Health Related Quality of Life and Costs of Healthcare Utilization of Norwegian Myasthenia Gravis Patients

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Abstract

Myasthenia Gravis is a chronic autoimmune disease that causes weakness in the skeletal muscles. It is a rare disease with a relatively small amount of knowledge about the patients' quality of life. The objective of this study was to increase the knowledge regarding the Health-Related Quality of Life (HRQOL) of Norwegian Myasthenia Gravis (MG) patients, as well as evaluating the validity of the generic HRQOL measurement instrument EQ-5D-5L as a measurement of HRQOL for Norwegian MG patients. In addition approximate costs of the patients' healthcare utilization due to MG was also calculated, in order to investigate the current costs associated with the disease. The study included 67 participants suffering from MG. The participants responded to the generic questionnaire EQ-5D-5L as well as the MG specific questionnaire Myasthenia Gravis Quality of Life 15 (MGQOL15). The mean HRQOL of 0.63 found for the whole sample was similar to levels of HRQOL in results of previous studies. Construct validity was tested for by comparing corresponding dimensions of HRQOL from the two questionnaires EQ-5D-5L and MGQOL15, and observing whether the resulting correlation $\rho > 0.4$. Most of the corresponding dimensions were found to satisfy this condition, however with many items of the MGQOL15 having no corresponding dimensions in the EQ-5D-5L, care should be taken when using only this questionnaire to study the HRQOL of MG patients. A mapping analysis was performed to make HRQOL estimations from the data of the MGQOL15 questionnaire. Due to restrictions regarding gathering of health data, possibly relevant health information was not gathered and available for the analysis. The selection of the sample population was considered to have a high risk of bias. Studies with better access to the an unbiased sample of patients could generalize their results with more certainty.

Preface

This thesis was written to fulfill the graduation requirements of the Health Economics, Policy and Management program at the University of Oslo. Due to difficulties regarding collection of health data, it's completion was prolonged from May 2022 to May 2023.

The idea of the project was originally conceived during an internship at UCB Pharma, where I was tasked with investigating the health related quality of life of Norwegian Myasthenia Gravis patients, as it has been done little research about quality of life for this patient group.

Unfortunately, due to restrictions regarding the collection of health data, the Regional Ethics Committee (REK) determined that the project required a complete project application. As this kind of application requires a project leader with a doctorate, the project was then changed to a Master thesis.

The project has first and foremost let me learn more about the purpose and usage of health related quality of life in health economic evaluations. I've also gained more experience with using R for statistical analysis.

I would like to thank my supervisor, Eline Aas, for her excellent guidance and understanding during the process. I'm grateful to have been given so much of her time despite her clearly busy schedule. I would also like to thank Fredrik Arneberg of UCB Pharma for his assistance and support. I also want to thank Nils Erik Gilhus for providing his expert opinions and Marit Hansen of the Myasthenia Gravis patient association for her assistance during the design and distribution of the survey.

Finally I would like to thank the respondents of the survey for their time responding to my questionnaire, making the project possible.

Jørgen Mørkved Opjordsmoen, May 7, 2023

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Chapter 1

Introduction

Myasthenia gravis (MG) is a chronic neuromuscular disease. Treatment of MG is in a state of active research with 18 clinical trials being listed on myastheniagravis.org[1] and 68 active trials on clinicaltrials.gov[2] as of May 14. 2023. As more advanced immunotherapy becomes available, knowledge of the Health Related Quality of Life (HRQOL) of MG patients becomes relevant when considering choices of treatment strategies. This project is intended to increase the general knowledge of the HRQOL of Norwegian MG patients, in order to generate useful knowledge for economic evaluations regarding patients with MG. Knowledge about the HRQOL of patients is required when making decisions about financing and funding of treatments in Norway (Legemiddelverket, 2021). Studies regarding the HRQOL of patients with uncommon diseases like MG are therefore crucial to ensure Norwegian MG patients get the most adequate care. To contribute to this, the HRQOL of the sample of Norwegian patients will be described and analyzed.

When making economic evaluations of medical treatments, one considers both the possible gains in terms of HRQOL but also the monetary costs of the various options. As such, decision makers requires knowledge of both the HRQOL of the patients as well as the costs of their utilization of health care. Therefore, this paper will also attempt to calculate some approximate costs of the healthcare utilization of the participants due to their MG condition.

Additionally, this project aims to increase the knowledge of the measurement instruments used for studying the HRQOL of MG patients. This will be done by investigating the relationship between the generic instrument EQ-5D-5L and the specific measurement of MG, Myasthenia Gravis-Quality of Life 15 (MGQOL15). Many studies use multiple instruments when studying the HRQOL of patients suffering from various diseases, often combining both generic and disease specific instruments. Both generic and disease specific instruments have their own benefits. Generic instruments produce results that can be generalized and compared

[1] Link: https://myasthenia.org/Research/Clinical-Trials

[2] Link: https://clinicaltrials.gov/ct2/results?cond=Myasthenia+GravisSearch=Applyrecrs=brecrs=arecrs=frecrs=c
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across diseases, but there may be aspects of specific diseases that the generic instruments are not fully able to capture, thus producing results that do not fully capture the true HRQOL of the patients. Differences in the results between the two methods may have ramifications for decisions regarding treatment of MG patients, resulting in choices that are not optimal since they are based on incomplete knowledge.

1.1 Structure

This paper will begin with a description of the disease itself as well as an overview of some of the literature regarding the HRQOL of MG patients (chapter 2). The symptoms of the disease and how the disease is diagnosed will be described. A description of the subgroups of the patients will be given, and various treatments of the disease will be described. Studies made on the HRQOL of MG patients will be presented, with a focus on Norwegian patients as well as generic and MG specific HRQOL instruments.

Theory on how HRQOL measurements are used in health economic evaluation will then be presented (chapter 3). After a brief description of health economic evaluations, measurements of health and HRQOL will be described. The Quality-Adjusted Life-Year (QALY) as a measurement of HRQOL will be explained. The differences between generic and disease specific instruments will be explained, and the generic measurement EQ-5D-5L and the disease-specific measurement MGQOL15 will be presented.

The methods of the paper will then be described (chapter 4). The sample population will be characterized and the method of collecting data will be described. The process of obtaining the two surveys is then described as well as their specific contents. A description of costs are then presented and the methods of statistical analysis is described.

The results of the project is then presented (chapter 5). The scores of the two surveys are described as well as the calculated costs. Correlations between the two surveys are then presented in order to study the differences between the two surveys. Finally, regression results are presented, showing how QALYs and costs depend on various characteristics.

The discussion focuses on comparing the two surveys (chapter 6) to examine how the results can give an indication of which survey appears more suitable to best describe the HRQOL of Norwegian MG patients. This is then followed up by a discussion of the weaknesses and possible sources of errors in the study.

Finally the paper concludes with the findings of the paper (chapter 7).

Chapter 2

Background

Myasthenia gravis (MG) is a rare, autoimmune neuromuscular disease. The disease being autoimmune means that it causes the immune system to to attack healthy cells in the body by mistake. MG affects the transmission from motoric nerves to striated muscles. There is typically a component of muscular fatigue in the weakness, and it is most pronounced after repeated and long lasting use of the muscles. The symptoms are typically varied across the day (Gilhus, 2012; Gilhus et al., 2016; Gilhus and Verschuuren, 2015; Querol and Illa, 2013).

Innervated cranial nerves are often affected. Seeing double, ptosis and weakness in mimic muscles as well as difficulties speaking and swallowing are typical symptoms of the disease (Gilhus, 2012; Gilhus et al., 2016; Gilhus and Verschuuren, 2015; Querol and Illa, 2013). The muscular weakness of the disease is typically symmetrical, with the exception of eye muscle palsy, which is often asymmetrical. MG associated with MuSK-antibodies [1] is often more serious, has less fluctuation and can easily result in muscle atrophy (Guptill et al., 2011).

MG has a prevalence of 150 per one million with a yearly incidence of 10 per one million (Andersen et al., 2010; Carr et al., 2010; Heldal et al., 2009). Most patients show their first symptoms later than the age of 50. In the older age group, men are slightly more represented than women, while for those showing symptoms before the age of 50, women are the majority. MG can also occur in children in a juvenile form (Liew and Kang, 2013). Changes of demographics and treatment of the disease, has resulted in a majority of older patients (Andersen et al., 2010; Carr et al., 2010; Heldal et al., 2009; Owe et al., 2006). There is some geographical variation in the occurrence. Juvenile MG is most typical in Eastern Asia, while MG assosiated with MuSK-antibodies is most common in the Mediterranean area.

[1] MuSK is an abbreviation for Muscle-Specific Kinase. MuSK protein are required for the formation and maintenance of the neuromuscular junction (DeChiara et al., 1996).

2.1 Diagnosis of Myasthenia Gravis

The symptoms of the disease are often unclear. Among younger patients the symptoms may be misinterpreted as an unspecified state of fatigue or a mental illness. Ptosis can represent a particular differential diagnostic challenge among older patients . The symptoms may be misunderstood as brain stem disease. Variation across the day and lateral differences of ptosis are signs that may indicate MG (Gilhus et al., 2016).

Among 70-80 % of patients with MG, antibodies against acetylcholine receptor in serum is found (Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013). Others are found to have antibodies against muscle-specific kinase (MuSK). Among patients with MG and purely ocular symptoms, only about 50 % have demonstrable antibodies, and when they do it is always against acetylcholine receptors (Kerty et al., 2014). MuSK-antibodies are investigated in those with a negative test for acetylcholine receptor antibodies and where there is still suspicion of MG. The time of response from the laboratory can take up to three weeks for antibodies against acetylcholine receptors and up to four weeks for MuSK-antibodies. Clear positive test results are considered to 100 % specific for MG. The specificity of a test refers to it's ability to designate an individual who does not have the disease as negative[2]. Positive results being considered 100 % specific for MG, thus means that there is no chance of a false positive result[3]. The low risk of a false positive results in a low threshold for taking the test. A patient with typical symptoms and detected antibodies has definite MG.

Neurophysiological testing with repetitive nerve stimulation and single fiber electromyography (SF-EMG) represent functional investigations of neuromuscular transmission. These types of testing give immediate answers, but are technically demanding and require specific expertise. Single-fiber EMG is the most sensitive type of testing, but the pathological findings are not specific for MG. The nerve-muscle transmission is selectively inhibited, and neurophysiological examination reflects this. In the case of MG without detectable antibodies, neurophysiological examination will usually show findings that are so characteristic that they confirm neuromuscular transmission disease and make the diagnosis probable (Chiou-Tan and Gilchrist, 2015; Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013).

How symptoms and findings respond to acetylcholinesterase inhibitor has diagnostic value. Previously it was common to make use of intravenous testing with edrophonium. With good antibody analyzes and neurophysiological testing available, this is done less often than before,

[2]Sensitivity is another measure of a test's ability to classify a person as having a disease or not. The test's sensitivity refers to it's ability to designate an individual with disease as positive.

[3]A false positive test result refers to a case where a test erroneously returns a positive result for a person who in reality should receive a negative result. A false negative test result refers to cases where a test erroneously returns a negative result for a person who in reality should receive a positive result.

but especially with purely ocular symptoms and findings, it may still be useful. The effect of a few days of oral treatment with pyridostigmine is worth recording diagnostically. Improvement of muscle strength by cooling down (ice-pack test) has sensitivity and specificity that can make it useful in containing ptosis (Gilhus et al., 2016).

About 10 % of MG patients have thymoma. Therefore, CT- or MR-examinations of the mediastinum should be performed for all patients. Among those without thymoma, thymic hyperplasia is common and can be seen as an enlarged gland on imaging. Neither sensitivity nor specificity for thymoma in CT and MR examinations is satisfactory. The presence of antibodies against titin in addition to antibodies against the acetylcholine receptor will strongly imply thymoma among younger patients. Patients without antibodies to titin very rarely have thymoma (Romi et al., 2005).

2.2 Subgroups

Pathogenesis, treatment response and prognosis largely depend on the MG subgroup (Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013). Correct subgroup diagnosis is therefore important. There is pathogenetic overlap between MG with onset before and after the age of 50. An older patient with thymic hyperplasia might actually belong in the early-onset group. (Heldal et al., 2014; Klein et al., 2013).

In the thymoma subgroup, MG is a paraneoplastic condition. About a third of all people with thymoma develop MG with antibodies against the acetylcholine receptor. Thymoma can be associated with several other autoimmune diseases, but much less often than with MG. It is important to treat both the muscle weakness and the thymoma. The treatment response is often slightly worse in this subgroup.

The first symptoms of MG are often eye symptoms and can appear purely ocular in the early phase. If after two years the patient still only has ocular symptoms, it is most likely that the disease remains ocular, although generalization with severe symptoms can also occur after a long time (Kerty et al., 2014).

Antibodies against acetylcholine receptors, MuSK and lipoprotein-related protein 4 (LRP4) are almost never found at the same time. There are clinical group differences between the patients, but not so prominent that the subgroups can be diagnosed clinically. While MuSK myasthenia is somewhat more severe, LRP4 myasthenia tends to be milder (Gilhus, 2012; Gilhus and Verschuuren, 2015; Maniaol et al., 2012; Querol and Illa, 2013).

The group of patients without detectable antibodies is heterogeneous. Some have antibodies with such low affinity that they are not identified by routine tests, only by non-commercial cell-based techniques (Maniaol et al., 2012). Such patients actually belong to one of the other subgroups. The others may probably have antibodies against other molecules in the postsynaptic membrane that affect neuromuscular transmission (Gilhus and Verschuuren, 2015; Querol and Illa, 2013).

Table 2.1: Table of Myasthenia Gravis Subgroups. Inspired by Gilhus et al. (2016).

Subgroups of Myasthenia Gravis	
Group I	Myasthenia gravis with onset age before 50 years. Thymus hyperplasia. Female obesity. Acetylcholine receptor antibodies. No titin antibodies.
Group II	Myasthenia gravis with onset age after 50 years. Thymus atrophy. Fairly equal gender distribution. Acetylcholine receptor antibodies. Titin antibodies may be present.
Group III	Myasthenia gravis with thymoma. 10–15% of all pateints. Onset at any age, most commonly in the elderly patients. Acetylcholine receptor antibodies. Titin antibodies in >95% of patients.
Group IV	Ocular myasthenia gravis. Symptoms and signs exclusively from the eye muscles (diplopia, ptosis). With or without acetylcholine receptor antibodies.
Group V	Myasthenia gravis with MuSK antibodies. No acetylcholine receptor antibodies. 1–5 % of all patients.
Group VI	Myasthenia gravis with LRP4 antibodies. Not acetylcholine receptor antibodies. 1–2 % of all patients.
Group VII	Myasthenia gravis without detectable antibodies. Heterogeneous group.

2.3 Treatment

Once a patient has been diagnosed, the treatment intensity is controlled determined based on the clinical picture (Zisimopoulou et al., 2013). Repeated measurements of acetylcholine receptor antibody can be an indicator of the development of the disease and are checked in case of uncertain diagnosis, generalization of ocular MG, significant worsening of symptoms or significant improvement of symptoms. Falling concentration of acetylcholine receptor antibodies usually means lower disease intensity.

2.3.1 Symptomatic medical treatment

The first-choice treatment for MG is drugs that increase the available amount of acetylcholine in the synapse (Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013; Skeie et al., 2010). In practice, the acetylcholinesterase inhibitor pyridostigmine is given. A good effect confirms the diagnosis. The dose is determined based on effect and side effects, primarily gastrointestinal. Acetylcholinesterase inhibitors increase available acetylcholine also in the parasympathetic nervous system.

The patients themselves can adjust the optimal dose, preferably within the limits set by the doctor. The standard single dose is 60 mg, but it can be reduced in case of side effects with the use of 10 mg tablets. MG with MuSK antibodies usually has the worst effect of acetylcholinesterase inhibitors (Guptill et al., 2011).

2.3.2 Immunosuppressive medical treatment

In the event of significant symptoms despite symptomatic treatment, immunosuppression is initiated. For the majority of patients, the combination of prednisolone and azathioprine is the best choice (Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013; Skeie et al., 2010). Prednisolone is usually given every other morning and in gradually increasing doses to reduce side effects. The azathioprine effect only comes after several months.

In the start-up phase, haematological tests and liver function is monitored closely. A moderate drop in leukocyte count is common. The concentration of liver enzymes in serum will usually increase, and up to a threefold increase does not indicate discontinuation of the drug and is often transient. Azathioprine hardly has negative long-term effects (Pedersen et al., 2013). Lack of the enzyme thiopurine methyltransferase usually leads to azathioprine side effects, but this can be tested before starting treatment (Gilhus and Verschuuren, 2015). With good control of the MG symptoms, the dose of prednisolone and azathioprine can be reduced. It is recommended to maintain a low dose for years, often lifelong, to prevent relapse (Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013; Skeie et al., 2010).

There is evidence that immunosuppressive treatment in ocular MG reduces the risk of generalization of the symptoms (Kerty et al., 2014). For

this subgroup, a small dose of prednisolone may be sufficient.

If the combination of prednisolone and azathioprine does not provide sufficient symptom control, or possibly leads to significant side effects, mycophenolate mofetil is recommended for patients with mild to moderate symptoms (Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013; Sanders et al., 2008; Skeie et al., 2010).

For MG with severe symptoms, rituximab is recommended as second-line treatment (Gilhus and Verschuuren, 2015; Iorio et al., 2015; Keung et al., 2013). This monoclonal antibody binds selectively to the CD20 molecule on B lymphocytes. Theoretically, it is therefore suitable for antibody-mediated diseases. Multiple reports indicate that around 80 % of patients with MG achieve a satisfactory treatment response, but there are no randomized studies (Iorio et al., 2015). The response rate consistently applies to patients who have not had a sufficient effect of first-line immunotherapy with prednisolone and azathioprine, typically they have also tried additional immunosuppressive agents.

The effect is particularly good in patients with MuSK antibodies. This group often responds worse to other therapy and have more severe courses. Rituximab is dosed as in rheumatic disease. Often, one treatment series seems to be sufficient in MG. However, the treatment is repeated if necessary. Optimal adaptation to other immunosuppressive treatment is poorly documented, but a combination with prednisolone and azathioprine is common (Gilhus et al., 2016).

The experiences with the use of rituximab for MG in a handful of patients in Norway have been quite good. The use of the drug is likely increasing, but controlled treatment studies are still ongoing. The concern for rituximab is particularly linked to the risk of serious side effects. Progressive multifocal leukoencephalopathy (PML) has not yet been reported in MG, but has been reported in rituximab-treated patients with other diseases (Gilhus et al., 2016).

Methotrexate, cyclosporine and tacrolimus are other immunosuppressive drugs that are sometimes used in treatment of MG (Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013; Skeie et al., 2010). Intravenous immunoglobulin is primarily used as an emergency treatment, but a few patients receive repeated infusions to achieve a sustained effect. It is expected that new monoclonal antibodies with a selective effect in the immune system will be tried to a larger extent(Gilhus and Verschuuren, 2015). Antibodies directed against complement and cytokines will be able to affect MG, and also targeted B-lymphocyte and T-lymphocyte antibodies.

2.3.3 Thymectomy

Thymectomy can improve the myasthenic weakness in patients with generalized symptoms and acetylcholine receptor antibodies, especially in patients with onset before the age of 50. Thymectomy is therefore recommended for patients with generalized symptoms and disease onset before the age of 50 (Cea et al., 2013; Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013; Skeie et al., 2010), but can also be considered in

those with onset between the ages of 50 and 65.

MG with thymoma represents a paraneoplastic condition (Marx et al., 2013). Thymomas can grow invasively but do not metastasize distantly. Pericardium, great vessels and diaphragm are exposed. The prognosis is linked to the development of the thymoma, and the follow-up must be both neurological and oncological. New worsening of the muscle weakness may indicate recurrence of a thymoma. A CT or MRI examination must then be carried out.

There is no evidence of a therapeutic effect of thymectomy in ocular MG or in MG with MuSK or LRP4 antibodies. Thymectomy is also not usually performed in MG without proven antibodies. However, some of these patients have low-affinity antibodies against the acetylcholine receptor that cannot be detected by routine testing (Gilhus et al., 2016).

Thymectomy should be performed early in the course of the disease. Increasingly, thoracoscopic techniques are used (Ye et al., 2013). The procedure is usually well tolerated, but prior treatment with intravenous immunoglobulin or plasma exchange is recommended in those with moderate or severe symptoms to ensure optimal muscle function in the postoperative phase. The positive effect of the intervention comes gradually over many months. It is crucial for the result that all thymus tissue is removed, including that which may lie scattered in mediastinal fatty tissue.

2.3.4 Emergency Treatment

In the case of a marked worsening of MG, it is important to have effective treatment that works quickly (Gilhus, 2012; Gilhus and Verschuuren, 2015; Querol and Illa, 2013; Skeie et al., 2010). This applies particularly in the event of imminent respiratory failure. Early respiratory support is then most important. Intravenous immunoglobulin and plasma replacement have approximately the same effect (Barth et al., 2011; Gajdos et al., 2008). Both treatments produce a marked improvement in muscle strength within 2-6 days in 80% of patients. The effect lasts for 2–3 months. The treatment is often combined with intensification, possibly initiation, of other immunosuppressive therapy. In the 20% that do not have sufficient effect, the treatment must be repeated, or one can switch from one to the other of the two alternatives. Intravenous immunoglobulin is somewhat easier to administer and has somewhat less serious side effects than plasma exchange, and such treatment is thus the first choice at most hospitals in Norway.

Respiratory support treatment is life-saving in myasthenic crisis. In the event of imminent respiratory failure, patients must be treated in the intensive care unit. The threshold for hospitalization for patients with myasthenic exacerbation should be low because of the risk of respiratory failure. Such failure can occur quickly. Increasing the dose of symptomatic drug treatment is rarely enough in threatening respiratory failure. When the patient receives ventilator treatment, the dose of acetylcholinesterase inhibitor is usually reduced temporarily to reduce mucus secretion in

the airways. Before the ventilator treatment ends, the medication is reintroduced in the optimal dose (Gilhus et al., 2016).

2.3.5 Supportive treatment

Patients with MG benefit from physical activity and well-adapted exercise. Infections should be treated early and effectively. Being overweight is bad, and smoking is strongly discouraged because of the respiratory effects. A few drugs have a negative effect on MG, primarily anesthetic drugs that inhibit neuromuscular transmission, then certain antibiotics (Gilhus et al., 2016).

Comorbidity often affects the condition. Side effects of drugs used for MG should be counteracted. It is particularly important to prevent osteoporosis during long-term treatment with prednisolone. This can be done by physical activity, a high intake of calcium and vitamin D, preferably with extra supplements, and possibly by preventive medication. For stable double vision and ptosis, operative treatment, or possibly prisms, can be helpful. Covering one eye removes double vision (Gilhus et al., 2016).

2.4 Health Related Quality of Life of MG patients

2.4.1 Health Related Quality of Life Norway

There has been some research done on Norwegian patients suffering from MG. In a study from 2015, Boldingh et al. conducted a research project focusing on the quality of life of Norwegian and Dutch patients suffering from MG, using the Short Form Health Survey 36(SF-36), a survey instrument for studying the Health Related Quality of Life (HRQOL) (Boldingh et al., 2015). The objective of the project was to compare the quality of life across borders and time. Among their conclusions was that there were no indications that quality of life for patients suffering from MG had improved since 2001 and that there were no health-related quality of life differences between the Norwegian and Dutch patients.

2.4.2 Health Related Quality of Life using generic measurments

Outside of Norway, there have been multiple studies on quality of life of patients suffering from MG. Using the SF-36 questionnaire, Paul et al. found that multiple quality of life aspects were negatively impacted by the disease. This impact was most marked in physical aspects (Paul et al., 2001). Twork et al. conducted a similar project in Germany. They also found a significant reduction in quality of life as a result of MG, and they found that the disease had a large negative economic impact both on the patients and the health system (Twork et al., 2010).

2.4.3 Health Related Quality of Life using specific measurements

Other research has been done using MG-specific survey instruments. Lee et al. used the MG specific questionnaire The Myasthenia Gravis Quality of Life 15 (MGQOL15) to estimate the HRQOL of patients in the US (Lee et al., 2018). They found that the participants of their study had poor QOL. Additionally, they focused on the differences between men and women, finding that the patients poor QOL as a result of MG was more severe for women in all aspects.

Using both of the MG specific questionnaires MGQOL15 and Myasthenia Gravis Activities of Daily Living (MG-ADL), Cutter et al. finds that MG patients registered in The Myasthenia Gravis Patient Registry (MGR) of America had severe impairments of HRQOL (Cutter et al., 2019). Having used two questionnaires, the authors also compared the scores of the two different questionnaires. The results of the comparison was a high correlation between the two surveys. Considering both surveys were MG specific this seems like an expected result.

Chapter 3

Theory

3.1 Economic evaluation of health care interventions

According to Drummond et al. economic evaluation of healthcare seeks to inform about the range of various different possible decisions (Drummond et al., 2015). A central question is whether the resources spent in order to provide various procedures, services or programmes, are best spent in this way rather than in some other way. These resources could possibly be used to provide healthcare for other patients with differing conditions, who might enjoy a larger gain from the use of these resources.

There are primarily two sides to economic evaluation, the costs and the consequences of possible actions, and the concern of choices. In order to reach a decision regarding the implementation of any program, treatment or service, it is important to both know what must be given up (costs) and what the overall expected benefits (consequences) will be. Since resources are limited, all desired outputs can not always be produced in all areas of human activity, and choices must be made regarding the prioritization of various options. These choices must be made based on some criteria. Identifying and making these criteria explicit when these criteria are used to make decisions, is part of what economic evaluation is about. Since patients and their clinicians are not always the best placed to identify the best courses of action, economic evaluation can also provide them with useful information.

There are two factors which have caused an increased importance of economic evaluation in health care decision-making in the last 20 years. As health care budgets have become more strained, there has been a shift from a sole focus on clinical effectiveness, to a focus including cost-effectiveness. Additionally, decision-making processes have emerged in various jurisdictions which enable the results of economic evaluations to be used.

Although economic evaluation can be applied to all health technologies, the area of pharmaceuticals has been the most prominent . In 1991 it was announced in the Commonwealth of Australia that economic analyses would be required in submissions to the Pharmaceutical Benefits Advisory Committee, the body that advises the minister on the listing of drugs on

the national formulary of publicly subsidized drugs. In the wake of this policy, similar policies have become fairly widespread, with approximately half of the countries in the European Union, as well as Canada and New Zealand, requesting economic analyses of pharmaceuticals as well as other health technologies. The United States as well as various countries in Latin America and Asia, have also expressed an interest in receiving economic data (Drummond et al., 2015).

3.2 Measuring Health

According to Drummond et al. (2015) measurements of health effects is the starting point for the assessment of health gain in economic evaluations. These measurements can be changes in rate of survival or changes in HRQOL as a result of therapy, for example. There are two ways health effects can be used in economic evaluations. An economic evaluation can be conducted alongside a single clinical study, or economic evaluation can be done using decision-analytic modelling. When using decision-analytic modelling one uses data of health effects to assess health gain in economic evaluations. Measurements of health effects can also be important in the assessment of costs. A bleeding complication will require health care resources to treat, in addition to the impacts it has on the health of the patient. Economic evaluations using individual patient data and those using decision-analytic models view health effects as events that can result in changes to costs and health status. Rather than clinical outcomes, this paper will focus on patient-reported outcome measures.

3.3 Health Related Quality of Life (HRQOL)

There are a large amount of different measures in the clinical evaluation literature used to capture the health effects of various interventions (Drummond et al., 2015). Some of these measures have restrictions, such as being limited to a single aspect or dimension of health. Effects on mortality and survival being a common example. However, there is more to health than simply the length of life. When seeking to implement health care interventions and treatments one is also concerned with how these will impact the HRQOL. There are many different measures of HRQOL. These measures typically describe different dimensions or attributes of HRQOL and how each dimension can be rated on a scale of levels. Many of these profiles provide a score based on the performance of each attribute. It seems intuitive to use this score as a measure of changes in health. However, the different attributes of HRQOL need to be weighted for the measure to be used to identify when health has improved or not. This is because some of the attributes may have a larger impact than others. If one attribute decreases but a less important one increases by a larger magnitude, the score might show and increase when the actual HRQOL has decreased, unless the attributes have been weighted properly. How one determines the weights of the various health dimensions of a measure, then

becomes a question. Asking people to provide the weights based on how they would rank each of the health states, is one way to do this. An example of how this can be done, is to ask people how much time in full health they would be willing to give up in order to avoid time in a particular health state.

3.4 Patient-Reported Outcome Measures

There are multiple alternatives when it comes to measuring HRQOL. One method which there has been an increasing interest for in clinical studies, are Patient-reported outcome measures (PROs) (Drummond et al., 2015). These include measures of patient satisfaction and HRQOL, and may also capture treatment effect aspects which are missed in clinical outcomes. There are two categories of quality-of-life measures; generic measures, and disease-specific also called condition-specific measures.

3.5 Generic Measures

Generic measures of HRQOL consider a range of dimensions of HRQOL which can be impacted by any disease. Some of these dimensions are physical function, mental well-being, social function and pain. Generic measures typically have a broader range of application, but unless there is an algorithm for generating a summary measure, comparing different treatments is difficult, as they might score differently in different dimensions. The Short Form-36 and the EQ-5D-5L are typical generic measures of HRQOL.

3.6 EQ-5D-5L

The EQ-5D-5L survey is a system developed by the EuroQoL group (Group, 1990). It was initially developed using six attributes: mobility, self-care, main, activity, social relationships, pain and mood. Later it was revised to the five attributes: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression (Brooks and Group, 1996; Drummond et al., 2015; Essink-Bot et al., 1993; Kind, 1996). Each attribute originally had three levels, no problem, some problems, and major problems, resulting in 243 possible health states. The states 'unconcious' and 'dead' were also added, making the total 245. Preferences for the scoring function were measured using the time trade-off technique on a random sample of 3000 adults in the United Kingdom (Dolan et al., 1995). Since the original survey was developed, the EuroQoL group have developed and tested a new five-level version of the survey, called the EQ-5D-5L. The motivation for developing this new version, was the growing evidence that the EQ-5D could suffer from ceiling effects, particularly when used in general population surveys but also in some patient populations. Meaning that there

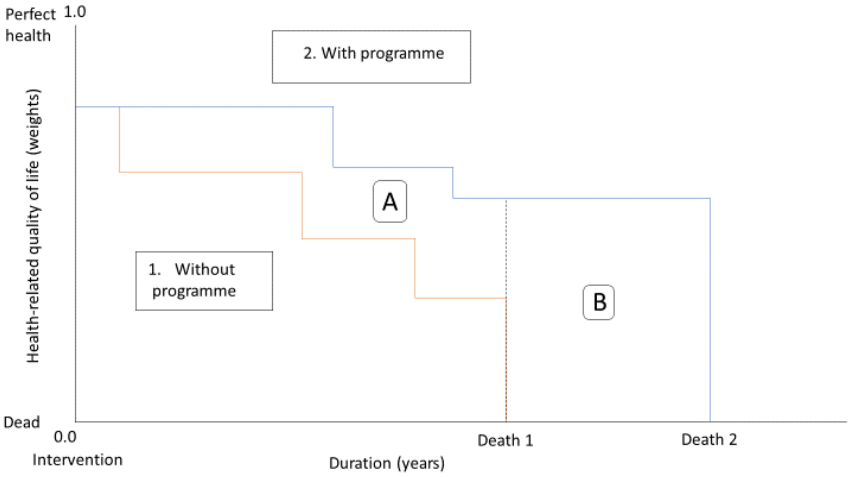

Figure 3.1: Illustration of effects on QALY of a hypothetical health care intervention. Inspired by Drummond et al.2015, Figure 5.2, pp 128.

might be issues detecting small changes in health, especially in patients with milder conditions (Herdman et al., 2011).

3.7 The Quality-Adjusted Life-Year (QALY)

The The Quality-Adjusted Life-Year (QALY) is the most widely used generic metric of health gain used by generic measures (Drummond et al., 2015). It is typically used to quantify the gain in HRQOL one could achieve from introducing a new health treatment, drug, or other interventions affecting the health of some individuals. The concept was first introduced in 1968 in a study on chronic renal failure led by Herbert Klarman (Klarman and Rosenthal, 1968). An advantage of the QALY is that it can combine gains in both reduced morbidity and mortality in one measure. It takes both the amount of a patient's life-years as well as the quality of life of these years, into consideration when measuring HRQOL. An illustration of the how the QALY measures changes in health effects is shown in figure 3.1. The figure shows two paths representing the HRQOL of a patient with and without a health care intervention. The lower path shows the HRQOL without the intervention, and the upper shows the path with the intervention. Without the intervention, the patient dies an earlier death at the time "Death 1", while with the intervention the patient lives until the time "Death 2". The area between the two curves shows the QALYs gained from the intervention. The intervention increases QALYs both by extending the lifetime of the patient, and by improving the HRQOL of the patient. Area A shows how much is gained from the improvement to quality of life, while area B shows the amount of QALY gained from a longer lifetime as well as the improved quality of life during this extended lifetime.

3.8 Disease-Specific Measures

These instruments tailor their dimensions in order to focus on the main areas that may have their quality-of-life reduced as a result of the specific disease. These measures are considered particularly useful in assessing efficacy of treatments, however their use in economic evaluations is limited, as they can mostly be used to compare different treatments for the particular disease. Like the case for generic measures, unless there is an algorithm for generating a summary measure, comparing different treatments is difficult (Drummond et al., 2015).

3.9 The Myasthenia Gravis-Quality of Life 15 (MGQOL15)

The MGQOL15 survey is a 15-item MG specific health-related quality of life questionnaire developed by Burns et al. (2008). The survey was developed as an abbreviated version of a previously developed 60-item MGQOL instrument. The length of this questionnaire was deemed to potentially lead to limitations, such as the time it would take to complete and interpret the questionnaire, as well as the interpretation of the results often not being straightforward, limiting the usefulness of the measures. Due to these potential issues, the authors suggested the development of an abbreviated version, which could increase the usefulness and decrease issues concerning patient fatigue. The 60-item instrument was derived from interviews with neuromuscular experts and MG patient focus groups (Mullins et al., 2008). It was tested in comparison to other measures of HRQOL such as the MG-specific Activities of Daily Living scores (MG-ADL) (Wolfe et al., 1999) and the SF-36 (Ware Jr and Sherbourne, 1992). There were two major steps involved in the process of developing the shorter questionnaire. First a factor analysis was performed on each of the 60 MG-QOL items. Favoring the items judged most responsive to clinical change, as well as most appropriate for the symptoms, and issues of MG, 20 items were selected for further analysis. In the second step, the 20 items chosen for further study were analyzed, focusing on how often the item was scored as improved when the patient improved in a trial using placebo or mycophenolate mofetil.

Chapter 4

Methods

4.1 Setting

The data sample was collected from members of the Facebook group of the Norwegian patient association group Myasthenia Gravis Norway. The collection of the data was performed during June 2022. To get access to data from Norwegian MG patients, a cooperation with the Norwegian patient association group Myasthenia Gravis Norway was established. The group is the largest MG patient association in Norway with 248 members as of the 29 of January 2023. An anonymous questionnaire was shared with members of the group on their Facebook page. The patients were asked various questions concerning demographic data, such as age, gender and region of residence, as well as tasked with responding to the two HRQOL questionnaires EQ-5D-5L and MGQOL15. The shared questionnaires were translated to Norwegian versions.

Permission regarding collection of health data was requested from the Norwegian Ethics Committee, but it was eventually decided that permissions were unnecessary due to the nature of the study.

The data was collected using the survey site Limesurvey. This site was chosen and deemed a satisfactory option as it is one of the approved sites for use of EQ-5D-5L by Euroqol.

4.2 Patient Population

The survey was shared with a group of about 248 possible respondents. There were 80 responses but 13 contained missing information and were therefore excluded from the analysis. The sample of complete responses therefore consisted of 67 observations. Counting only the complete responses, the response rate was then 27.02 %. This rate was calculated assuming the number of members of the group was the same during the sharing of the survey as it was in January 2023. Ideally the response rate would have been calculated based on the number of members during the period the survey was shared, but as it seems unlikely for this number to have changed substantially, this approximate response rate is deemed sufficient. Table 4.1 shows the characteristics of the respondents.

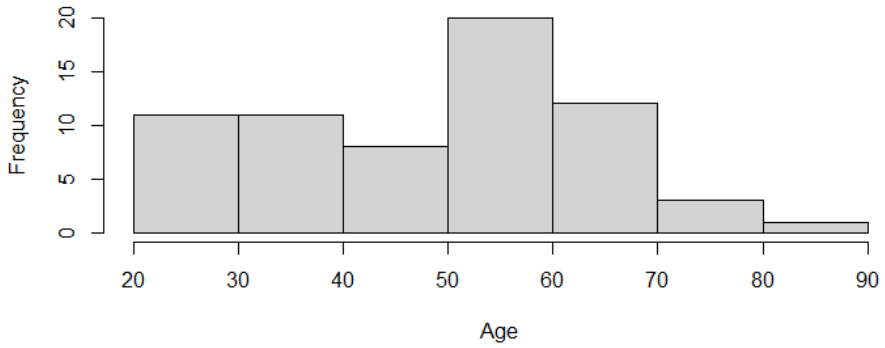

Figure 4.1: Age distribution of the respondents.

The ages of the respondents ranged from 22 to 90, with the median and the mean ages being fairly close to each other at 52 and 49. The most common age range was between 50 and 60 years with slightly more than 20 % of the the respondents fitting within this range, while the second most common range of 60 to 70 years was almost half as common at around 11 %. The respondents were categorized into the two subgroups Early Onset Myasthenia Gravis (EOMG) and Late Onset Myasthenia Gravis (LOMG), based on their onset age of disease. Patients with an onset age below 50 were included in the EOMG subgroup, while those with onset age larger than 50 were included in the LOMG subgroup. Table 4.1 reports the number of patients in the two subgroups, as well as the number of patients with Juvenile MG, referring to onset ages lower than 16 years.

An overview of the ages of the respondents can be seen in Figure 4.1.

There was a dominance of female respondents, with 82 % of the respondents being female and 18 % being male, meaning more than four fifths of the respondents were women.

Due to the small number of respondents, retaining the anonymity of the respondents was a concern. The respondents were questioned about characteristics like age, gender and area of residence. If all of this information was represented in this paper, it might be possible for someone to determine the identity of some of the respondents. This was a particular concern regarding the counties of residence, where the number of responses could be especially small for single counties. Due to this concern, the counties have been aggregated into four categorical regions: South-east, West, Middle, and North. The distribution of the counties was based on how they are categorized on the Norwegian government's overview of Norwegian health regions. The south-eastern health region consists of Agder, Vestfold og Telemark, Viken, Oslo, and Innlandet. The western region consists of Rogaland, and Vestland. The middle region consists of Møre og Romsdal, and Trøndelag. The northern region consists of Nordland, and Troms og Finnmark. All counties were represented with

Table 4.1: Table of descriptive statistics of the sample.

Descriptive Statistics	Total cohort n=67	
Female [n; %]	55	82.09
Age [mean ± SD]	49.06	15.64
Mean age at onset [yrs ± SD]	37.05	16.27
Disease duration [yrs ± SD]	11.86	11.47
Age at onset [n; %]		
LOMG (>50 year)	16	23.88
EOMG (⩽50 year)	51	76.12
Juvenile MG (<16 years)	4	5.97
Work status [n; %]		
Working	22	32.83
Student	4	5.97
Pension	6	8.96
Sick leave	7	10.45
Rehabilitation	2	2.99
Social security	30	44.78
Region [n; %]		
Helse Sør-øst	29	44
Helse Vest	14	21
Helse Midt	13	20
Helse Nord	10	15

no seemingly large outliers. Trøndelag and Viken were the counties with the most respondents while Agder and Møre og Romsdal were the counties with the least.

The respondents were asked about their work status. There were two categories that were larger by a significant margin. The most common category was for receiving disability benefits, with a percentage of 44.78 %, while the second largest was for working regularly, with a percentage of 32.83 %.

4.3 Health Outcomes

4.3.1 EQ-5D-5L

The EQ-5D-5L questionnaire was chosen as the generic questionnaire of the project for primarily two reasons. First of all, it is the recommended instrument of HRQOL measurement by Norwegian health authorities (Legemiddelverket, 2021). Secondly, it is a relatively short questionnaire, compared to SF-36, for example. The english version of the EQ-5D-5L questionnaire is shown in Table 4.2.

A Norwegian version of the survey was obtained through the EuroQol Group. As this is the offical Norwegian translation it has been produced using a standardized translation protocol which conforms to internationally recognized guidelines, which aim to ensure equivalence to the original English version and involve a forward/backward translation process and cognitive debriefing.

4.3.2 Myasthenia Gravis Quality of Life 15 (MGQOL15)

There were two MG specific HRQOL questionnaires that were considered for this project, MGQOL15 and MG-ADL. Originally, the MG-ADL questionnaire seemed the better option due to it's shorter length. However, due to recommendations from experts, MGQOL15 was chosen in it's stead, as MG-ADL is a survey intended for interviews between doctor and patient. Unlike the EQ-5D-5L survey however, there is no official Norwegian translation of the MGQOL15 survey. A Norwegian translation was therefore developed by the author with assistance from various parties. This survey translation has therefore not been validated. The translation was done attempting to keep the words and sentences as close as possible to their English counterparts, while retaining the original meaning. In some cases translating sentences word for word results in a proper representation of the original meaning. However, in many other cases doing so often results in word choices and sentence structures that are not well suited to ask the intended question. During the translation process, sentences were translated word for word when possible, and effort was made to use the same sentence structure and one to one translation when possible. Table 4.3 shows the original English version of the MGQOL15 questionnaire.

Table 4.2: Reproduction of the EQ-5D-5L questionnaire. The table is only a reproduction of the questions themselves, not of how the questionnaire shared with the respondents looked to the respondents. The Norwegian version shared with the respondents is shown in Appendix A.

Under each heading, please tick the ONE box that best describes your health TODAY.	
EQ-5D-5L	
Mobility	
I have no problems in walking about	☐
I have slight problems in walking about	☐
I have moderate problems in walking about	☐
I have severe problems in walking about	☐
I am unable to walk about	☐
Self-care	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
Usual activities (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐
Pain/discomfort	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
Have extreme pain or discomfort	☐
Anxiety/depression	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

Table 4.3: Reproduction of the MGQOL15 questionnaire. The table is only a reproduction of the questions themselves, not of how the questionnaire shared with the respondents looked to the respondents. The Norwegian version shared with the respondents is shown in Appendix A.

Please indicate how true each statement has been (over the past few weeks).
MGQOL15
I am frustrated by my MG
I have trouble using my eyes
I have trouble eating because of MG
I have limited my social activity because of my MG
My MG limits my ability to enjoy hobbies and fun activities
I have trouble meeting the needs of my family because of my MG
I have to make plans around my MG
My occupational skills and job status have been negatively affected by MG
I have difficulty speaking due to MG
I have trouble driving due to MG
I am depressed about my MG
I have trouble walking due to MG
I have trouble getting around public places because of my MG
I feel overwhelmed by my MG
I have trouble performing my personal grooming needs

4.4 Costs

The respondents were asked about their usage of medical services in the last 6 months prior to the survey. Usage of medical services was split into three categories: visits to a general practitioner (GP), visits to a specialist and days hospitalized. Assumptions of costs of the patients' utilization of medical services were then calculated, using the DRG weights of the 2023 ISF regulations (Helsedirektoratet, 2023). Based on recommendations from experts, visits to a specialist was assigned the DRG code 901D. Using the weight 0.056 of the DRG code and the DRG unit price of 49 484 NOK, the cost of this kind of healthcare utilization was calculated to be 2 820 NOK. Days hospitalized was assigned the DRG code 12. However, since this DRG weight is based on the full stay, rather than individual days, an assumption of mean hospital days had to be made. The mean days were chosen to be

6 as this is half of the amount of days before the trim point. With this assumption and the the DRG weight of 1.372, the unit price of a days hospitalization was calculated as 10 284 NOK. In the recommendations from the expert there was no recommendation for a DRG code regarding visits to a GP, this cost was therefore assumed to be 500 NOK. Using these assumed costs, each patient's approximate cost was calculated for every service, as well as the approximate total cost of the medical services used for every patient, in the 6 month period prior to responding to the survey.

4.5 Statistical Analysis

Data analysis was performed using the statistical package R version 4.3.0 (Auckland, New Zealand).

4.5.1 Construct Validity

To evaluate the validity of using the EQ-5D-5L on the sample population construct validity was performed. This method tests whether corresponding items of a condition specific instrument have constructs similar to the dimensions of a generic instrument. To do so the items of the two questionnaires which seem like they in theory should be correlated were chosen, and item-level correlations were explored. The questions from the MGQOL15 questionnaire which were deemed to be likely correlated with the Mobility dimension of the EQ-5D-5L were the questions: "I have trouble walking due to MG", and "I have trouble getting around public places because of my MG". The question from the MGQOL15 questionnaire which was considered likely to be correlated with the Self care dimension of the EQ-5D-5L was the question: "I have trouble performing my personal grooming needs". The question from the MGQOL15 questionnaire which was considered likely to be correlated with the Anxiety/Depression dimension of the EQ-5D-5L was the question: "I am depressed about my MG". When it came to the Usual activities dimension of the EQ-5D-5L, there was no clear single item of the MGQOL15 that was a clear match, but there were multiple possible candidates among the options. The chosen items were the questions: "I have trouble getting around public places because of my MG", "I have trouble performing my personal grooming needs", "I have limited my social activity because of my MG", "My MG limits my ability to enjoy hobbies and fun activities", "I have to make plans around my MG", and "I have trouble driving due to MG". Unlike the Usual activities dimension, the Pain/discomfort dimension did not seem to have any corresponding items in the MGQOL15 quesionnaire. Similarly, there were multiple items of the MGQOL15 which had seemingly no counterpart in the EQ-5D-5L, namely the items: "I feel overwhelmed by my MG", "I am frustrated by my MG", "I have trouble using my eyes", "I have trouble meeting the needs of my family because of my MG", "My occupational skills and job status have been negatively affected by MG", and "I have difficulty speaking due to MG". To investigate the item-level correlations, the Pearson correlation

coefficient, ρ (rho), was calculated between the items. To demonstrate item convergent validity, items measuring the same construct should have a correlation of $\rho > 0.4$ (Mulhern et al., 2014).

4.5.2 Regressions

In order to explore how HRQOL, QALYs and costs of healthcare utilization of the patients in the dataset were affected by characteristics such as age and how long they have had the disease, regressions were performed. Using the Ordinary Least Squares (OLS) regression method, the regression model:

$$a_i = \alpha_i + \beta_i b_i + \varepsilon_i$$

was estimated. Where a_i is patient i's QALY, α_i is a constant term, b_i is a vector of the independent variables such as age and duration of disease, β_i is a vector of coefficients corresponding to the variables, and ε_i is the error term. The regression was repeated using different control variables, to investigate which model was the best fit, and how the coefficients changed based on the inclusion of the other variables. Goodness of fit is a term that refers to a statistical test which determines how well the data sample fits a distribution from a population with a normal distribution. When running OLS regressions, the statistical measure of fit R-squared is reported. The closer this statistic is to 1, the better the goodness of fit of the regression model is.

To estimate a model on the costs of the patients' healthcare utilization, a Generalized Linear Model (GLM) was used. The GLM was chosen over the OLS, because when dealing with costs the response variable will always be positive and vary over a wide range, making it unsuitable for an OLS model. Instead the GLM:

$$c_i = f(\alpha_i + \beta_i b_i + \varepsilon_i)$$

was used. Where c_i is the estimated costs of patient i's healthcare utilization, $f(\mu_i)$ is the link function of the model. The vector b_i contains the same variables as the ones used in the OLS regressions, and β_i is a vector of coefficients corresponding to the variables,. a Poisson distribution was chosen as the probability distribution. So the GLM can be written as:

$$ln(E(c_i)) = \alpha_i + \beta_1 b_i + \varepsilon_i$$

GLM models do not produce an R-squared statistic, however an Akaike information criterion (AIC) statistic can be used instead. The Akaike information criterion is a metric used to compare the fit of the regression models, similarly to the R-squared statistic. The best model fit is the one with the lowest AIC value.

4.5.3 Mapping

In order to make HRQOL estimations from the data of the MGQOL15 questionnaire, mapping was performed. Mapping is used to determine

HRQOL estimations from data from disease specific questionnaires where no health state preference-based measure is available. According to Drummond (2015), the approach estimates the relationship between a non-preference-based measure and a generic preference-based measure, using statistical association. A degree of overlap is required, and the two measures must be administered on the same population. To fully perform the method, two data sets are required. This was not possible in this analysis. The lack of a second dataset will be discussed in chapter 6. To determine statistical association between the two measures regression techniques are used. Regressions using the OLS regression method, was done on the following regression model:

$$y_i = \alpha_1 + \beta_1 x_i + \beta_2 z_i + \varepsilon_i$$

where y_i is the HRQOL detemined by the EQ-5D-5L questionnaire of patient i, α_1 is a constant term, x_i is the MGQOL15 score of patient i, z_i is a vector of other variables such as whether patient i had EOMG and the duration of their disease, and ε_i is the error term.

Chapter 5

Results

5.1 Health outcomes

5.1.1 EQ-5D-5L

The results of the EQ-5D-5L questionnaire are shown in Table 5.1. The table shows the the mean scores of the respondents. In addition to the scores of the total sample being shown in the table, the scores of the subgroups EOMG and LOMG, are also shown. The patients are placed in the subgroups based on whether they had EOMG or LOMG. The respondents were given five levels of severity of HRQOL to choose from for each question, ranging from having no issues in the HRQOL dimension, to having extreme issues in the HRQOL dimension. As these levels are essentially a ranking of how much the respondent's MG causes them trouble in the corresponding dimension, each level was transformed into a numerical value from 1 to 5, where a value of 1 corresponds to having to problems in the dimension, and a value of 5 corresponds to the highest level of issues presented by the dimension. A value of 1 for the Mobility dimension thus corresponds to having no problems walking about, while a value of 5 corresponds to being unable to walk.

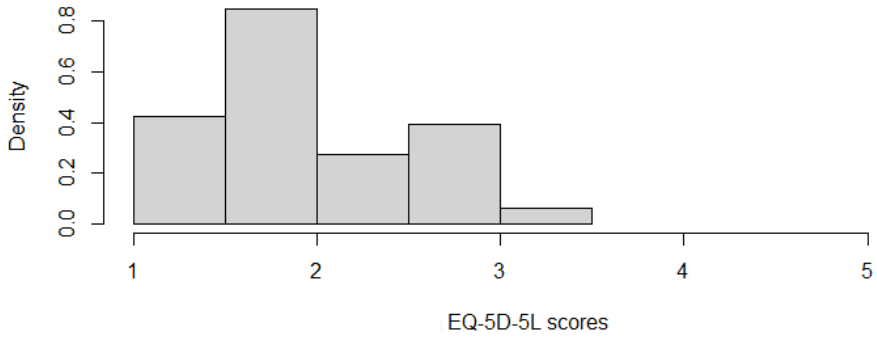

Figure 5.1: Distribution of EQ-5D-5L scores.

Table 5.1: Mean EQ-5D-5L scores and mean QALYs of the total sample, and divided by subgroups EOMG and LOMG.

EQ-5D-5L	Total		EOMG		LOMG	
	Mean	SD	Mean	SD	Mean	SD
Mobility	1.97	1.00	1.84	0.92	2.4	1.18
Self-care	1.45	0.68	1.41	0.64	1.53	0.83
Usual activities	2.24	0.89	2.13	0.85	2.6	0.99
Pain/discomfort	2.39	0.99	2.35	1.07	2.53	0.64
Anxiety/depression	1.78	0.86	1.86	0.92	1.53	0.64
QALY	0.63	0.20	0.64	0.20	0.60	0.21

We see from Table 5.1 that for the total sample population the mean values are all between 1 and 2.5, with the standard deviations all being close to one. This seems to also be the case for the two subgroups as well, with no major outliers. The smallest mean value for the total sample population was in the Self-care dimension with a value of 1.45, while the largest value was in the Pain/discomfort dimension with a value of 2.39. While there are some differences between the subgroups, like the mean value being relatively higher in the LOMG subgroup compared to the other subgroups, overall the scores are relatively similar between the subgroups.

Finally the table shows the composite scores of the survey, calculated using an algorithm, representing the QALYs of the respondents.

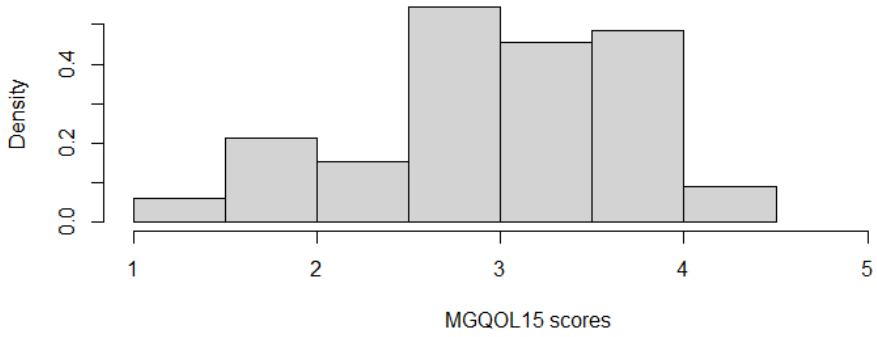

Figure 5.2: Distribution of MGQOL15 scores.

5.1.2 Myasthenia Gravis Quality of Life 15 (MGQOL15)

The results of the MGQOL15 are represented in table 5.2, in a similar custom to how the results of the EQ-5D-5L questionnaire were represented in table 5.1. The results are reported for the total sample, as well as the subgroups EOMG and LOMG. While the nature of the questions of the MGQOL15 are slightly different from that of the EQ-5D-5L, asking the respondents to rank how much they agree to a statement about their quality of life for a health dimension on a scale, rather than pick between five statements representing the rankings of quality of life for the dimension, the five rankings can similarly be transformed into values from 1 to 5, showing a decreasing HRQOL as the value increases. With the amount of questions in the MGQOL15 questionnaire, it becomes harder to easily compare the scores between the subgroups. However, similar to the results of the EQ-5D-5L questionnaire, the values seem fairly similar between subgroups, with mostly small differences. The final values of the table reports the mean of the mean values for each subgroup, as well as the mean MGQOL15 score of the participants. The MGQOL15 score is the sum of all the individual scores of the various items of the questionnaire. As such, the possible scores range from 15 if a respondent was to rank each item of the questionnaire as the lowest option in terms of severity, to 75 if they picked the highest severity option for every item.

Table 5.2: Mean MGQOL15 scores of the total sample, and divided by subgroups EOMG and LOMG.

MGQOL15	Total		EOMG		LOMG	
	Mean	SD	Mean	SD	Mean	SD
I am frustrated by my MG	3.75	1.25	3.74	1.25	3.8	1.32
I have trouble using my eyes	3.3	1.38	3.35	1.31	3.13	1.64
I have trouble eating because of MG	2.48	1.08	2.43	1.06	2.67	1.17
I have limited my social activity because of my MG	3.8	1.21	3.8	1.20	3.8	1.32
My MG limits my ability to enjoy hobbies and fun activities	3.89	1.05	3.94	1.07	3.73	1.03
I have trouble meeting the needs of my family because of my MG	3.01	1.25	2.98	1.27	3.13	1.24
I have to make plans around my MG	3.95	1.05	4.02	1.07	3.73	1.03
My occupational skills and job status have been negatively affected by MG	3.83	1.42	3.98	1.32	3.33	1.67
I have difficulty speaking due to MG	2.47	1.25	2.57	1.28	2.13	1.12
I have trouble driving due to MG	2.54	1.38	2.61	1.36	2.33	1.50
I am depressed about my MG	2.3	1.17	2.43	1.20	1.87	0.99
I have trouble walking due to MG	2.65	1.24	2.53	1,33	3.07	0.80
I have trouble getting around public places because of my MG	2.33	1.16	2.22	1.15	2.73	1.16
I feel overwhelmed by my MG	2.6	1.14	2.59	1.20	2.67	0.96
I have trouble performing my personal grooming needs	1.83	0.95	1.84	0.93	1.87	1.06
Mean score	2.98	0.73	3.00	0.74	2.93	0.70
Mean MGQOL15 score	44.73		45.03		43.99	

5.2 Construct validity

To evaluate the construct validity (convergent and discriminant validity) of the EQ-5D-5L compared to the MGQOL15 when used on a sample of MG patients, Pearson correlations were calculated as described in section 4.5.1. The results of the calculations are displayed in Table 5.3. The Figures 5.3 and 5.4 shows a visualization of the correlations. Table 5.3 shows the Pearson correlations between items of corresponding dimensions in the two questionnaires. For clarity's sake no correlations between non-corresponding dimensions have been included. Additionally, items with no corresponding dimensions in the other questionnaire have been excluded. Meaning the Pain/discomfort dimension of the EQ-5D-5L questionnaire is excluded as well as the "I feel overwhelmed by my MG", "I am frustrated by my MG", "I have trouble using my eyes", "I have trouble meeting the needs of my family because of my MG", "My occupational

Table 5.3: Correlations of corresponding HRQOL dimensions in the total sample. Only the correlations of the corresponding dimensions are displayed. The complete table is shown in Appendix A.

All patients

	EQ-5D-5L			
MGQOL15	Mobility	Self care	Usual activities	Anxiety/Depression
Walking	0.85			
Public places	0.78		0.63	
Personal grooming		0.61	0.50	
Eating				
Social			0.34	
Hobbies			0.24	
Plans			0.30	
Driving			0.40	
Depression				0.70

Table 5.4: Correlations of corresponding HRQOL dimensions in the EOMG subgroup of the sample. Only the correlations of the corresponding dimensions are displayed. The complete table is shown in Appendix A.

EOMG

	EQ-5D-5L			
MGQOL15	Mobility	Self care	Usual activities	Anxiety/Depression
Walking	0.90			
Public places	0.82		0.66	
Personal grooming		0.57	0.49	
Eating				
Social			0.40	
Hobbies			0.27	
Plans			0.39	
Driving			0.43	
Depression				0.71

skills and job status have been negatively affected by MG", and "I have difficulty speaking due to MG", items of the MGQOL15 questionnaire. The correlations had a total possible range between -1 and 1. Where -1 would mean perfect negative correlation, 0 would mean no correlation and 1 would mean perfect correlation.

We can see from Table 5.3 that there is in general significant correlation between the dimensions one would expect. We see that the largest value for the EQ-5D-5L Mobility dimension is the "I have trouble walking" dimension of the MGQOL15 survey, with a correlation of 0.85. As the questions asked in both these surveys are quite similar, it is natural that the correlations would be quite large. We also see that the question "I have trouble getting around public places because of my MG" is also quite highly correlated with the EQ-5D-5L Mobility dimension, with a correlation of 0.78, which also makes sense as this question also deals with mobility. These items both demonstrate convergent validity as defined in section 4.5.1, as $\rho > 0.4$.

From Table 5.3 we also see that the Self care dimension of the EQ-5D-

Table 5.5: Correlations of corresponding HRQOL dimensions in the LOMG subgroup of the sample. Only the correlations of the corresponding dimensions are displayed. The complete table is shown in Appendix A.

LOMG

	EQ-5D-5L			
MGQOL15	Mobility	Self care	Usual activities	Anxiety/Depression
Walking	0.80			
Public places	0.65		0.46	
Personal grooming		0.73	0.56	
Eating				
Social			0.21	
Hobbies			0.24	
Plans			0.17	
Driving			0.44	
Depression				0.57

5L and the "I have trouble performing my personal grooming needs" also fulfill the requirements of convergent validity, with a ρ of 0.61, however the ρ correlation is smaller than it was for both of the correlations between the Mobility dimension and the MGQOL15 items. We can see from Table 5.3 that The Anxiety/Depression dimension of the EQ-5D-5L also displays convergent validity with the "I am depressed about my MG" item of the MGQOL15 with a ρ of 0.70. As these two dimensions are clearly related, these might be the dimensions one might expect to be most correlated of all the items.

When it comes to the Usual activities dimension of the EQ-5D-5L questionnaire, the results are less clear. The dimension displays convergent validity with some of the items of the MGQOL15, namely the questions "I have trouble getting around public places because of my MG" with a ρ of 0.63, "I have trouble performing my personal grooming needs" ρ of 0.50 and "I have trouble driving due to MG" ρ of 0.40, but fails to display it for the items "I have limited my social activity because of my MG" ρ of 0.34, "My MG limits my ability to enjoy hobbies and fun activities" ρ of 0.24, and "I have to make plans around my MG" ρ of 0.30. When testing for so many different items, it makes sense that some would not have high correlations. However, what might be considered odd here is that the highest correlations of the dimension are for the MGQOL15 items that are more strongly correlated with other EQ-5D-5L dimensions, while the MGQOL15 items that one might think should be more strongly correlated with the Usual activites dimension, as opposed to other dimensions, fail the test of $\rho > 0.4$, besides the item about problems driving, which only barely passes. Table 5.4 shows the same results for the subgroup of patients with EOMG while table 5.5 shows that same results for the subgroup of patients with LOMG. We see similar results from these tables as from table 5.3.

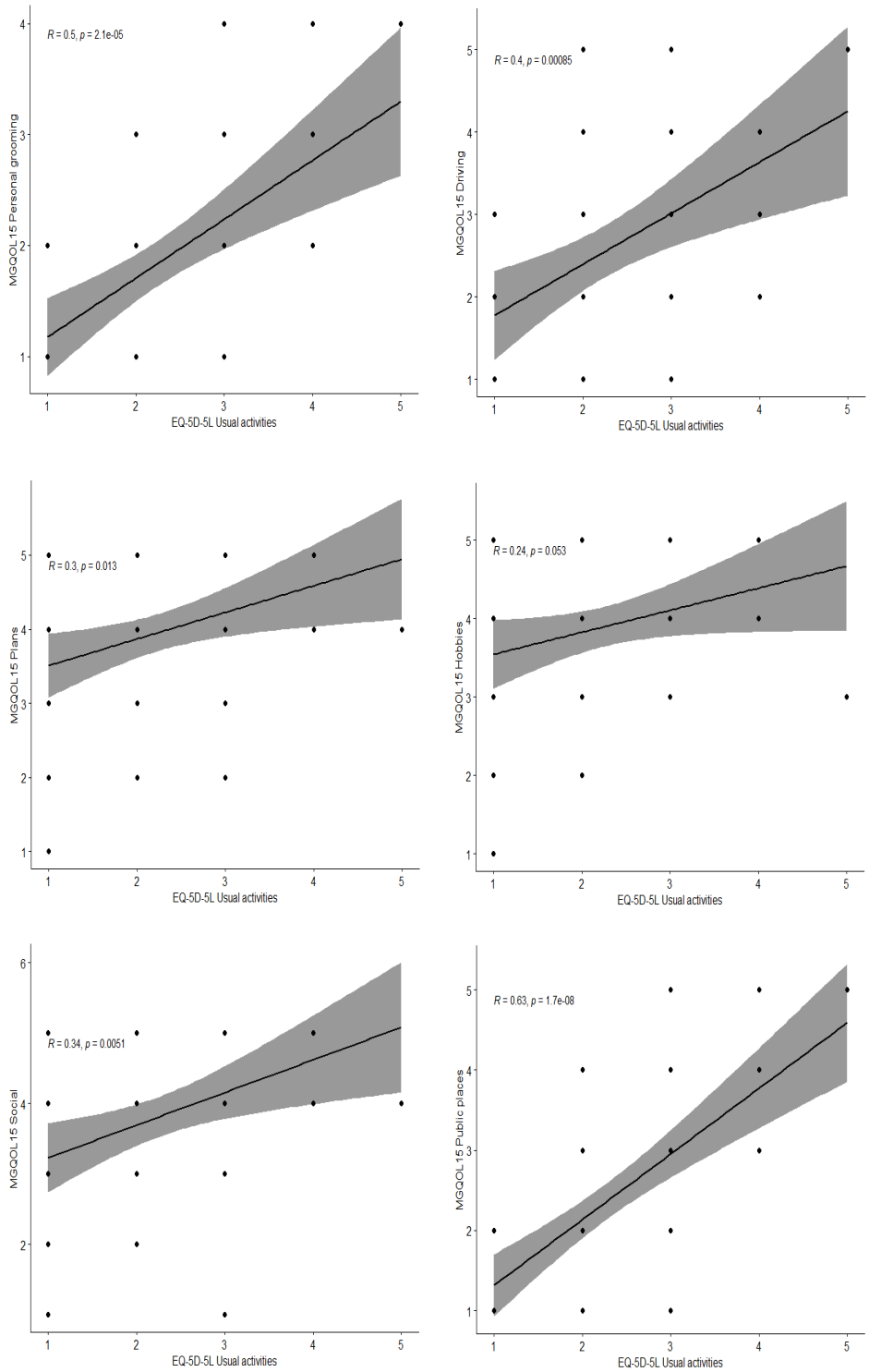

Figure 5.3: Correlations of corresponding EQ-5D-5L and MGQOL15 dimensions. The figure displays the correlations between EQ-5D-5L Usual activities and MGQOL15 "I have trouble performing my personal grooming needs", EQ-5D-5L Usual activities and MGQOL15 "I have trouble driving due to MG", EQ-5D-5L Usual activities and MGQOL15 "I have to make plans around my MG", EQ-5D-5L Usual activities and MGQOL15 "My MG limits my ability to enjoy hobbies and fun activities", EQ-5D-5L Usual activities and MGQOL15 "I have limited my social activity because of my MG", EQ-5D-5L Usual activities and MGQOL15 "I have trouble getting around public places because of my MG".

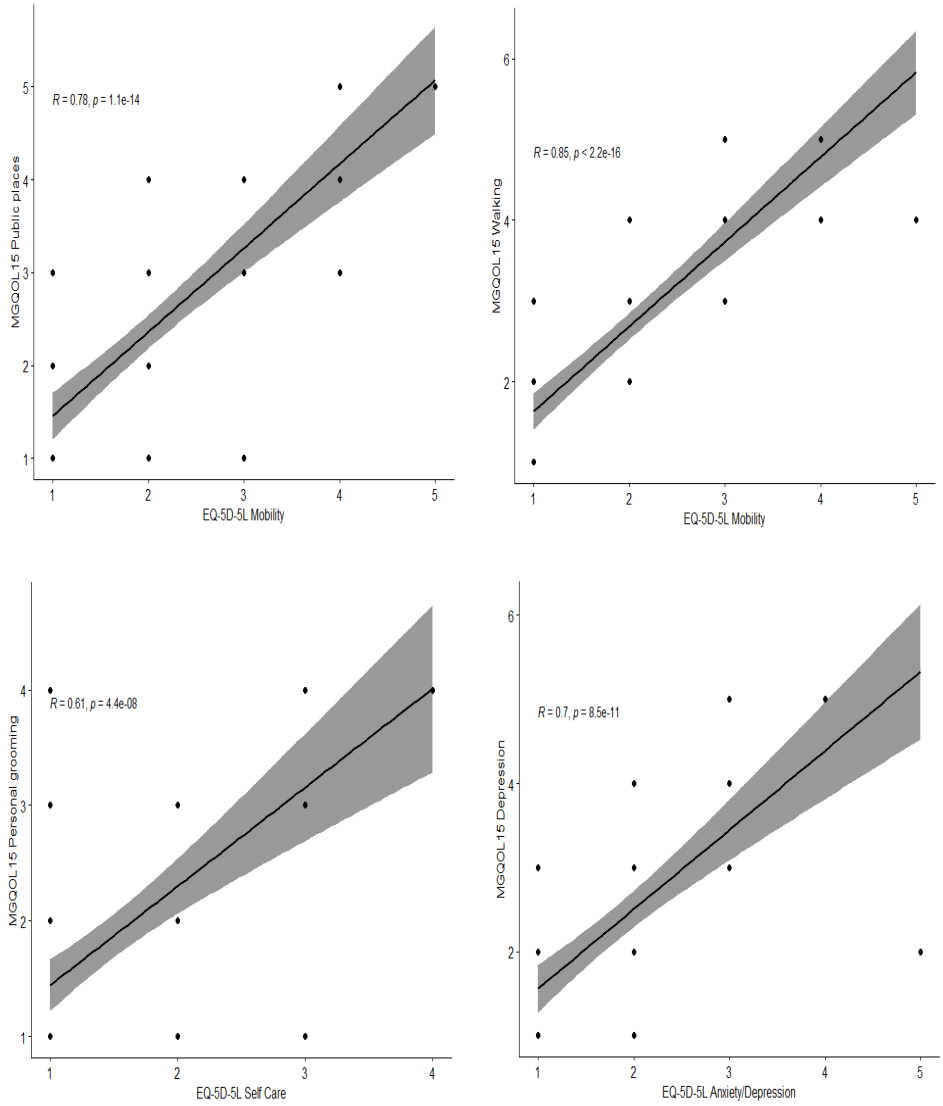

Figure 5.4: Correlations of corresponding EQ-5D-5L and MGQOL15 dimensions. The figure displays the correlations between EQ-5D-5L Mobility and MGQOL15 "I have trouble getting around public places because of my MG", EQ-5D-5L Mobility and MGQOL15 "I have trouble walking due to MG", EQ-5D-5L Self care and MGQOL15 " have trouble performing my personal grooming needs", EQ-5D-5L Depression and MGQOL15 "I am depressed about my MG".

Table 5.6: OLS regression testing whether gender affects the occurence of EOMG in the sample.

EOMG	(1)
Intercept	0.8333***
	(0.0551)
Male	-0.3333**
	(0.1293)
Observations	67
R^2	0.09412

5.3 Regressions

To explore how the HRQOL and costs of the of healthcare utilization of the patients in the dataset were affected by characteristics, regressions were performed.

Table 5.6 shows a regression based on regressing gender on a EOMG variable. These variables are both dummy variables, with either a value of 0 or 1. If the patient is male the gender coefficient is 1, while if the patient is female the gender coefficient is 0. Likewise, if the patient had EOMG, the EOMG variable is 1, while if the patient had LOMG the EOMG variable is 0. We don't include dummy variables for both cases, since this would lead to the dummy variable trap, leading to a case where the independent variables are colinear. The regression shown in Table 5.6 was done to test whether the gender affected the occurrence of EOMG in the patients. The resulting coefficient for gender shows that being male was expected to reduce the occurrence of EOMG by 33 % on the patients in the dataset. The resulting coefficient was statistically significant at a 5 % confidence level. Due to this connection between the two variables, only the EOMG variable was included in further regressions to avoid confounding, an effect where a dependent variable effects both the dependent and an independent variable in a regression.

Table 5.7 shows regressions done using the HRQOL of the patients as the dependent variable. Seven different regressions are shown using various coefficients. The standard deviations of the coefficients are displayed in parentheses underneath their respective values.The dependent variable in these regressions is the patients QALYs. This means that the minimum value of the dependent variable is zero and the maximum value is one. The coefficients of the independent variables represent how much a 1 unit increase would increase the QALY. For example if we look at regression (2) in table 5.7, we see that the value of the "Age" coefficient is 0.0212. This means that aging 1 year is estimated to coincide with an increase in HRQOL by 0.0212. If a hypothetical patient had a QALY of 0.67 one year, they

Table 5.7: OLS regressions of QALYs. The significance of each coefficient is represented by a number of "*". One "*" represents the coefficient being statistically different from zero at a 10 % significance level, two represents the same for a 5 % significance level and three represents the same for a 1 % significance level.

QALYs	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Intercept	0.6463***	0.1844	0.6191***	0.6633***	0.6045***	0.5950***	0.2106
	(0.0826)	(0.1887)	(0.0361)	(0.0514)	(0.0524)	(0.1633)	(0.2098)
Age	-0.0002	0.0212**				0.0001	0.0222***
	(0.0016)	(0.0081)				(0.0025)	(0.0082)
Age quadratic		-0.0002***					-0.0002***
		(0.0001)					(0.0001)
Duration of disease			0.0015	-0.0069		0.0011	-0.0100
			(0.0022)	(0.0073)		(0.0031)	(0.0079)
Duration of disease quadratic				0.0002			0.0003
				(0.0002)			(0.0002)
EOMG					0.0422	0.0339	0.0059
					(0.0597)	(0.0946)	(0.0949)
Observations	67	67	67	67	67	67	67
R^2	0.0002	0.1035	0.0074	0.0297	0.0078	0.0113	0.1481

would then be expected to have a QALY of 0.6912 the next year, based on this model. The "Age quadratic" coefficient is an additional quadratic control variable for the age. The "Duration of disease" coefficient represents how many years it has been since the patient was diagnosed with MG. Similarly to the age of the patient it shows how much a 1 year increase in having lived with MG is expected to impact the QALY. As previously explained, the EOMG variable is a dummy variable with a value of 1 if the patient had EOMG and 0 if they had LOMG. This means that regression (5) for example, patients with EOMG are estimated to have 0.0422 higher HRQOL than those with LOMG. The table also reports the R-squared values of the regressions. We see that these are mostly quite small, but there is also significant variation. The smallest of the values is in the first regression (1) which simply regresses age on the QALY. With such a small R-squared value, we see that this model is a bad fit of the model. We see from the table that the regressions which are the best fits of the model, are the ones which include the quadratic coefficients of age, models (2) and (7). Based on the significance levels and the R-squared values it seems that the age of the patients is by far the most significant factor in determining their HRQOL, of the coefficients used for this regression. The other coefficients are not significantly different from zero in any of the regressions. Including the other variables does however increase the R-squared value showing that the regression including all the variables is the best fit of the model.

5.4 Usage of medical services and costs

Table 5.8 shows the respondents healthcare utilization in the last 6 months prior to survey. From this table we can see that the average amount of visits to a GP or a specialist, was about once every second month. The mean amount of days hospitalized was substantially larger than this, but the more striking difference is the high variance of the days hospitalized. With a standard deviation of 18.59 it was more than three times as large as the standard deviation of visits to the GP at 4.95, and more than six times as large as the standard deviation of visits to a specialist at 3.00. This shows that there is a much higher variation of this type of usage than the other two. Less patients use this kind of treat, but those who do use more of it.

Table 5.8: Healthcare utilization and calculated costs of the sample.

Use and costs of medical services in the last 6 months			
Use of medical services in the last 6 months [mean ± SD]			
GP	2.82	4.95	
Specialist	2.94	3.00	
Days hospitalized	7.67	18.59	
Use of medical services in the last 6 months, including only those who made use of medical services [mean ± SD, n]			
GP	4.34	5.58	43
Specialist	3.49	2.96	55
Days hospitalized	17.46	26.58	26
Mean costs of medical services in the last 6 months [mean ± SD]			
GP	1417	2475	
Specialist	8204	8477	
Hospital	70742	191238	
Total	80362	197384	
Mean costs of medical services in the last 6 months, including only those who made use of medical services [mean ± SD, n]			
GP	2174	2792	43
Specialist	9844	8370	55
Hospital	179575	273426	26
Total	91446	208320	58

Table 5.8 also shows the usage of medical services, when excluding for those that did not make any use of medical services. We see from this that most of the respondents, 55 out of 67, visited a specialist in this period. We also gain more insight into the cause of standard deviation of days hospitalized being so large. We see that the number of patients

Table 5.9: Log-linear regressions of costs using a Poisson distribution. The significance of of each coefficient is represented by a number of "*". One "*" represents the coefficient being statistically different from zero at a 10 % significance level, two represents the same for a 5 % significance level and three represents the same for a 1 % significance level.

Costs	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Intercept	12.1633***	12.5816***	11.4452***	11.8959***	10.7479***	12.2884***	12.0512***
	(0.0016)	(0.0040)	(0.0008)	(0.0010)	(0.0012)	(0.0034)	(0.0047)
Age	-0.0290***	-0.050***5				-0.0203***	0.0078***
	(0.0000)	(0.0002)				(0.0001)	(0.0002)
Age quadratic		0.0002***					-0.0003***
		(0.0000)					(0.0000)
Duration of disease			-0.0678***	-0.1808***		-0.0584***	-0.1810***
			(0.0001)	(0.0002)		(0.0001)	(0.0002)
Duration of disease quadratic				0.0032***			0.0033***
				(0.0000)			(0.0000)
EOMG					0.1273***	-0.0113***	0.1527***
					(0.0013)	(0.0021)	(0.0023)
Observations	67	67	67	67	67	67	67
Akaike Inf. Crit.	8138024	8125805	7884236	7453849	8813892	7551896	7096500

having used this kind of service was substantially smaller than the other two categories. Additionally, we see that the standard deviation is even larger for these respondents, meaning there was a large difference of the length of hospitalization between those who were hospitalized. These factors combined may explain why this standard deviation is so large.

Additionally, Table 5.8 shows some mean approximate costs based on the calculated costs of healthcare utilization. The costs of medical services used, excluding for those who did not use any services, were also calculated and is shown in Table 5.8. We can see that the mean costs of hospitalization were far larger than the mean costs of visiting a GP or a specialist. This difference is even more pronounced when excluding those who did not use the medical services. The approximate costs between visiting a GP and a specialist were also substantial, but in total the difference was far smaller between the visits to a specialist and hospitalization.

To study the effects on the costs of the healthcare utilization of the MG patients, regressions on the calculated costs were performed. The regressions are shown in Table 5.9. The regressions were performed using the same coefficients as the ones used for the regreesions in HRQOl shown in Table 5.7. These regressions were done using a Generalized log linear model with a Poisson distribution. To interpret a Poisson regression coefficient one takes e to the power of the coefficient. If we consider the

coefficient of EOMG in regression (5), for example, we take e to the power of 0.1273:

$$e^{0.1273} = 1.1358$$

Since this coefficient is on a log scale, this means that the EOMG coefficient tells us that patients with EOMG are estimated to have 1.1358 more costly healthcare utilization than the patients with LOMG. The table also reports the AIC of the regressions. Regression (7) has the lowest AIC and is therefore the best fit of the model, however the differences between the different regressions are relatively small considering the large AIC values, implying that there may not be much a difference.

5.5 Mapping

A mapping aproach was performed on the MGQOL15 score, using the HRQOL of the EQ-5D-5L questionnaire as described in section 4.5.3, in order to make it possible to predict health state preference values for the MGQOL15. The results of the mapping is shown in Table 5.10. We see that both the intercept and the coefficient for MGQOL15 are statistically significant at a 1% significance level. We see from both regressions that the models estimate an increase of 1 in the MGQOL15 score to lead to a decrease of about 0.01 HRQOL. The intercepts show values that are larger than 1 which should in theory not be possible. This is most likely the case because the intercept is based on the MGQOL15 score being 0. However the minimum value of the MGQOL15 score is 15, leading to this misleading intercept.

Table 5.10: Mapping of the EQ-5D-5L on the MGQOL15 using an OLS regression.

HRQOL	(1)	(2)
Intercept	1.0738***	1.0370***
	(0.0898)	(0.0967)
MGQOL15 Score	-0.0098***	-0.0098***
	(0.0019)	(0.0019)
EOMG		0.0522
		(0.0508)
Observations	67	67
R^2	0.2812	0.2931

Chapter 6

Discussion

6.1 Comparison of the two surveys

6.1.1 Health Related Quality of Life (HRQOL)

When looking at the values of the total sample in Table 5.1 and Table 5.2, it is quickly apparent that the values of the MGQOL15 questionnaire are generally larger than those of the EQ-5D-5L questionnaire. The mean of the EQ-5D-5L values is 1.97 while the mean of the MGQOL15 values is 2.98. A full level of difference. There are only two values of the EQ-5D-5L dimensions that are above 2, the Usual activities dimension and the Pain/discomfort dimension, while in the MGQOL15 questionnaire only the question about personal grooming needs is below 2. The largest of the EQ-5D-5L values is 2.39 related to the Pain/discomfort dimension, while the largest of the MGQOL15 values is regarding the item "I have to make plans around my MG" with a value of 3.95, more than a full level of difference. The difference between the smallest values of the two surveys, is of less magnitude than between the largest values between the two surveys, with a value of 1.45 for the Self-care in the EQ-5D-5L questionnaire and a value of 1.83 for the question "I have trouble performing my personal grooming needs" in the MGQOL15 questionnaire. However, the MGQOL15 value being larger than the EQ-5D-5L value is also the case here. Similar findings hold true when comparing the other subgroups. The values of the MGQOL15 questionnaire tend to be larger than those of the EQ-5D-5L questionnaire.

What conclusions can be drawn from these results, are debatable. Intuitively, the result seems to imply that the EQ-5D-5L questionnaire is less sensitive to capture the issues facing the MG patients than the MGQOL15. If this is the case, results from the EQ-5D-5L survey when measuring the HRQOL of MG patients may be skewed in a way that makes it seem like the HRQOL of MG patients is better than it really is. However, an opposite explanation could be that the results of the MGQOL15 are the skewed ones, rather than the results EQ-5D-5L, as the questions are all focused on issues commonly found in MG rather than measuring 5 dimensions of health. While this is a plausible explanation for the difference in the means of the values, it is still strange how

the scores from the MGQOL15 questionnaire are larger than those from the EQ-5D-5L questionnaire, even for dimensions one would think are comparable. For example the value of the Mobility dimension in the EQ-5D-5L questionnaire is 1.97, while the MGQOL15 question "I have trouble walking due to MG" has a mean score of 2.65. It is plausible that the values of this question should have relatively similar results, but the difference is quite large. This could perhaps be partly explained by the nature of how the questions are asked. The EQ-5D-5L asks the respondents how much they agree with five statements of different levels of severity, while the MGQOL15 asks the respondents to say how much they agree with a statement, where the more they agree the higher degree of severity there is.

6.1.2 Construct Validity

The construct validity was tested by testing the item correlation of corresponding dimensions of the two questionnaires. Testing for whether the condition $\rho > 0.4$ holds, between the various dimensions. In general the condition held for the items being tested, with the exception being the items related to the Usual activities dimension of the EQ-5D-5L questionnaire. Construct validity was therefore mostly considered to hold, demonstrating that these dimensions of the MGQOL15 have similar constructs in the EQ-5D-5L. However, there were also multiple dimensions of the MGQOL15 which had no strongly correlated EQ-5D-5L dimension, implying that there may be issues faced by MG patients that are not fully captured by the EQ-5D-5L questionnaire.

6.2 Mapping

A mapping procedure was performed by regressing the MGQOL15 score on the EQ-5D-5L HRQOL using an OLS regression. The regression was performed both when including and not including a dummy variable for whether the patient belonged in the EOMG subgroup. Whether the patient had EOMG or not made no difference regarding the magnitude of the coefficient for the MGQOL15 score. In both regressions it was -0.0098, or about -0.01 rounding up. The regressions appeared to produce a strange magnitude for the intercept coefficient. The intercept shows the HRQOL value when the MGQOL15 score is 0. A natural assumption would then be that the intercept should be 1, representing perfect HRQOL since the HRQOL is decreasing with an increasing MGQOL15 score. However, the lowest value of the MGQOL15 is 15 rather than 0. This means that the intercept has become larger than 1 despite the max value of HRQOL being 1.

While an estimation of the two measures has been made in order to determine a statistical association between the two measures, a full mapping procedure also requires a second estimation dataset in order to apply the results to obtain the predicted health state preference values. With only one dataset, this part of the procedure was not a possibility for

this study, but the results can potentially be used by others on a different dataset.

6.3 Comparison with other studies

Comparing the HRQOL results of this project with results of other studies seems to imply that the participants of this study have fairly comparable HRQOL to the results of other studies. Using the mean HRQOL value of the total population of the sample, 0.63, when comparing with the results of other studies this appears similar to what many other studies have found. In a study from 2001 Paul et al. found a mean HRQOL of 58.4, in an American study on 27 patients. Boldingh et al. (2015) reported HRQOL values ranging from 82.7 to 48.0, depending on the subgroup, with most of the subgroups fitting between 60 and 80, in their study on patients from Norway and Netherlands from 2015. In their study from 2010, Twork et al. (2010) reported an average HRQOL of 60.7 of their German participants.

This result might be considered somewhat surprising considering the selection of participants for this study. With all participants being chosen based on their affiliation with the Norwegian MG patient association, as well as being interested in participating in a survey regarding their HRQOL, it doesn't seem unreasonable to believe that the sample would be biased and result in generally lower HRQOL scores than what most other studies find. There are multiple possibilities for why this bias does not seem to have occurred when compared to other studies. The simplest explanation would be that the members of the patient association is in fact representative of the total MG population, and the method of selection did not cause error based on a bias. A different explanation could be that the sample was in fact biased, and that the mean HRQOL of the Norwegian patient population is higher than what has been observed in previous studies.

6.4 Challenges and limitations of study

Due to the voluntary nature of the survey and the small number of possible respondents, a large concern regarding the completion of the project was how to gather a sufficient amount of data material to be able to produce results of statistical significance. It was therefore deemed important to keep the complete survey as simple as possible, while still gathering important information, in order to maximize the amount of respondents. It was a concern that many of the MG patients would find responding to the survey to be too much of a hassle due to the nature of their disease.

During the design of the study, the small size of the number of potential respondents led to a concern that there would be too few observations for any statistical analysis to be statistically significant. As such, achieving as large of a percentage of respondents as possible was an important focus. This focus affected multiple choices, such as which HRQOL instruments to use and how many questions could be asked. The decision to make

the survey anonymous, was also made on this basis, further limiting what information could be gathered. Keeping the survey anonymous seemed the only feasible way to get permission to gather the kind of health data required for this project.

A consequence of making the survey anonymous was a lack of control over which individuals could fill out the survey. One potential issue that could arise for this solution, would be individuals filling out the form multiple times, thus giving an incorrect view of the sample. As the site used for the surveys could track the the ip of the respondents, ensuring that the same individuals would not be able to give multiple responses, this was not a concern for this solution in particular. However, there was no control over who responded to the survey. This meant that an individual without MG could in theory have clicked the link to the survey and filled out the questionnaire. This seemed like a difficult issue to solve while keeping the survey anonymous.

A potential solution could have been to give the link to a third party, such as the leaders of the patient organization, and ask respondents interested in filling out the survey to contact the third party. The third party could then have controlled whether the respondent was truly suffering from MG and only supplied the survey link once the respondents MG condition was confirmed. This way the anonymity of the patient would be retained, even while their condition was confirmed. However, while this was considered, it was eventually concluded that such a solution would be far too convoluted to be feasible. It was hypothesized that such a solution would seem far too bothersome for most of the patients, leading a small sample of the population. Besides this kind of solution seeming too complicated to be feasible, the issue was also deemed not to be particularly critical. It was considered unlikely that any non-MG patients would reply to the survey unintentionally. For someone who does not suffer from MG to reply to the survey, they would have to do so intentionally, knowing they were not intended for the survey. Therefore someone without MG would have to have some kind of motivation to falsely respond to the questionnaire. Such motivations seem highly implausible. The only such motivation that comes to mind is a wish to skew the results in a way such that the severity of the disease seemed more grave than it is in reality, in hopes that this would somehow influence any decision making regarding the treatment of the disease. This seems like it would be an extremely inefficient way to affect the decision making, with an extremely low chance of having any effect. As such it does not seem like a possible rational motivation. Overall, it was possible for someone without MG to have responded to the survey, but it does not seem particularly plausible.

The selection of the population sample is another concern regarding the validity of the results. The survey was only shared among patients who had joined the patient group. Assuming that the members of this patient group have differences in characteristics compared to the total MG population of Norwegian patients, is very reasonable. It seems likely that, on average, the members of the patient group would tend to be more affected by their disease than the total MG population. This would mean

that the results of the survey would be skewed towards higher scores in the two surveys and lower HRQOL, further affecting the analysis and findings of this paper. There may be more differences in the averages between the patient group and the total patient population, such as age for example, but these kind of differences seem less clear, as well as less problematic for the final results.

The problem of the selection bias of the sample was an issue that was clear from the start of the project, but any solutions to the problem seemed feasible. To gain an unbiased sample the survey would have to be shared with the entire patient population or a randomized sample of the total population. Either way, access to the entire population would be a necessity for this kind of solution. This was considered to be implausible within the timeframe of the assignment. Sharing the survey to the members of the patient group seemed the only option available, which could lead to sufficient data material, for statistical analysis.

A lack of demographic characteristics might be another issue of the study. In order to receive permission to gather the data from the surveys, care was taken not to ask questions which would gather unnecessary medical information. This focus may have been misguided as some of this information may have been crucial to the analysis of the data. Questions about the patients', quantitative myasthenia gravis score, their medications, type of antibodies, or thymus histology, may have enriched the results further.

The translation of the MGQOL15 survey is another source of possible errors. As mentioned earlier, there is no validated Norwegian version of the MGQOL15 survey, and the survey therefore had to be translated. The translation was done with a focus on retaining the original focus and purpose of the questions, but there may still have been interpretation errors.

Chapter 7

Conclusion

The objective of this paper was to increase the general knowledge of various aspects regarding the HRQOL of Norwegian MG patients, in order to generate useful knowledge for economic evaluations of treatments for the disease. To do so, a sample of Norwegian MG patients was surveyed, regarding their HRQOL and their healthcare utilization. Based on the generic questionnaire EQ-5D-5L, the HRQOL of the patients was calculated and presented. When compared with the results of other studies, the results seem fairly similar to previous studies. Based on the possibly biased selection of the study, the similar results could be construed as a positive finding. However, it could also be pointed out that the HRQOL of this patient group does not seem to have improved much in the years between the other studies and this one.

Based on the patients' utilization of healthcare and assumptions about the corresponding DRG codes, approximate costs of the patients' utilization of healthcare was calculated.

A construct analysis was also performed between the generic HRQOL questionnaire EQ-5D-5L and the disease specific HRQOL questionnaire MGQOL15, in order to assess the validity of the EQ-5D-5L as an instrument to measure the HRQOL of Norwegian MG patients. The results mostly showed sufficient convergent validity for corresponding dimensions of quality of life, but there were also multiple items of the MGQOL15 without corresponding dimensions in the EQ-5D-5L. Overall, based on the construct analysis and the generally higher mean scores of the MGQOL15, the EQ-5D-5L appears to give somewhat incomplete information regarding the HRQOL of Norwegian MG patients, and studies investigating the HRQOL of Norwegian MG patients should possibly supplement use of the EQ-5D-5L with other measurements of HRQOL to obtain the most accurate data of the patients' HRQOL.

Based on the limitations of this study, generalizations from the results of the study can be hard to justify. Further studies on the HRQOL of Norwegian MG patients should ideally be sampled randomly from the full population of patients, in order to gain a representative and non-biased sample. Furthermore, permissions to gather more data regarding the patients' current treatments, as well as medical data regarding the

patients' subgroup, would likely enrich the analysis in key areas.

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Appendix A

Appendix Tables

Table A.1: Reproduction of the Norwegian version of the EQ-5D-5L questionnaire. The table is only a reproduction of the questions themselves, not of how the questionnaire shared with the respondents looked to the respondents.

Velg den ENE boksen som best beskriver helsen din I DAG.	
EQ-5D-5L	
GANGE	
Jeg har ingen problemer med å gå omkring	☐
Jeg har litt problemer med å gå omkring	☐
Jeg har middels store problemer med å gå omkring	☐
Jeg har store problemer med å gå omkring	☐
Jeg er ute av stand til å gå omkring	☐
PERSONLIG STELL	
Jeg har ingen problemer med å vaske meg eller kle meg	☐
Jeg har litt problemer med å vaske meg eller kle meg	☐
Jeg har middels problemer med å vaske meg eller kle meg	☐
Jeg har store problemer med å vaske meg eller kle meg	☐
Jeg er ute av stand til å vaske meg eller kle meg	☐
VANLIGE GJØREMÅL (f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)	
Jeg har ingen problemer med å utføre mine vanlige gjøremål	☐
Jeg har litt problemer med å utføre mine vanlige gjøremål	☐
Jeg har middels store problemer med å utføre mine vanlige gjøremål	☐
Jeg har store problemer med å utføre mine vanlige gjøremål	☐
Jeger ute av stand til å utføre mine vanlige gjøremål	☐
SMERTER / UBEHAG	
Jeg har verken smerter eller ubehag	☐
Jeg har litt smerter eller ubehag	☐
Jeg har middels sterke smerter eller ubehag	☐
Jeg har sterke smerter eller ubehag	☐
Jeg har svært sterke smerter eller ubehag	☐
ANGST / DEPRESJON	
Jeg er verken engstelig eller deprimert	☐
Jeg er litt engstelig eller deprimert	☐
Jeg er middels engstelig eller deprimert	☐
Jeg er svært engstelig eller deprimert	☐
Jeg er ekstremt engstelig eller deprimert	☐

Table A.2: Reproduction of the Norwegian version of the MGQOL15 questionnaire. The table is only a reproduction of the questions themselves, not of how the questionnaire shared with the respondents looked to the respondents.

MGQOL15
Min MG diagnose frustrerer meg.
Jeg har problemer med synet.
Jeg har problemer med å spise på grunn av MG.
Jeg har begrenset min sosiale aktivitet på grunn av min MG.
Min MG begrenser mine muligheter til å drive med hobbyer og aktiviteter jeg liker.
Jeg har problemer med å dekke behovene til familien min på grunn av min MG.
Min MG diagnose krever at jeg planlegger.
Min yrkeskompetanse og jobbstatus har blitt negativt påvirket av MG.
Jeg har problemer med å snakke på grunn av MG.
Jeg har problemer med å kjøre bil på grunn av MG.
Jeg er deprimert på grunn av min MG.
Jeg har problemer med å gå på grunn av MG.
Jeg har problemer med å komme meg rundt på offentlige steder på grunn av min MG.
Jeg føler meg overveldet av min MG.
Jeg har problemer med å utføre mine personlig pleiebehov.

Table A.3: Complete correlation table of the total sample.

All patients

	EQ-5D-5L				
MGQOL15	Mobility	Self care	Usual activities	Anxiety/Depression	Pain
Walking	0.85	0.41	0.55	0.00	0.32
Public places	0.78	0.44	0.63	0.09	0.26
Personal grooming	0.51	0.61	0.50	0.22	0.25
Eating	0.13	0.13	0.23	0.21	0.28
Social	0.21	0.20	0.34	0.31	0.37
Hobbies	0.10	0.22	0.24	0.33	0.31
Plans	0.17	0.14	0.30	0.32	0.33
Driving	0.32	0.30	0.40	0.17	0.25
Depression	-0.04	-0.12	0.06	0.70	0.24
Overwhelmed	0.08	-0.06	0.23	0.41	0.34
Frustrated	0.15	0.08	0.19	0.22	0.24
Eyes	0.03	-0.03	0.10	0.18	0.22
Family needs	0.19	0.17	0.37	0.26	0.39
Occupational skills	0.08	0.05	0.25	0.22	0.19
Speaking	0.25	0.29	0.29	0.23	0.22

Table A.4: Complete correlation table of the patients in the EOMG subgroup in the sample.

EOMG

	EQ-5D-5L				
MGQOL15	Mobility	Self care	Usual activities	Anxiety/Depression	Pain
Walking	0.90	0.38	0.52	0.01	0.30
Public places	0.82	0.41	0.66	0.14	0.28
Personal grooming	0.41	0.57	0.49	0.25	0.24
Eating	0.03	0.22	0.29	0.19	0.23
Social	0.24	0.22	0.40	0.30	0.44
Hobbies	0.09	0.30	0.27	0.30	0.32
Plans	0.17	0.10	0.39	0.33	0.34
Driving	0.40	0.27	0.43	0.13	0.37
Depression	0.12	-0.06	0.18	0.71	0.34
Overwhelmed	0.12	-0.05	0.31	0.47	0.38
Frustrated	0.19	0.09	0.24	0.18	0.29
Eyes	0.23	0.12	0.23	0.24	0.35
Family needs	0.27	0.33	0.54	0.29	0.37
Occupational skills	0.26	0.22	0.38	0.20	0.19
Speaking	0.31	0.38	0.42	0.14	0.21

Table A.5: Complete correlation table of the patients in the LOMG subgroup in the sample.

LOMG

	EQ-5D-5L				
MGQOL15	Mobility	Self care	Usual activities	Anxiety/Depression	Pain
Walking	0.80	0.59	0.67	0.20	0.48
Public places	0.65	0.53	0.46	0.01	0.11
Personal grooming	0.79	0.73	0.56	0.11	0.32
Eating	0.31	-0.10	0.00	0.44	0.54
Social	0.15	0.17	0.21	0.39	0.05
Hobbies	0.21	0.01	0.24	0.45	0.34
Plans	0.33	0.26	0.17	0.23	0.34
Driving	0.24	0.42	0.44	0.32	-0.35
Depression	-0.38	-0.25	-0.13	0.57	-0.33
Overwhelmed	-0.06	-0.12	-0.07	0.08	0.08
Frustrated	0.05	0.04	0.04	0.47	-0.03
Eyes	-0.36	-0.37	-0.14	-0.07	-0.34
Family needs	-0.04	-0.28	-0.19	0.17	0.53
Occupational skills	-0.14	-0.29	0.13	0.22	0.36
Speaking	0.28	0.07	0.05	0.69	0.39