort	39.4%	33.3%	
I have moderate pain or discomfort	24.2%	13.7%	
I have severe pain or discomfort	6.5%	4.4%	
I have extreme pain or discomfort	0.8%	1.1%	
Mean (SD)	2.1 (0.9)	1.8 (0.9)	< 0.0001
HUI-3: Pain or Discomfort	*N* = 540	*N* = 9000	
Free of pain and discomfort	15.2%	45.0%	< 0.0001
Mild to moderate pain or discomfort that prevented no activities	31.1%	38.2%	
Moderate pain or discomfort that prevented some activities	37.0%	11.1%	
Moderate to severe pain or discomfort that prevented some activities	11.7%	4.1%	
Severe pain or discomfort that prevented most activities	5.0%	1.7%	
Mean (SD)	2.6 (1.0)	1.8 (0.9)	< 0.0001

symptoms were connected and have an impact on several aspects of daily life.

In our study, respondents reported significant *breathing* problems with a frequency that is consistent with previous research [27]. Breathing problems were also reported to be among the most bothersome symptoms in a recent qualitative study [29], and were found to be connected to *sleeping* difficulties in another study [30]. Indeed, many MG respondents in our MRW study reported a markedly higher prevalence of sleeping problems and with fatigue compared to the general population, with frequencies in line with previous research [31–33], and we observed moderate to strong associations between these dimensions. Other studies [34] found lower correlations between fatigue and sleep among people diagnosed with MG. Importantly, *fatigue* should be considered independently from muscle weakness according to a paper on physical and mental fatigue in patients with MG [32]. Jackson et al. connected

muscle fatigue/physical functioning with patients' ability to participate or perform activities of daily living [29]. Our results indicated that patients experienced a variety of problems with usual activities, with a regularity that is considerably higher than the general population. Moreover, we observed multiple significant strong associations between fatigue and activities of daily living such as social activities, homework, hobbies, and employment. The study performed by Jackson et al. furthermore observed that the inability to participate in hobbies, sports, or work also led to financial problems and had a large emotional impact [29]. Fatigue has been associated with emotions and depression in several studies [31, 32]. We also observed strong associations between feeling fatigued and feeling overwhelmed and frustrated, but no strong associations with anxiety or depression. A study on mental health in patients with MG by Marbin et al. observed symptoms of moderate to severe depression in

Table 8 Comparison of problems with usual activities between respondents of MRW and the general population

Instrument/domain	MRW	POPUP	*P* value
EQ-5D-5L: Usual activities	*N* = 1299	*N* = 9000	
I have no problems doing my usual activities	29.1%	76.6%	< 0.0001
I have slight problems doing my usual activities	36.0%	14.4%	
I have moderate problems doing my usual activities	26.5%	6.2%	
I have severe problems doing my usual activities	6.1%	2.2%	
I am unable to do my usual activities	2.3%	0.6%	
Mean (SD)	2.2 (1.0)	1.3 (1.4)	< 0.0001
EQ-5D-5L bolt on: Social relations	*N* = 1299	*N* = 9000	
I have no problems with social relationships	55.2%	53.9%	0.0006
I have slight problems with social relationships	23.7%	25.7%	
I have moderate problems with social relationships	14.2%	12.5%	
I have severe problems with social relationships	5.5%	5.3%	
I have extreme problems with social relationships	1.4%	2.7%	
Mean (SD)	1.7 (1.0)	1.8 (1.0)	0.0004
MG-QoL-15r (mean, SD) and frequency	*N* = 1177	*N* = 9000	
I have limited my social activity	1.0 (0.8)	0.8 (0.8)	< 0.0001
Not at all	30.1%	46.0%	< 0.0001
Somewhat	41.6%	31.8%	
Very much	28.3%	22.2%	
I am limited in my ability to enjoy hobbies and fun activities	1.1 (0.7)	0.5 (0.7)	< 0.0001
Not at all	19.9%	61.5%	< 0.0001
Somewhat	46.4%	26.4%	
Very much	33.7%	12.2%	
I have trouble meeting the needs of my family	0.8 (0.8)	0.3 (0.5)	< 0.0001
Not at all	39.9%	78.1%	< 0.0001
Somewhat	39.5%	16.4%	
Very much	20.6%	5.6%	
I have to make plans around an illness or condition that I suffer from	1.2 (0.7)	0.3 (0.6)	< 0.0001
Not at all	15.7%	74.6%	< 0.0001
Somewhat	44.3%	17.8%	
Very much	40.0%	7.6%	

Table 8 continued

Instrument/domain	MRW	POPUP	P value
I am bothered by limitations in performing my work/housework	1.2 (0.7)	0.3 (0.6)	< 0.0001
Not at all	19.6%	75.1%	< 0.0001
Somewhat	42.0%	18.1%	
Very much	38.4%	6.9%	
I have lost some personal independence (e.g., driving, shopping, running errands)	0.8 (0.8)	0.3 (0.6)	< 0.0001
Not at all	40.4%	83.6%	< 0.0001
Somewhat	35.7%	11.6%	
Very much	23.9%	4.8%	

15.1% and moderate to severe anxiety disorder in 15.6% using the HADS questionnaire [35]. In our study, we corroborate the depression result (18%); however, 70% of patients in MRW experienced symptoms of moderate to severe anxiety which is markedly higher. The data from the Marbin study were collected in 2017 before the COVID period started, whereas the MRW baseline data were collected in 2020 and 2021, in the middle of the coronavirus pandemic. This pandemic led to higher levels of anxiety in the general population [36], and perhaps to an even greater extent in the MG population. The discontinuation of medical follow-up of patients and the reduced availability of ventilators during the coronavirus crisis might be contributing factors to the feelings of anxiety among people suffering from MG. Mental health scores of people suffering from MG have been consistently lower compared to the general population, using several instruments [27, 29, 31, 32], which is in line with our observations. However, we did not find any strong associations between the mental health dimensions and all other dimensions including sleeping, fatigue, breathing, and usual activities.

Effect of Disease Severity

Although the HRQoL of individuals diagnosed with MG was lower than the general population on almost all instruments and dimensions, we found that the magnitude of this difference was largely impacted by the severity of the disease. This finding was confirmed in other studies showing associations between MG severity and MG-QoL-15r scores, quality of life scores, and employment status [35, 37]. An exception to this finding was mental health for which we did not find an association with disease severity. This is in contrast with a systematic literature review conducted by Gelinas et al. on the humanistic burden of MG, who reported that patients with more severe symptoms and longer hospital stays experienced significantly more depression and anxiety [31]. It is unclear why our study did not replicate those results.

Recommendations on Healthcare Policy

It has been established in this paper and in previous research [27] that the HRQoL of people diagnosed with MG is significantly lower compared to the general population. This is the result of MG impacting not only health-related quality of life but also affecting other dimensions of quality of life, such as social, emotional, and economic aspects [27]. Many of these aspects are connected to each other and reinforce each other [29, 30, 32, 33]. Therefore, healthcare policy should not solely focus on improving common MG symptoms caused by muscle weakness but also consider the impact of these symptoms on all facets of patients' daily lives.

The detection and treatment of anxiety and depression should be an important element in

Table 9 Comparison of outcomes by disease severity

Instrument/domain	Mild MG[a]	Moderate MG[a]	Severe MG[a]	General population	*P* value for differences between MG categories
Breathing/Dyspnea	*N* = 132	*N* = 124	*N* = 62	*N* = 126	*N* = 318
PROMIS-Dyspnea: General shortness of breath, mean (SD)	1.9 (2.3)	3.2 (2.4)	4.9 (2.2)	0.0 (0.7)	< 0.0001
Fatigue	*N* = 133	*N* = 125	*N* = 60	*N* = 2576	*N* = 318
FACIT-Fatigue scale, mean (SD)	35.5 (10.1)	26.9 (9.8)	19.2 (8.7)	43.5 (8.3)	< 0.0001
Sleep disturbance	*N* = 134	*N* = 125	*N* = 60		*N* = 319
PROMIS-Sleep Disturbance, mean (SD)	51.2 (7.9)	54.2 (7.6)	57.2 (7.6)	50.0 (10.0)	< 0.0001
HADS-Anxiety	*N* = 443	*N* = 442	*N* = 215	*N* = 9000	*N* = 1100
Normal	2.7%	8.8%	7.9%	63.6%	< 0.0001
Mild	17.4%	26.7%	28.8%	16.1%	
Moderate	51.0%	45.0%	47.4%	10.9%	
Severe	28.9%	19.5%	15.8%	9.4%	
Score, mean (SD)	12.1 (2.2)	11.2 (2.5)	11.1 (2.3)	6.4 (4.6)	< 0.0001
HADS-Depression	*N* = 443	*N* = 442	*N* = 215	*N* = 9000	*N* = 1100
Normal	17.4%	27.4%	30.7%	84.0%	0.043
Mild	65.5%	56.6%	43.7%	9.2%	
Moderate	16.3%	13.8%	24.2%	4.2%	
Severe	0.9%	2.3%	1.4%	2.7%	
Score, mean (SD)	9.1 (1.7)	8.7 (2.0)	8.9 (2.3)	5 (4.1)	0.020
HUI-3: pain/discomfort	*N* = 222	*N* = 194	*N* = 104	*N* = 9000	*N* = 520
Free of pain and discomfort	26.1%	9.3%	3.9%	45.0%	< 0.0001
Mild to moderate pain or discomfort that prevented no activities	45.1%	26.3%	13.5%	38.2%	
Moderate pain or discomfort that prevented some activities	21.6%	49.5%	43.3%	11.1%	
Moderate to severe pain or discomfort that prevented some activities	6.3%	11.9%	23.1%	4.1%	
Severe pain or discomfort that prevented most activities	0.9%	3.1%	16.4%	1.7%	
Mean (SD)	2.1 (0.9)	2.7 (0.9)	3.4 (1.0)	1.8 (0.9)	< 0.0001

Table 9 continued

Instrument/domain	Mild MG[a]	Moderate MG[a]	Severe MG[a]	General population	P value for differences between MG categories
I am bothered by limitations in performing my work (including work at home)	N = 456	N = 445	N = 218	N = 9000	N = 1119
Not at all	39.0%	8.1%	3.2%	75.1%	< 0.0001
Somewhat	47.2%	43.8%	28.4%	18.1%	
Very much	13.8%	48.1%	68.4%	6.9%	
Score, mean (SD)	0.8 (0.7)	1.4 (0.6)	1.7 (0.5)	0.3 (0.6)	< 0.0001
I have lost some personal independence (e.g., driving, shopping, running errands)	N = 456	N = 445	N = 218	N = 9000	N = 1119
Not at all	66.0%	28.5%	11.0%	83.6%	< 0.0001
Somewhat	28.3%	44.5%	34.9%	11.6%	
Very much	5.7%	27.0%	54.1%	4.8%	
Score mean (SD)	0.4 (0.6)	1.0 (0.8)	1.4 (0.7)	0.3 (0.6)	< 0.0001

[a]Mild MG, MG-ADL total score 0–4; moderate MG, MG-ADL total score 5–9; severe MG, MG-ADL total score $\geq$ 10

MG care [32], as these mood disorders are frequently reported among patients with MG [35]. Fatigue was previously found to be associated with the patient's tendency to perform usual activities [29], which in turn also affects patient's overall HRQoL. Our study confirms the finding that fatigue has a strong connection with the patient's ability or inclination to perform usual activities, and between usual activities and feeling of frustration, feeling overwhelmed, and social relationships. The routine use of screening tools for mental health conditions in specialized MG care centers has been recommended before [35] and is also supported by our evidence.

Previous evidence has also suggested that many patients with MG may benefit from respiratory physiotherapy to alleviate symptoms of dyspnea [38]. Furthermore, breathing was found to be moderately to strongly connected to fatigue and sleep in our study, together with a higher frequency of reporting these problems.

Likewise, connections between sleeping and breathing were found elsewhere [30]. This high frequency of problems and their interrelationships are supportive evidence for encouraging respiratory physiotherapy in patients with dyspnea, as this may also be beneficial for improving patients' fatigue and insomnia.

Many patients reported high levels of dissatisfaction with their current symptom level [39], and this is not surprising given the evidence we found in our study. Neurologists should be aware that patients' frustration with their HRQoL may persevere even if MG is considered well treated from a neurologist's perspective [40]. The importance of a patient-centered approach to MG treatment seems to be crucial in optimizing patient satisfaction and hence their HRQoL [39]. New therapies must achieve improvements for patients not only in physical functioning caused by muscle weakness but also in other dimensions of HRQoL such as fatigue, sleep, and mental health as this

will have a positive spillover effect to other dimensions of quality of life.

Limitations

The presence of selection bias cannot be excluded in digital studies, even though care was taken to minimize this bias by allowing a large and diverse patient population to enroll in the MRW study. Access to the internet and a smartphone device were necessary to enroll in MRW, and only patients who were in contact with PAGs and social media were made aware of the study; therefore, it is likely that more proactive patients were overrepresented. On the other hand, patients with (severe) ocular problems might be underrepresented as the regular use of a smartphone was needed to enter data. In MRW, the study population has a higher proportion of female participants compared to other MG-specific cohorts [25, 41–45], which might have affected results as QoL in women has been documented to be lower than men in several studies [46]. Furthermore, the high proportion of anxiety in this patient population might also have an impact on the participation in this study. In addition, although the sample size of the entire study was high, the sample sizes available for the instruments differed significantly. This was in part due to the administration schedule (not every instrument was administered every month), but it is likely that the symptom severity might have had an influence on the instrument-specific completions. The MRW sample also consisted of people from Japan which was not a country included in the POPUP study. Given the different life philosophy in that country compared to Western European and North American countries, with a different attitude towards enduring difficulties and diseases, this might have biased HRQoL results. The effect of the Japanese ethos is, however, limited given that Japanese patients comprised only 6.5% of the MRW sample, with 38% Italian patients and 31% from the USA.

In POPUP, selection bias was minimized by stratifying recruitment from the general population on age, gender, education, and region; however, it is unclear whether participants from online panels differ from the general population and how this may impact HRQoL values. Potential participants in POPUP were offered a small compensation in points that can be exchanged for gifts for example, which could have encouraged more people with a lower socioeconomic status to participate [47].

Further limitations of our analysis are that some of the dimensions from the instruments administered are combined dimensions and it is difficult to interpret these results. For example, the pain/discomfort dimension of the EQ-5D-5L is often abbreviated to the pain interpretation; however, neurologists specialized in MG are indicating this might be more likely discomfort (e.g., eyelid droop, swallowing problems, problems with speech, etc.) than pain.

CONCLUSION

This direct comparison of the HRQoL in patients with MG and the general population using two international studies in large populations revealed a high burden in all dimensions of health and HRQoL. Patients with MG experience more problems in physical and mental health, in their activities of daily living, and in their social and working relationships. All these findings were consistent across all available items and PROMs that were relevant for each HRQoL dimension that was investigated.

Furthermore, problems in one dimension were often associated with problems in other dimensions. In particular, experiencing (physical) fatigue was associated with problems with sleeping, breathing, performing usual activities (house work, hobbies, employment, fun activities), loss of personal independence, difficulties in maintaining social relationships, with emotions of frustration, feeling overwhelmed, and with self-confidence. This study also demonstrated that all HRQoL dimensions worsened with more severe disease. One exception was mental health, and particularly moderate to severe anxiety, which was experience by a majority people suffering from MG.

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Declarations

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