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ORIGINAL RESEARCH

People Diagnosed with Myasthenia Gravis have Lower health-related quality of life and Need More Medical and Caregiver Help in Comparison to the General Population: Analysis of Two Observational Studies

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ABSTRACT

Introduction: Myasthenia gravis (MG) is a neuromuscular disease causing extreme muscular fatigue, triggering problems with vision, swallowing, speech, mobility, dexterity, and breathing. This analysis intended to estimate the health-related quality-of-life impact, the medical burden, and the need for caregiver help of people diagnosed with MG.

Methods: MyRealWorld-MG (MRW) is an observational study among adults diagnosed with MG in 9 countries. The General Population Norms (POPUP) observational study enrolled representative members of the general population in 8 countries. In both digital studies, respondents entered personal characteristics and provided data on medical conditions, EQ-5D-5L, HUI3, MG-Activities of Daily Living (MG-ADL), sick leave, caregiver help, and medical care utilization.

Results: In MRW ($n = 1859$), 58.4% of respondents had moderate-to-severe MG. Average utility values were lower in MRW versus POPUP (0.739 vs. 0.843 for EQ-5D-5L; 0.493 vs. 0.746 for HUI3), and declined with more severe disease (0.872, 0.707, 0.511 EQ-5D-5L utilities and 0.695, 0.443, 0.168 HUI3 utilities for mild, moderate, and severe MG, respectively). Taking sick leave in the past month was 2.6 times more frequent among people diagnosed with MG compared to the general population (34.4% vs. 13.2%) and four times more people diagnosed with MG reported needing help from a caregiver (34.8% vs. 8.3%). Use of medical care was twice as likely in MRW in comparison with POPUP (51.9% vs. 24.6%).

Conclusion: This direct comparison of people diagnosed with MG and the general population using two large international studies revealed significant negative impact of MG. Results were consistent across all outcomes, in all countries.

Keywords: Myasthenia Gravis; Health-related quality of life; HRQoL; HUI3; EQ-5D-5L; Burden; Unmet need; Utility; MG-ADL; Caregiver

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Key Summary Points

Utility values in people diagnosed with myasthenia gravis (MG) are lower than in the general population, and also decline with more severe disease.

People diagnosed with MG have to take 2.6 times more sick leave than members of the general population, and three times more people suffering from MG are unable to work at all due to their illness.

Four times more people diagnosed with MG reported needing regular help from a caregiver.

Utilization of medical care (including hospitalizations, visits to A&E, visits to specialists) was twice as likely in MG patients compared to the general population.

INTRODUCTION

Myasthenia gravis (MG) is a rare, chronic, autoimmune condition causing disrupted communication between the central nervous system and muscles. This results in weakness of the skeletal muscles of the body and both voluntary and involuntary ocular, respiratory, and bulbar muscles. MG usually first affects ocular muscles, causing ptosis and diplopia. The development of generalized MG, whereby also bulbar, limb, and respiratory muscles are affected, occurs in up to 80% of people diagnosed with MG, usually within 2 years of disease onset [1–3]. This may cause problems with swallowing, speech, breathing, dexterity, and mobility. Moreover, 15–20% of people diagnosed with MG experience at least one myasthenic crisis during their lifetime [4], whereby respiratory failure may cause a life-threatening situation often requiring intubation and mechanical ventilation [5]. Besides physical impairments, a high prevalence of mental disorders such as anxiety and depression has been found in MG [6].

Due to the unpredictable manifestation of the disease, the variable nature and severity of symptoms [7], and the poor prognosis of generalized MG [8], the development of MG needs to be closely monitored. Several MG-specific patient-reported outcome measures (PROMs) have been validated for this purpose, such as the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, which assesses patients' functional status and symptom burden. Moreover, MG-specific PROMs are preferred as primary outcomes in clinical trials, as objective assessments might not reflect the patient-perceived symptom burden accurately [9]. In addition to disease specific measures, standardized generic PROMs are often used in clinical research to provide a multi-perspective assessment [10], and to ensure responsiveness and comparability across populations [11]. Generic PROMs such as the EuroQol five-dimensions (EQ-5D) questionnaire and the Health Utilities Index mark 3 (HUI 3) are instruments that may be used to quantify the effect of any disease on respondents' health-related quality of life (HRQoL).

Several studies have demonstrated that the MG patient population has impaired HRQoL in comparison to the general population, as multiple facets of life are being affected by their disease [12, 13]. However, it has not been well documented whether these HRQoL impairments are related to more severe disease. The development of new treatments, such as efgartigimod [14] and ravulizumab [15], has shown to improve the HRQoL of people diagnosed with generalized MG. However, more detailed assessment of HRQoL is required to make sure that findings can be generalized across studies [13].

This study aims to compare the HRQoL of people diagnosed with mild MG compared to moderately and severely affected patients, and of people diagnosed with MG compared to the general population, to document the burden that people diagnosed with MG experience.

METHODS

Datasets

Two observational, digital, international studies have been conducted among members of the general population diagnosed with MG: (1) the General Population Norms study (POPUP), and (2) the MyRealWorld-MG study (MRW). Sample sizes in both studies were not based on formal calculation but driven by the aim of representativity for the general population and by feasibility for MRW.

POPUP is a multinational digital study recruiting 9000 members of the general public in eight countries (US, Canada, UK, Italy, Spain, Germany, The Netherlands, and Belgium). The main objective of this study was to document international generic HRQoL population norms, which can be used as a baseline against which outcomes of patients with a particular disease can be compared to quantify their disease burden [16]. Additionally, data specific to MG was collected to serve as a comparator on the MG measures used in MRW. In all eight countries, samples were interlaced drawn from representative panels operated by market research companies based on previously agreed variables (age, gender, education, and region). Stepped random sampling methods and propensity weighting were used to ensure that participants with a variety of profiles were enrolled in the study. Potential participants were invited via e-mail and were offered points for completing the online survey, which could later be converted into a selection of gifts. Data used in this analysis concern only the baseline data collected in January–March 2021; data from a second wave of data collection (Q1 2023) were not included.

MRW is a digital, prospective, observational, longitudinal multi-country study, conducted among 1859 adults diagnosed with MG from nine countries (US, UK, Canada, Italy, Germany, Spain, France, Denmark and Japan; data cut July 2022). The objective of this study was to provide a comprehensive real-world, long-term view of the impact of MG in a large, diverse cohort of people diagnosed with MG from their perspective. Patients were informed about the study via clinical centers and patient advocacy groups (PAGs). Patients could register themselves online, after which they entered disease characteristics (diagnosis, disease duration, antibody status, treatments received), and monthly data on their experience of living with MG over a 2-year period, using a smartphone application designed by Vitacces Ltd. More detailed information on the rationale and design of the study is available in the study protocol, published in 2019 [17]; the analysis presented here uses baseline data from when the patients joined the study.

Outcome Measures Collected in Both Studies

In addition to basic demographics, such as age, gender, and country, participants were asked about their living situation (living alone, living with family, in a nursing home) and their need of help from a caregiver in their daily activities. Furthermore, participants were prompted to report any existing comorbidities and side-effects of medication they are taking, and to provide the number of health care visits during the past month (nurse, general practitioner, specialist, physiotherapist, ER visit, hospital admissions). The frequency and duration of sick leave in the past month was also documented. HRQoL data were collected using the EQ-5D-5L and the HUI 3, and the most frequently used outcome measure in MG, the MG-ADL, was also administered. Licenses for all PROMs were obtained in all appropriate languages.

EQ-5D-5L

The EQ-5D-5L is a generic instrument to measure HRQoL and consists of a descriptive system assessing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is described in a single item with five severity levels ranging from “having no problems” to “having extreme problems” [18]. The results of the EQ-5D-5L questionnaire can be converted into preference-based quality weights (utility values) on a scale

anchored at 1 (full health) and 0 (for a state as bad as being dead), allowing for negative values for states considered worse than dead. Besides the descriptive system, the questionnaire includes a health thermometer, visual analogue scale (EQ VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health) on which respondents rate their overall health on the day of completion [18]. For the calculation of EQ-5D-5L utility values in POPUP, the country-specific value sets [19–30] were applied to the respondents from each corresponding country. Utility values for the MRW sample were calculated by applying the country-specific value sets to the whole patient population, as sample sizes were insufficient in most countries.

HUI 3

The Health Utilities Index (HUI 3) is a generic, preference-based, comprehensive system for measuring respondents' current health status on eight dimensions of health: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each level is described with five or six levels of ability/disability [31, 32]. HUI 3 responses can also be summarized into utility values which have good agreement with EQ-5D utilities, but are not interchangeable [33]. The Canadian value set was applied to all data from POPUP and MRW as this is the only available value set to transform the HUI 3 responses to utility values.

MG-ADL

The MG-ADL is an MG-specific symptom scale with eight items (talking, chewing, swallowing, breathing, brushing teeth and combing hair, rising from a chair, double vision, and eyelid droop) across four domains (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, with higher scores implying more severe disease) indicating the total symptom burden [34, 35]. In this study, a total MG-ADL score of 0–4 was considered mild, 5–9 moderate, and 10 or higher severe. These cut-offs were established based on input from neurologists and inclusion criteria from clinical trials, where a score of 5 and above was used to classify patients as moderate-to-severe, and are currently being utilized in multiple publications and analyses [36, 37]. The MG-ADL scale was originally designed for clinical settings to be completed by a neurologist while examining his/her patient. A dedicated study on the concordance between direct self-assessment (by the patient) and the proxy-assessment (by the neurologist) indicated excellent concordance between the two assessment approaches [38]. Applying that study's results to this research, the patient-reported MG-ADL can be considered a reliable estimation of the patient's symptom burden.

Ethical statement

Ethical approval was obtained in all countries for both studies from Salus IRB (US, UK, Germany, Netherlands, Denmark), CPP (France), KULeuven (Belgium), Veritas IRB (Canada), local ethical approval (Spain, Italy), and MINS-IRB (Japan) [17], and the authors received permission to access the data. Informed consent to collect data and to analyze and report anonymzed and aggregate data was obtained from all participants from both studies. The study was performed in accordance with the Declaration of Helsinki.

Statistical analysis

Data from both studies were compared using descriptive analyses. In POPUP, all data were complete and there were no missing data. In MRW, all analyses are based on all available data, no data were imputed, nor were any observations deleted from the analysis. For categorical variables, the proportions for each level were presented; for continuous variables, the mean, standard deviation (SD), and the 25% and 75% percentiles are shown. Visually, distributions were compared with a box plot, a histogram, or with Kernel densities. Statistical testing for differences between the populations or between severity groups in MG-ADL score

was carried out with a generalized estimating equation model, with a normal distribution and an identity link. Testing for differences in utility values (based on the EQ-5D-5L or the HUI-s descriptive system) was carried out using a transformation of the dependent variable: the utility was transformed into a utility complement (= 1-utility) in order to obtain a right-skewed distribution which is more amenable to statistical modeling. In those models, an identity link and a normal distributions were used. Testing for differences in proportions needing a caregiver, taking time off sick, and needing medical care during the past month between the general population and people diagnosed with MG was carried out with a chi-square test.

RESULTS

Patient Characteristics

POPUP enrolled 9000 members of the general public, whereas the MRW study enrolled 2074 people diagnosed with MG (Table 1). Among the people diagnosed with MG, 11.6% had ocular disease, 35.0% had generalized disease, and 53.4% had both ocular and generalized MG at baseline. Furthermore, 43.4% had received a thymectomy in the past, 59.0% were AChR antibody-positive, and 5.6% were MUSK antibody-positive. The mean disease duration was 9.3 years (SD 9.9 years). About 86.2% of patients were treated at baseline, and received as current treatments: 75.6% anti-chollinergics, 43.3% cortico-steroids, 19.7% azathioprine, 14.7% mycophenolate, 3.4% ciclosporine, 6.7% tacrolimus, 1.6% methotrexate, 4.4% eculizumab, 4.5% rituximab, and 3.7% plasma exchange.

In the comparison between the two populations, POPUP has a more equal gender distribution (51.2% female) than MRW (68.8%). Just over half (55.9%) of people diagnosed with MG are able to live independently, compared to 70.5% of respondents in the general population sample. Results from the EQ VAS show that people diagnosed with MG rated their own health on average 14 points lower than the general population. The most frequently occurring co-morbidities among people diagnosed with MG are thyroid problems, anxiety, depression, and respiratory problems (Supplementary Table S1). Furthermore, these patients suffered markedly more often from

Table 1 Respondent characteristics in POPUP and MRW

		POPUP $n = 9000$	MRW $n = 2074$
MG-ADL	Mild: 0–4	93.6%	41.7%
	Moderate: 5–9	3.5%	39.6%
	Severe: 10 and over	2.9%	18.7%
Gender	Female	51.2%	68.8%
	Male	48.8%	31.2%
Age category	18–34	27.6%	17.0%
	35–54	36.9%	44.6%
	55 +	35.5%	38.4%
Age	Mean (SD)	47.1 (15.5)	49.9 (14.8)
Living situation	At home without help from a caregiver	70.5%	55.9%
	At home with help from a caregiver	3.1%	6.4%
	With a family member	26.0%	37.2%
	In a nursing home	0.3%	0.1%
	In a long-term care rehabilitation facility	0.1%	0.4%
EQ VAS	Mean	75.7	61.7
	SD	17.4	22.1
	Q1	69	48
	Median	80	65
	Q3	90	80

MG Myasthenia gravis, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *VAS* Visual Analogue Scale, *SD* standard deviation, *Q1, Q3* first, third quartile, *POPUP* General Population Norms Study dataset, *MRW* MyRealWorld-MG study dataset

respiratory disease, osteoporosis, and thyroid problems/disorder than the general population.

MG-ADL

Within the MRW patient population, 41.7% had mild MG, 39.6% had moderate disease, and 18.7% suffered from severe MG at baseline. MRW respondents had a mean total MG-ADL score of 5.8, which was strongly contrasting with the 1.2 mean score of the general population sample from POPUP ($p < 0.0001$, Fig. 1), in which only 3.5% of respondents approximated the symptom burden of moderate MG and 2.9% of severe MG. The POPUP respondents who had the symptom burden of moderate to severe MG were mostly younger males, living in the US and were in need of a caregiver.

Underpinning the difference in total MG-ADL score between the populations are marked differences on all 8 items. The proportion of patients in MRW reporting problems across all dimensions accumulates to 53%, whereas this was only 9% in the POPUP sample. For example, MRW patients experienced shortness of breath with exertion (51.0%) or at rest (10.7%) much more often than POPUP participants (19.9% and 2.8%, respectively) (Supplementary Table S2).

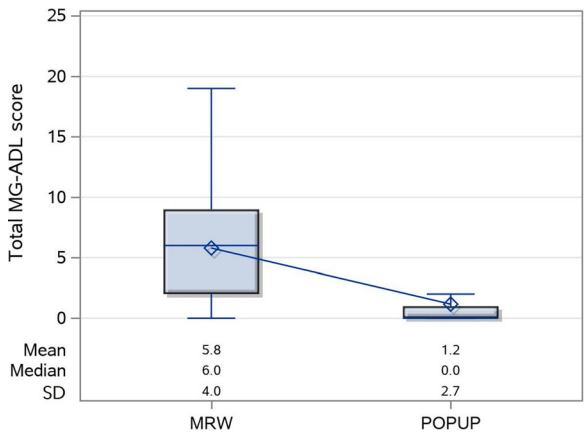


Fig. 1 Comparison of the distribution of the MG-ADL total score between respondents from MRW and POPUP. *MG-ADL* Myasthenia Gravis Activities of Daily Living scale, *MRW* MyRealWorld-MG dataset, *POPUP* General Population Norms Study dataset, *SD* standard deviation

EQ-5D-5L

People diagnosed with MG had significantly lower EQ-5D-5L utility values compared to the general population in all countries ($p < 0.001$; Table 2). Mean utility values were lowest in the UK and highest in Germany in both the general and the MG population. The utility difference between these two populations was the smallest in Germany (− 0.081), while the largest difference was found in the US (− 0.142). The proportion of participants with a utility value of 1 indicating "perfect health" was 32.7% in POPUP, whereas this was only 9.9% in MRW. The proportion of patients with a negative utility value was however fairly similar between MRW patients and POPUP participants, with 1.5% and 1% respectively.

Examination of EQ-5D utilities by MG-ADL classification categories showed a statistically significant and meaningful difference between people diagnosed with MG who carry a mild symptom burden versus those who are moderately or severely affected ($p < 0.001$). People diagnosed with mild MG had a mean EQ-5D-5L utility of 0.872, which is comparable to, and even higher than, the average general population respondents in the POPUP study (0.843). Moderately and severely affected patients scored on average 0.165 and 0.361 lower than mildly affected patients (Fig. 2).

Figure 3 displays the left-skewed distribution of utility values in the general population, with a density peak near full health. This is in contrasts to the utility distribution among people diagnosed with moderate-to-severe MG, which displays a low density at full health and a peak around 0.7, with a markedly larger tail towards negative utility values. In Fig. 4, Kernel densities by disease severity show the distribution of EQ-5D-5L utilities among patients suffering from mild, moderate and severe disease. People with mild MG have a similar utility distribution than members of the general public, but as the disease severity worsens the distribution is shifted to the left.

Table 2 EQ-5D-5L and HUI 3 utility values: comparison of the respondents from MRW and from POPUP

EQ-5D-5L	All	Belgium	Canada	Denmark	France	Germany	Italy	Netherlands	Spain	UK	US	Japan
MRW, n	1299		19	20	44	96	470		155	37	357	101
Mean	0.739		0.761	0.763	0.845	0.797	0.764		0.740	0.681	0.696	0.712
SD	0.233		0.182	0.233	0.182	0.208	0.236		0.203	0.221	0.256	0.166
Q1	0.643		0.700	0.687	0.824	0.747	0.707		0.643	0.580	0.574	0.618
Median	0.795		0.809	0.832	0.893	0.851	0.816		0.771	0.710	0.743	0.735
Q3	0.906		0.891	0.919	0.958	0.934	0.909		0.878	0.837	0.883	0.841
POPUP, n	9000	1000	1000			1000	1000	1000	1000	1000	2000	
Mean	0.843	0.834	0.846			0.878	0.866	0.821	0.846	0.799	0.838	
SD	0.202	0.203	0.184			0.189	0.202	0.210	0.184	0.213	0.220	
Q1	0.791	0.782	0.794			0.861	0.844	0.769	0.794	0.735	0.780	
Median	0.913	0.895	0.919			0.943	0.953	0.883	0.919	0.837	0.940	
Q3	1.000	1.000	1.000			1.000	1.000	1.000	1.000	1.000	1.000	
HUI 3	**All**	**Belgium**	**Canada**	**Denmark**	**France**	**Germany**	**Italy**	**Netherlands**	**Spain**	**UK**	**US**	**Japan**
MRW, n	540		11	7	44	52	158		59	7	157	45
Mean	0.493		0.439	0.709	0.564	0.498	0.594		0.459	0.509		0.495
SD	0.343		0.299	0.150	0.311	0.393	0.314		0.363	0.306	0.344	0.296
Q1	0.220		0.290	0.680	0.335	0.160	0.46		0.180	0.210	0.090	0.28
Median	0.565		0.380	0.760	0.635	0.585	0.645		0.480	0.590	0.370	0.52
Q3	0.790		0.710	0.780	0.830	0.845	0.85		0.740	0.780	0.640	0.67
POPUP, n	9000	1000	1000			1000	1000	1000	1000	1000	2000	
Mean	0.746	0.754	0.736			0.743	0.778	0.779	0.758	0.706	0.731	
SD	0.273	0.242	0.272			0.263	0.205	0.257	0.264	0.307	0.323	

Table 2 continued

HUI 3	All	Belgium	Canada	Denmark	France	Germany	Italy	Netherlands	Spain	UK	US	Japan
Q1	0.660	0.670	0.620			0.660	0.73	0.68	0.680	0.590	0.600	
Median	0.850	0.850	0.850			0.850	0.85	0.88	0.850	0.820	0.870	
Q3	0.930	0.920	0.950			0.920	0.93	0.97	0.930	0.920	0.970	

POPUP utilities are based on the separate country samples using the corresponding country-specific value sets, while utility values for MRW are derived by applying each country's value set to the entire MRW sample

POPUP General Population Norms Study dataset, *MRW* MyRealWorld-MG study dataset, *SD* standard deviation, *Q1*, *Q3* first, third quartile

HUI 3

Utilities based on the results of the HUI 3 survey confirmed that people diagnosed with MG experience statistically significant lower utility values (decrement of 0.253, $p < 0.001$) compared to the general population (Table 2). This difference was accumulated through all domains, but was especially noticeable in the comparative proportion of no problems with dexterity, ambulation, cognition, and pain (Supplementary Table S3). The proportion of participants with a utility of 1 (indicating "perfect health") was markedly lower in MRW (1.9%) compared to POPUP (11.8%). Conversely, the proportion of participants reporting negative utilities (a health state considered worse than death) was three times higher in MRW (9.3% vs. 3.6%).

The HUI 3 utilities also showed a significantly strong association with MG severity ($p < 0.001$), with declining utility values for people suffering from mild (0.695), moderate (0.443), and severe (0.168) MG (Fig. 2). The histogram of HUI 3 utilities shows a peak near 0.95 among the general population, whereas the distribution is much flatter and shifted towards the left for the people suffering from MG (Fig. 3). The HUI 3 instrument is also better at differentiating utility values between members of the general population and patients with mild MG (Fig. 4). The utility distribution for people diagnosed with moderate and severe disease is also situated to the left, indicating worse utilities experienced by these patients.

The correlation between the utilities based on the Canadian HUI 3 value set, and the EQ-5D utilities based on each respondent's country-specific dataset are strong and statistically significant: overall the correlation = 0.66 ($p < 0.0001$), and separately for each population the correlation = 0.65 in POPUP and correlation = 0.67 in MRW (both $p < 0.00021$).

Work Productivity Loss and Need for Caregiver

Sick leave was taken by 34.4% of people diagnosed with MG in the past month, which is

nearly three times more than the working or studying general population (13.2%, $p < 0.0001$), (Table 3). In addition, a higher proportion of respondents indicated not being able to work at all due to illness (16.8% vs. 4.8%, respectively, $p < 0.0001$).

One-third (34.8%) of people diagnosed with MG reported needing help from a caregiver with daily activities, in stark contrast to 8.3% in POPUP ($p < 0.0001$,Table 4). Caregivers were mostly family members or friends; fewer than 10% of caregivers for people diagnosed with MG were professionals. The number of hours of caregiver help did not differ between populations. The impact on the careers of caregivers of people diagnosed with MG was large however: more caregivers had to stop working, and almost two day's work was given up among the caregivers who decided to reduce their working hours.

Use of Medical Resources

The proportion of people diagnosed with MG that had any type of medical care visit in the past month was twice as large in comparison with the POPUP sample (51.9% vs. 24.6%, $p < 0.0001$; Table 5). In addition, people diagnosed with MG paid significantly more visits to specialist (0.834 vs. 0.184 visits) and the A&E department (0.110 vs. 0.013 visits). Both the hospitalization rate and the length of stay were high among people diagnosed with MG with 0.125 hospitalizations per month and an average of 9.4 days length of stay (LOS) in the general ward and 2.3 days in the ICU ward.

DISCUSSION

A review of MG from patients' perspectives concluded that patients with MG often have unmet (treatment) needs, and that high-quality studies into patient-centered needs are therefore necessary [39]. This study provided a comparison of the HRQoL between people diagnosed with MG and the general population. A considerable gap between the HRQoL of people diagnosed with MG was found in this direct comparison using multiple widely used generic and disease-specific PROMs. The observed impairment of HRQoL due to MG and the contrast with the general population is congruent with previous research, which in all cases highlighted a similar magnitude of impact accumulated through physical, mental, and social discomfort [12, 40–42].

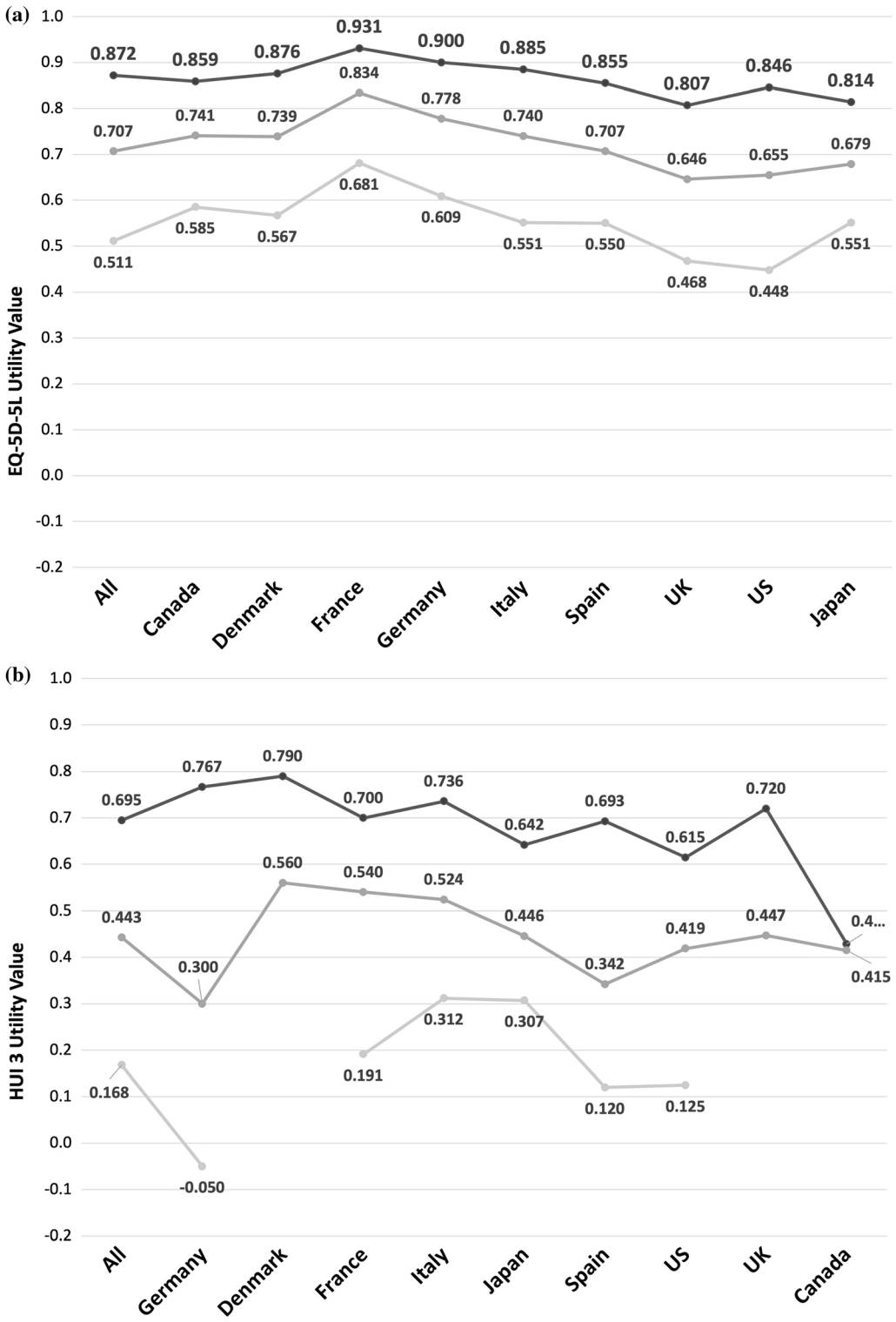
Age and Gender Adjustment

In comparison with the POPUP sample, the MRW sample consisted of a somewhat younger population and relatively fewer males, which is consistent with MG being more prevalent among females [2, 43]. We sought to determine whether this difference imposed a significant effect on our findings by adjusting the POPUP sample for the age and gender distribution of the MRW sample in a separate comparison. This adjustment only had a minor effect on the results; hence, we decided not to include the adjusted data in order to maintain the national representatives of the POPUP data. Besides, age- and gender-adjusted results of the POPUP study showed a (slightly) larger difference in outcomes, making the current estimates of unmet need in people diagnosed with MG conservative.

Comparison with Published Literature

The mean MG-ADL total scores in the MRW study is comparable to what was observed in other studies: 6.2 [41], 4.0 [12], 5.8 (for Generalized MG) [44], and is within the range of "Ever-refractory" (9.1) and "Nonrefractory" (5.1) [45].

Our study established that people diagnosed with MG had lower EQ-5D-5L utility values compared to the general population in all research countries. A recent systematic literature review [13] documenting the humanistic burden of MG included 4 studies (2009–2019) which reported EQ-5D utilities in people diagnosed with MG. Utilities observed among people diagnosed with MG were 0.626 ± 0.286 in one study [46]. Furthermore, Barnett et all (2018) [47] found in another study that the mean EQ-5D utility decreased with increasing


(a)
EQ-5D-5L Utility Value
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
0.872
0.859
0.876
0.931
0.900
0.885
0.855
0.807
0.846
0.814
0.707
0.741
0.739
0.834
0.778
0.740
0.707
0.646
0.655
0.679
0.511
0.585
0.567
0.681
0.609
0.551
0.550
0.468
0.448
0.551
All
Canada
Denmark
France
Germany
Italy
Spain
UK
US
Japan
(b)
HUI 3 Utility Value
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
0.695
0.767
0.790
0.700
0.736
0.642
0.693
0.615
0.720
0.443
0.300
0.560
0.540
0.524
0.446
0.342
0.419
0.447
0.4...
0.415
0.168
-0.050
0.191
0.312
0.307
0.120
0.125
All
Germany
Denmark
France
Italy
Japan
Spain
US
UK
Canada

◀**Fig. 2** Comparison of the EQ-5D-5L utility values (**a**) and HUI 3 utility values (**b**) by country and by disease severity. utility value calculations: the EQ-5D-5L utility values for *All* are derived by applying the country-specific value set to each respondent's responses and averaging across all respondents, while utility values for MRW are derived by applying each country's value set to the entire MRW sample. All HUI 3 utility values are derived by applying the Canadian value set. *MG-ADL* Myasthenia Gravis Activities of Daily Living scale, *EQ-5D-5L* EuroQoL 5 Dimensions and 5 levels per dimension, *HUI 3* Health Utilities Index, *POPUP* General Population Norms Study dataset, *MRW* MyRealWorld-MG study dataset

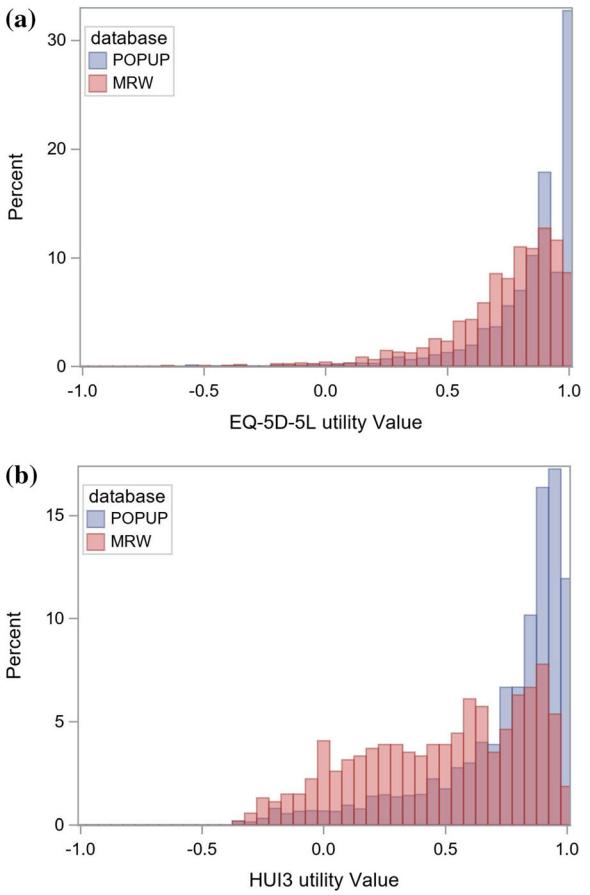


Fig. 3 The distribution of EQ-5D-5L utility values (**a**) and HUI 3 utility values (**b**) between MRW and POPUP. *EQ-5D-5L* EuroQoL 5 Dimensions and 5 levels per dimension, *HUI 3* Health Utilities Index, *MRW* MyRealWorld-MG dataset, *POPUP* General Population Norms Study Dataset

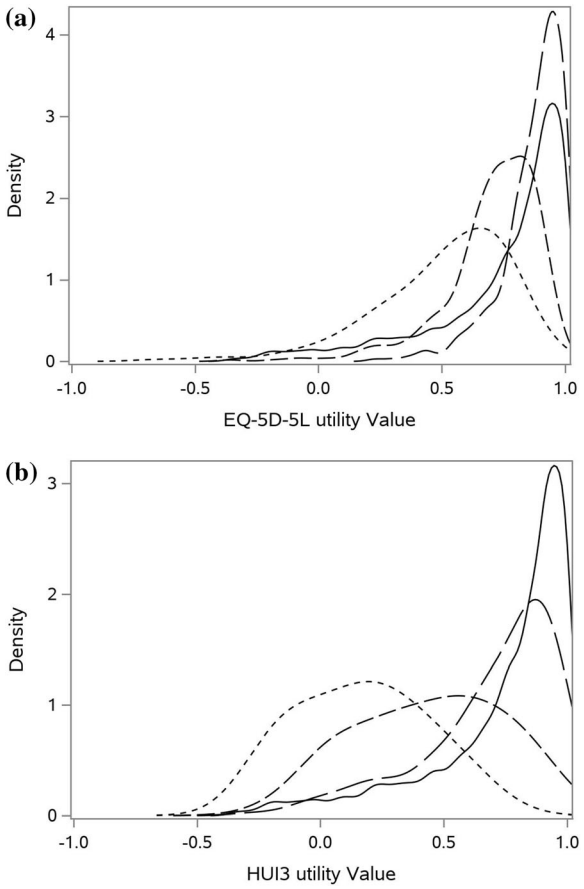


Fig. 4 Kernell density comparing the EQ-5D-5L utility values (**a**) and HUI 3 utility values (**b**) between patients of different severity from MRW and respondents from POPUP. *EQ-5D-5L* EuroQoL 5 Dimensions and 5 levels per dimension, *HUI 3* Health Utilities Index, *MRW* MyRealWorld-MG dataset, *POPUP* General Population Norms Study Dataset

(more severe) MGFA class: Class I, 0.89 ± 0.06, Class II, 0.78 ± 0.16, Class III, 0.58 ± 0.24, and Class IV, 0.61 ± 0.22. This is consistent with our results, which showed a declining gradient in utility values from mild to severe MG, however we observed a wider range of utilities, especially towards the lower end. Similarly to our study results, mean EQ VAS scores among people diagnosed with MG from previous studies were also found to be lower than the population norms we estimated based on POPUP: 53 ± 20 [46], 68 ± 20 [47], and 67.7 ± 19.4 [48] EQ VAS scores.

Table 3 Comparison of sick leave taken between respondents in MRW and POPUP

	POPUP *n* = 9000	MRW *n* = 1329
Sick leave		
% Did take time off work/studies in the past month due to illness	13.2%	34.4%
Mean number of days ± SD (range)	12.4 ± 11.5 (3–21)	14.7 ± 12 (3–30)
% Did not take time off work/studies in the past month due to illness	86.8%	65.6%
Of those		
Not been ill	79.9%	79.9%
Been ill but did not take any time off	9.6%	
Cannot work/study because of my illness	4.8%	16.8%
Other (e.g. retired, unemployed, housewife)	5.7%	3.3%

POPUP General Population Norms Study dataset, *MRW* MyRealWorld-MG study dataset, *SD* standard deviation

A smaller proportion of people diagnosed with MG (55.9%) reported to live independently compared to the general population (70.5%). The high level of dependency on others of people diagnosed with MG has also been established in previous research [12], reporting a high rate (86%) of patients living in a dependent partnership. Lehnerer et al. (2021) [12] investigated the lost productivity of MG, reporting that 72.6% of formerly working people diagnosed with MG experienced limitations regarding employment, of whom 45.8% had to stop working altogether. This is a markedly larger proportion than the 10.1% observed in the MRW study. This difference may partially be explained by the differences in severity distribution, in age, country of living, and perhaps in the proportion of patients with ocular problems. Our results are also lower than work productivity losses reported by Winter et al. [49], where a 40% unemployment rate due to MG was found, despite the fact that almost 90% of the people diagnosed with MG had MGFA Class I or II. A Danish cohort study investigating labor market participation and long-term sick leave among people diagnosed with MG found that MG increased the odds of unemployment with almost six times and sick leave with nine times within 2 years compared to the general population [50], a markedly larger impact than the threefold increase for both unemployment and sick leave established in our study. Furthermore, Boscoe et al. [51] did not report a significant difference between people diagnosed with refractory and nonrefractory MG regarding employment status, whereas in our study a much higher proportion of moderate-to-severe patients took sick leave or could not work in comparison to mild patients.

About one in three people diagnosed with MG reported needing a caregiver in the MRW study, which is similar to the findings of The Centre for International Economics (CIE) [52] investigating the cost of MG to patients and their community, reporting that one-third of people diagnosed with MG require their partner to be their primary caregiver.

Comparison of HRQoL with Other Neuromuscular Disorders (NMDs)

A systematic literature review comparing EQ-5D scores in chronic diseases with the general population concluded that patients with neurological disorders have the highest reduction in HRQoL [53]. This is consistent with other studies reporting markedly lower mean EQ-5D values than in our POPUP study (0.739) for patients with ALS (0.59 [54], 0.54 [49], and 0.55 [55]), multiple sclerosis (0.6 [56], 0.31 [57], 0.59 [58], 0.59 [59], 0.68 [60], and 0.78 [61]),

Table 4 The use of a caregiver compared between respondents in MRW and POPUP

	POPUP $n = 9000$	MRW $n = 1551$
Need help with regular activities from a caregiver		
Yes	8.3%	34.8%
Among those who have indicated they needed a caregiver		
Type of caregiver		
Family member/partner	75.9%	72.8%
Friend	14.1%	14.9%
Nurse or healthcare assistant	4.6%	6.8%
Other (e.g., housecleaner, colleague, neighbor)	5.4%	5.5%
Hours of help needed per week		
0–7	41.6%	45.3%
8–14	32.5%	27.0%
15–49	19.0%	19.0%
50 +	6.9%	8.7%
Impact on the caregiver's life		
Had to stop work	14.5%	17.0%
Had to cut down work	23.2%	16.1%
Average hours cut down per week (SD)	3.4 (2.3)	13 (7.5)
Emotional impact	31.0%	73.9%
Tiredness	23.1%	66.1%
Other	9.6%	11.9%
Unknown	13.9%	7.3%

POPUP General Population Norms Study dataset, *MRW* MyRealWorld-MG study dataset, *SD* standard deviation

Duchenne muscular dystrophy (0.4 [62]), Alzheimer's disease (self-reported: 0.77 [63] and 0.71 [64], proxy-reported: 0.6 [63], and 0.30 [64]) and Parkinson's disease [0.59 [65], 0.71 [66], and 0.62 [67] (median)].

Limitations

Although care was taken to minimize bias in the data collection, it cannot be excluded that selection bias was present in these digital data collections, as only individuals with access to the internet and a smartphone device could enroll. In MRW, the study population has a higher proportion of female participants compared to other MG-specific cohorts [40, 45, 68–71], which might affect results as QoL in women has been documented to be lower than men in several studies. As this is a cross-sectional study, the severity distribution observed in MRW is not representative of the whole MG patient population. Indeed, potential participants of the MRW study were made aware of the study through PAGs and social media; therefore, a possible bias to more proactive individuals cannot be excluded. Furthermore, patients were required to enter their monthly data via an application on their smartphone; therefore, patients with (severe) ocular problems (common in MG) would be prevented from participating. In POPUP, the recruitment of members of the general population was carried out by different market research companies in each country, which may have caused inconsistencies in the recruitment process. In addition, potential participants were offered a small compensation, which could have encouraged more people with a lower socioeconomic status to participate [72]. Lastly, it is important to keep in mind the multidimensionality of HRQoL when interpreting our results. This study compared the outcomes of two generic instruments, an MG-specific instrument, and several variables regarding the need for a caregiver and the use of medical resources, thus not covering all aspects. For a more comprehensive picture of the HRQoL of people diagnosed with MG compared to the general population, a tandem paper has been published, identifying the burden people diagnosed with MG suffer with a focus on problems with breathing, fatigue, sleep, mental health, and pain/discomfort (Dewilde 2023, under review).

Table 5 The utilization of medical resources compared between respondents in MRW and POPUP

	POPUP ***n*** **= 9102**	**MRW** ***n*** **= 811**
Had any type of medical care visit in the past month	24.6%	51.9%
Mean number of visits in the past month	Mean (SD)	Mean (SD)
Nurse/healthcare worker visit	0.132 (1.898)	0.076 (0.266)
GP/family doctor visit	0.211 (0.622)	0.366 (0.482)
Specialist visit	0.184 (0.76)	0.834 (0.373)
Visits to physiotherapist/rehabilitation center	0.092 (1.138)	0.113 (0.317)
Hospital outpatient visit	0.064 (0.54)	0.158 (0.365)
A&E visit	0.013 (0.169)	0.110 (0.313)
Hospital admission	0.009 (0.089)	0.125 (0.33)
Days in hospital	0.022 (0.325)	9.366 (10.286)
Days in ICU	0.003 (0.1)	2.318 (1.81)
Other visits	0.022 (0.323)	0.058 (0.234)

POPUP General Population Norms Study dataset, *MRW* MyRealWorld-MG study dataset, *GP* general practitioner, *ICU* Intensive Care Unit, *A&E* Accident and Emergency services, *SD* standard deviation

CONCLUSION

This direct comparison of the HRQoL between people diagnosed with MG and the general population using two international studies in large populations revealed a high burden in people diagnosed with MG in all domains of HRQoL. People diagnosed with MG experience more problems in physical as well as mental health, in their activities of daily living, and in their social and working relationships. This also has an economic impact as people diagnosed with MG utilize more medical resources, more often need a caregiver, and take more sick leave than members from the general population. As a result, people diagnosed with MG have lower utility values. These results were consistent across all PROMs, in all countries.

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Disclosures. Sarah Dewilde, the principal investigator of the study, Nafthali Tollenaar and Mathieu F Janssen have been commissioned by argenx BV and received honoraria to design the

study, analyze and report the data. Glenn Phillips, Sandra Paci and Femke De Ruyck are employees of argenx BV, the sponsor of the study.

Compliance with Ethics Guidelines. Ethical approval was obtained in all countries for both studies from Salus IRB (US, UK, Germany, Netherlands, Denmark), CPP (France), KULeuven (Belgium), Veritas IRB (Canada), local ethical approval (Spain, Italy), and MINS-IRB (Japan) [17] and the authors received permission to access the data. Informed consent to collect data, analyze and report anonimzed and aggregate data was obtained from all participants from both studies. The study was performed in accordance with the Declaration of Helsinki.

Data Availability. Anonymized, aggregated study data is available upon reasonable request through the corresponding author (for POPUP) and through the Scientific Advisory Board (for MyRealWorld-MG).

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