Leber Hereditary Optic Neuropathy: Patient burden, utility estimates, and carer burden

Across three studies, the presented research was designed to describe and value the burden and HRQoL of LHON patients and carers.

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What is the Wider Carer and Family Burden in Leber Hereditary Optic Neuropathy? A Mixed-Methods Study

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INTRODUCTION

- Leber Hereditary Optic Neuropathy (LHON) is a maternally inherited mitochondrial disease which leads to central vision loss due to optic neuropathy [1,2].
- Visions loss starts with a painless blurring and clouding of the central vision, typically in one eye at first, that rapidly progresses to blindness in both eyes [3].
- The condition typically presents in young adulthood [4] and causes significant impacts on many aspects of patients' lives including daily activities, emotional functioning, relationships, studies, work, recreation and finances [5].
- As such, the condition can be difficult to adjust to which anecdotally leads to substantial impacts on informal carers and family members.

OBJECTIVE

This study was designed to describe the burden of LHON for informal carers and family members using qualitative and quantitative methods.

METHODS

- Informal carers and family members (N=9, aged 18+) of patients diagnosed with LHON completed in-depth interviews.
- Participants were recruited through a patient advocacy group (PAG) in the United Kingdom (UK) and the study sponsor.
- Interviews explored how daily activities were affected as well as physical, social, emotional, work, educational and financial impacts.
- Participants completed the EQ-5D-5L, CarerQol-7D, Work Productivity and Activity Impairment (WPAI) Questionnaire and a background questionnaire containing socio-demographic and clinical questions relating to themselves and the person they cared for.
- The study protocol was reviewed by an Independent Review Board. All study participants provided informed consent.
- Socio-demographic, clinical and HRQoL data were summarised using descriptive statistics.
- Utility scores for the EQ-5D-5L were calculated using the Hernandez et al. (2020) mapping function.
- Six scores for the CarerQoL-7D were derived using preference weights generated for the UK [6].
- Seven domain scores for the WPAI were generated using scoring algorithms [7].
- Interview data were analysed using content analysis.

QUANTITATIVE RESULTS

- Nine informal carers and family members in the UK participated in the study (age range 30-70; 8 females; 5 parents).
- Of the care recipients, n=6 were male (mean age 32, range 17-73), n=7 had the ND4 mutation, n=1 had the ND6 mutation (n=1 unknown), and all had received treatment in the past (n=6 Idebenone, n=1 GS010, n=3 other).
- **EQ-5D-5L:** The mean EQ-5D-5L utility value was 0.893 (SD= 0.245, range 0.244 – 0.988) and the mean EQ-VAS score was 84.2 (SD=8.5, range 72.5 – 95.0), see **Figure 1.**
- Seven of the nine participants responded that they had no problems in any of the EQ-5D-5L domains.
- **CarerQol-7D**: The mean CarerQol-7D utility was 78.4 (SD= 21.0, range 31.9 – 96.9) and the mean CarerQol VAS score was 6.67 out of 10 (SD= 3.12, range 0.00 - 9.00), see **Figure 1**.

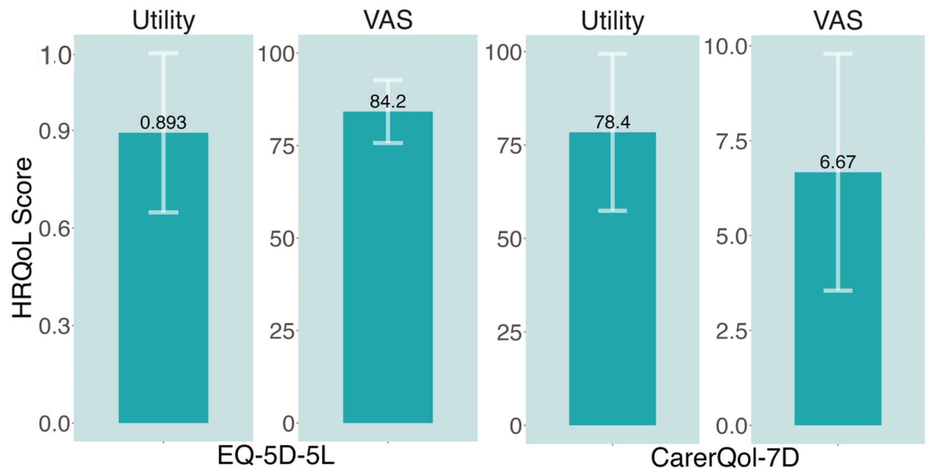

Figure 1. Mean EQ-5D-5L and CareQol-7D utility value and VAS scores

- **WPAI:** Most carers were in employment (n=7, 78%). Mean absenteeism was 14%, however, this value was driven by a single carer who was currently unable to work.
- Of those in work, mean presenteeism was 15%.
- Mean work productivity loss was also 15% and mean activity impairment was 36.7%, see **Figure 2**.

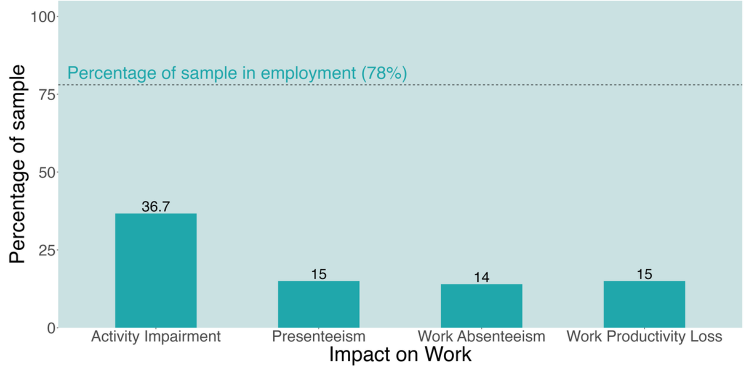

Figure 2. Mean WPAI domain scores

QUALITATIVE RESULTS

- Qualitative findings (N=9) revealed substantial burden for many carers and family members.
- The most prominent impacts were emotional (e.g., guilt, devastation), including many participants who described the specific emotional impact of LHON being a maternally inherited disease (n=8/9 were female).
- Impacts to daily life, social life and relationships, work and career, finances and the wider family were also described.
- A summary of carer and family impacts is presented in **Figure 3**.

Carers reported feelings of devastation at the time of diagnosis. Mothers discussed immense feelings of guilt for passing on a gene that caused their child's vision loss. Worry about the future was a prominent theme across interviews. The profound emotional impacts of caring for someone with LHON had knock on effects on other areas of life.

> *"Watching your firstborn child's every plan, every hope, every dream change overnight, that's absolutely devastating"* **CG05, parent**

Due to the genetic nature of the condition, carers reported that family members worried about themselves or their children developing symptoms in future to the extent that some sought professional help to cope with this anxiety, while others decided against starting a family or having more children.

> *"Mum, I've got a disease that I've passed onto my child, it could cause him to go blind in the future', she said, 'and I was about to have another child', she said, 'and now I can't"* **CG01, parent**

Financial impacts included the cost of travel and accommodation for appointments and self-funded treatment. Carers who had a partner with LHON who did not work, supported them financial and reported limited money for themselves or luxuries such as holidays.

> *"Financially, it's quite hard because I get all the mortgage taken out of my account and I buy all the food… I'd love just to be able to go out and do a massive shopping trip to myself but the end of the month, normally we don't have that much left"* **CG07, partner/spouse**

Carers discussed how their daily routine and activities had changed to accommodate their care tasks. Several carers reported that they prioritised the individual with LHON's daily activities over their own and had limited time to participate in leisure activities and hobbies.

> *"I have to spend more time at home than perhaps the average person would do, they'd get more involved in outdoor activities, clubs, societies, all that sort of thing, which is not really viable for me"* **CG04, partner/spouse**

Some carers described the limited time they had to socialise, while others reported intentionally isolating themselves to avoid discussing LHON with friends. One carer had even cut ties with friends due to a lack of support and understanding. A few carers reported that the physical and emotional demands of providing could cause a strain on their relationship with their partner.

> *"There's a lot of friends I don't really want to see because I don't want to sit and talk about it"* **CG01, parent**

Most carers had taken time off work around the time of diagnosis to provide support. One participant had been signed off work due to the emotional impacts of the diagnosis, while others had reduced their hours and work trips to cope with the logistical and emotional demands of providing care.

> *"I've needed to be part time really, to have the time and emotional energy to deal with things that suddenly crop up"* **CG08, parent**

Figure 3. Map of carer impacts from qualitative analysis

DISCUSSION AND CONCLUSIONS

- The qualitative findings suggest a substantial burden for many carers and family members with impacts reported across numerous aspects of daily life.
- However, the burden described in the qualitative data was incongruent with the quantitative measures.
- Questionnaire results suggest a relatively small burden to carers with minimal impacts on HRQoL, work and regular activities reported. For example, the mean EQ-5D utility was 0.89, compared with a UK population average of 0.85 in adults aged 45-54 [8].
- This demonstrates the value of conducting mixed-methods research to understand the impact of disease and the importance of selecting measures which capture population-relevant concepts.
- A potential limitation of the current study is the sample size was small (N=9) and included three participants which were a carer or family member of the same individual with LHON meaning their experiences may have been disproportionally represented.
- **This research demonstrates the substantial burden associated with LHON and potential spillover effects on carers and family members.**

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Characterising Patient Burden in Leber Hereditary Optic Neuropathy Using Mixed Methods Research

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INTRODUCTION

- Leber hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease which leads to central vision loss due to optic neuropathy [1,2].
- The condition typically emerges in young adults and is more common among men [3].
- Symptoms start with a painless blurring and clouding of the central vision, typically in one eye at first, which rapidly progresses to blindness in both eyes [4].
- However, the impact of different levels of vision loss on health-related quality of life (HRQL) is not well documented.
- GS010 (GenSight Biologics) is a gene therapy for the treatment of LHON in patients with an ND4 mutation.
  - The health economic model for GS010 included eight health states defined by level of visual acuity (LogMAR).
  - Health state vignettes characterising the experience of patients with LHON were required to support cost effectiveness analyses.

OBJECTIVE

This study used mixed methods to develop and validate health state vignettes characterising the burden of LHON at different levels of visual acuity.

METHODS

- Eight health state vignettes were developed in line with the GS010 model structure (see **Table 1**).
- A brief targeted literature review was conducted which aimed to characterise the patient experience of LHON and understand the different impacts of the condition at various levels of visual acuity.
  - Published health state vignettes describing another rare inherited eye condition, RPE65-mediated inherited retinal disease (IRD), were drawn upon to develop the vignettes [5].
- Secondary analyses of data from the REFLECT trial [6] were conducted to characterise the patient experience of LHON. Visual Function Questionnaire (VFQ-25) [7] data were summarised by LogMAR group. Median values for each group were described to identify potential points of difference between health states.
- Draft health state vignettes were developed based on the findings from the literture review and trial data.
- Semi-structured qualitative interviews were conducted with individuals living with the condition (N=9) as well as clinical experts (N=5) to develop and validate the content of the draft health state vignettes.
  - Participants were recruited from patient advocacy groups (PAGs) in the United Kingdom (UK) and Republic of Ireland (ROI) or through the study sponsor.
- The draft health state vignettes were revised following feedback.

Table 1. Health state definitions

Health state	Definition
On-chart health states	
HS1	LogMAR <0.3
HS2	LogMAR ≥0.3 and <0.6
HS3	LogMAR ≥0.6 and <1.0
HS4	LogMAR ≥1.0 and <1.3
HS5	LogMAR ≥1.3 and <1.7
Off-chart health states	
HS6	Counting fingers (LogMAR ≥2.0)
HS7	Hand motion (LogMAR ≥2.3)
HS8	Light perception (LogMAR ≥4.0)

RESULTS

Draft health states

- Eleven key concepts were included in the draft vignettes: a description of the condition including the severity of visual impairment; ability to read words on a page, cross a street safely and recognise people; ability to see at different times of the day and go outside independently; ability to use electronic devices; ability to drive and use other modes of transport; emotional impacts; social impacts; ability to conduct usual activities; ability to participate in sport; pain experienced; and ability to participate in work or education.

Patient and clinician interviews

- Nine patients and five clinicians reviewed the vignettes for their accuracy and representativeness. Key revisions to the vignettes in response to feedback were made:
  - Impact of LHON on central vision specified. Possible effects to peripheral vision as well as potential for further deterioration described.
  - Probable use of low vision aids to support reading and recognition included.
  - Statement added describing ability to navigate familiar and unfamiliar environments. Reference to time of day removed.
  - Logistic and emotional challenges of socialising specified. Statement added describing difficulty of having a visual impairment that is not obvious.

Finalised vignettes

- An overview of the final concepts included in the vignettes is presented in **Table 2**, with examples from health state 1 and health state 8.

Table 2. Overview of concepts included in health states, with examples from health state 1 and health state 8

Concept	Health state 1 (LogMAR <0.3)	Health state 8 (light perception/LogMAR≥4.0)
Description of condition	You have an eye condition that has caused a mild impairment of your central vision. You have some use of your peripheral vision. You have been told that your vision may continue to deteriorate.	You have an eye condition that has left you with almost complete central vision loss. You are able to detect the difference between light and dark. You have very limited use of your peripheral vision.
Reading and recognition	You can read words on a page with minimal difficulty. You can usually recognise people when you meet them.	You cannot read words on a page and rely on read aloud technology. You can only recognise someone by their voice.
Electronic devices	You are able to use mobile phones, tablets and computers with minimal or no adaptation.	You rely on adaptations (e.g. read aloud technology) to use electronic devices like mobile phones, tablets and computers.
Mobility and navigation	You can navigate familiar and unfamiliar environments independently with minimal difficulty.	You can mostly navigate familiar environments with minimal difficulty. You are unable to navigate unfamiliar environments without the assistance of another person or visual aid.
Transport	You are able to drive. However, you may find driving a little difficult and may not feel confident because of your visual impairment.	You are unable to drive and get limited use of public transport. Your vision loss means that you rely on friends, family members, or taxis to take you where you need to go.
Emotional impact	Your vision loss can be very difficult to come to terms with. You sometimes feel frustrated and worry about the future. You sometimes feel anxious or depressed.	Your vision loss is devastating, and you find it very difficult to come to terms with. You often feel frustrated and worry about the future. You often feel anxious or depressed.
Social impact	You can mostly socialise normally and are able to meet new people. You are able to go to social events such as restaurants.	You find socialising difficult and are socially isolated. You find it hard to meet new people because of your vision loss. Social activities such as going to a restaurant can be extremely logistically and emotionally challenging. This limits the enjoyment you feel from such events and the type of social events you can attend.
Dependency/usual activities	You are able to conduct most of your usual activities (e.g. shopping, cooking and paperwork) without help from others.	You rely on others to help you conduct most of your usual activities (e.g. shopping, cooking and paperwork).
Sports/leisure activities	You can physically do most sports, such as gym work, with minimal assistance. Your vision loss limits some of the types of sports you can take part in.	You can physically do some sports, such as gym work, with assistance. Your vision loss limits the types of sports you can take part in.
Pain	Your eye condition does not cause you any pain.	Your eye condition does not cause you any pain.
Work/education	You are able to participate in work or education with minimal assistance. Your condition means that some career paths and roles may not be an option for you.	You rely on support from others and adaptations to participate in work or education. Your condition means that some career paths and roles may not be an option for you.

RESULTS

Literature review

- The review identified several key concepts to help characterise the patient experience of LHON. Losing vision disrupts many daily activities and affects an individual's ability to live and act within the social world. The loss of skill, ability and independence experienced has significant social and emotional impacts. Although many patients develop the practical and emotional coping mechanisms to overcome daily hassles and challenges, their limited sight means many have fewer options in life which can lead to continued feelings of loss and frustration.

Trial data

- A summary of responses to key variables is presented in **Figure 1**, which summarises data for 21 items which helped form our understanding of the patient experience of LHON. The data demonstrate that the impacts of LHON increase progressively with each health state and also help provide differentiation between health states.

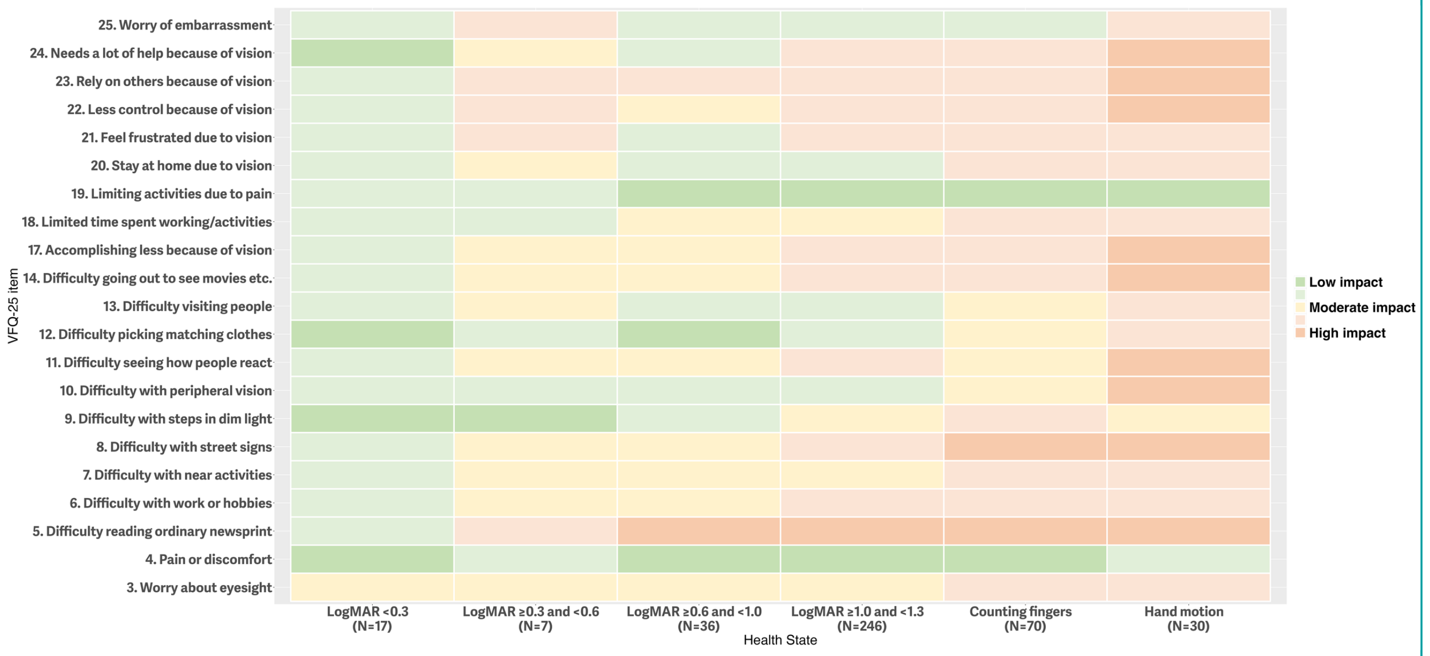

Figure 1. Item-level VFQ-25 by visual acuity in LHON patients in the REFLECT trial (data not available for health states 5 and 8)

DISCUSSION AND CONCLUSIONS

- In this study, different sources of information were brought together to develop eight health state vignettes which describe the burden of LHON at different levels of visual acuity.
- However, VFQ-25 data from the REFLECT trial was not available for health states 5 and 8, so some vignettes were developed without this.
- During interviews, patients were assigned a health state to review based on self-reported visual function as they were unable to recall their most recent LogMAR score. Therefore, there is some uncertainty about whether patients were reviewing the health state matching their current level of visual acuity.
- It was also difficult to describe the type of adaptations patients required which was variable depending on their own circumstances.
- The model structure did not allow for the description of other potential factors influencing HRQL such as time since diagnosis.
- **This work emphasises and characterises the impacts of the condition beyond the loss of visual function.**
- **It is hoped that these summaries will inform decision makers about the wider benefits of reversing LHON-related sight loss.**

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Utility Estimates for Vision Loss in Leber Hereditary Optic Neuropathy

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INTRODUCTION

- Leber Hereditary Optic Neuropathy (LHON) is a maternally inherited mitochondrial disease that leads to central vision loss due to optic neuropathy [1,2].
- The condition typically emerges in young adults and is more common among men [3].
- Vision loss starts with a painless blurring and clouding of the central vision, typically in one eye at first, that rapidly progresses to blindness in both eyes [4].
- LHON has a significant impact on many aspects of patients' lives including daily activities, emotional functioning, relationships, studies, work, recreation, and finances [5].
- GS010 (GenSight Biologics) is a gene therapy for the treatment of LHON in patients with an ND4 mutation.
- Quality of life weights (utilities) can be used to assess the net benefit of treatment.

OBJECTIVE

This study was designed to estimate patient utilities associated with varying levels of visual acuity in LHON.

METHODS

- Previous research combined secondary analysis of trial data, in-depth qualitative interviews with patients, and expert opinion to develop eight LHON health state vignettes describing the wider impact of vision loss on health related quality of life (HRQL).
- The vignettes varied by level of visual acuity as defined by LogMAR score, where a lower LogMAR score equates to better visual acuity. The vignettes ranged from mild vision loss (LogMAR<0.3) through to light perception (LogMAR≥4). An example vignette is presented in **Figure 1.**
- Members of the public from the United Kingdom (UK) (n=301) and the Republic of Ireland (ROI) (n=61) were recruited via an online recruitment platform (Prolific) and completed an online survey (hosted on Qualtrics) in which they rated the vignettes using the Health Utilities Index-3 (HUI-3) and EQ-5D-5L.
- Participants were randomised to value four (out of eight) health state vignettes, which were presented in a random order to each participant.
- HUI-3 data were scored using the associated multiple attribute utility function [6].
- EQ-5D-5L data were scored using the Hernandez et al. (2020) mapping function [7].
- A sub-sample (n=120) also completed a one to one time trade off (TTO) interview (including visual analogue scale [VAS] assessment) to assess all eight vignettes.

Scan the QR code in the bottom right of this poster to see more information about how the health state vignettes were developed.

HS6 – Counting fingers

- You have an eye condition that has left you with almost complete central vision loss. You can count fingers held up in front of you. You have limited use of your peripheral vision. You have been told that your vision may continue to deteriorate.
- You cannot read words on a page and rely on read aloud technology. You can only recognise someone by their voice.
- You rely on adaptations (e.g. read aloud technology) to use electronic devices like mobile phones, tablets and computers.
- You can mostly navigate familiar environments with minimal difficulty. You are unable to navigate unfamiliar environments without the assistance of another person or visual aid.
- You are unable to drive and get limited use of public transport. Your vision loss means that you rely on friends, family members, or taxis to take you where you need to go.
- Your vision loss is devastating, and you find it very difficult to come to terms with. You often feel frustrated and worry about the future. You often feel anxious or depressed.
- You find socialising difficult and feel socially isolated. You find it hard to meet new people because of your vision loss. Social activities such as going to a restaurant can be very logistically and emotionally challenging. This limits the enjoyment you feel from such events and the type of social events you can attend.
- Your visual impairment is not always obvious to other people which adds to the difficulties you experience.
- You rely on others to help you conduct many of your usual activities (e.g. shopping, cooking and paperwork).
- You can physically do some sports, such as gym work, with assistance. Your vision loss limits the types of sports you can take part in.
- Your eye condition does not cause you any pain.
- You rely on support from others and adaptations to participate in work or education. Your condition means that some career paths and roles may not be an option for you.

Figure 1. Example health state vignette – Counting fingers (equivalent to LogMAR 2.0)

RESULTS

Sample characteristics

- The online sample (N=362) included 301 participants from the UK and 61 participants from the ROI.
- Average age 46.5 years, 51% female, 49% employed full-time, and 39% had a diagnosis of a chronic illness.
- The TTO sample (N=120) included 100 participants from the UK and 20 participants from the ROI.
- Average age 46, 52% female, 52% employed full-time, and 63% had a diagnosis of a chronic illness.

Utility estimates

- Generally, utilities were lower for states with lower visual acuity.
- There was minimal 'misordering' of health states, where a 'better' health state had a lower utility value than a 'worse' health state (EQ-5D-5L valuations of health states 4 and 5, TTO valuations of health states 6 and 7). None of these mis-orderings fell outside of the 95%CIs. Results are presented in **Figure 2.**

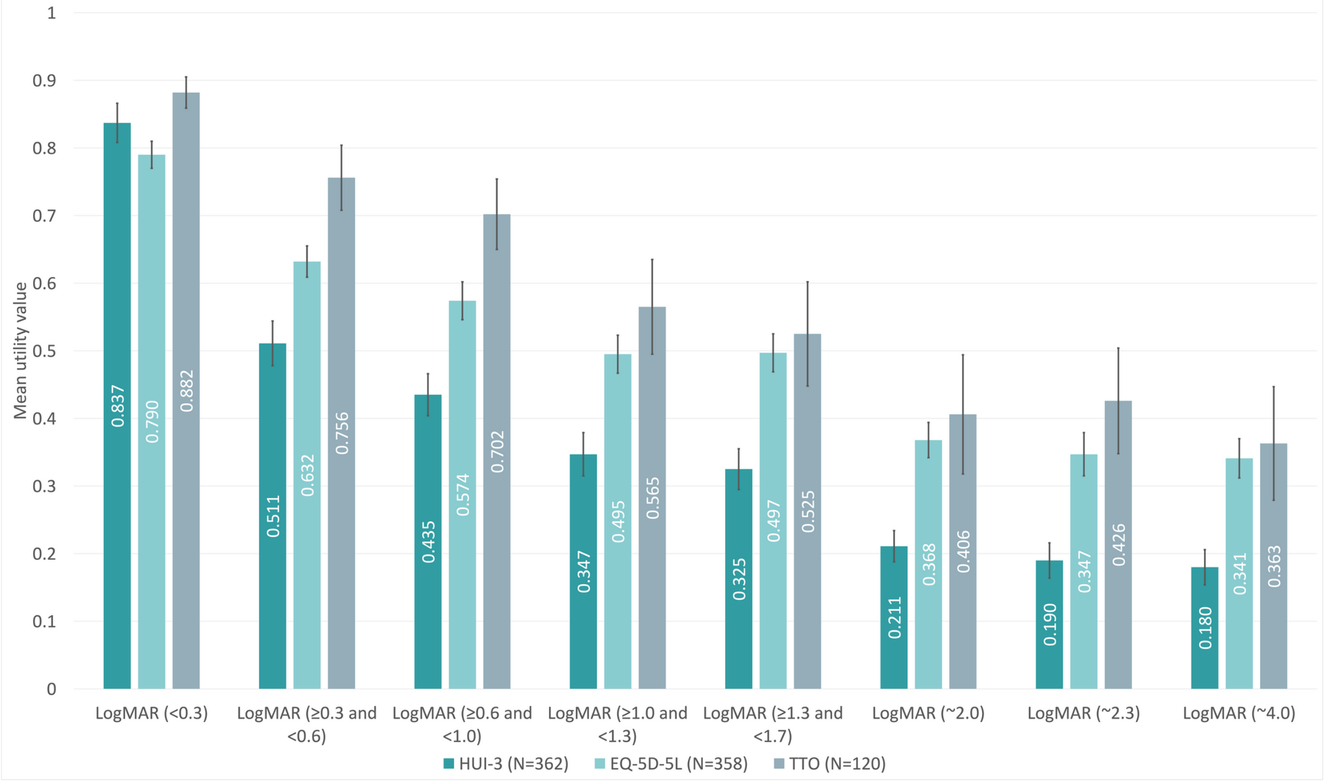

Figure 2. Health state utilities based on HUI-3, EQ-5D-5L and TTO valuations of health state vignettes. Error bars show confidence intervals 95%.

To see the results for UK and ROI separately, scan the QR code on the bottom right of this poster.

DISCUSSION

- This study describes utilities for eight health states describing different levels of vision loss in LHON patients.
- The utility results varied by the methods used to generate them. HUI-3 results showed the greatest level of difference by visual acuity.
- The HUI-3 scores were lower than the EQ-5D-5L scores which is likely due to the inclusion of a question specifically related to vision in the HUI-3.
- The utility results are dependent on the accuracy of the vignettes. Trial data and qualitative interview data were combined to develop vignettes. Iterative rounds of review were undertaken to establish content validity. However, trial data were not available for all health states.
- In vignette development interviews, clinical experts discussed the similarity and potential overlap between health states. Clinical experts were unable to differentiate the HRQL impacts in similar health states. This could explain the small amount of 'misordering' between health states.
- The vignettes did not allow for the description of other potential factors influencing HRQL such as time since diagnosis.
- As members of the general public were required to imagine living in the health state described when making valuations, there is uncertainty around how feasible it was for people to imagine living with a visual impairment.

CONCLUSION

The data suggest that early prevention of decline in vision loss through therapeutic intervention could lead to substantial net gains in HRQL.

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Supplementary data: Utility Estimates for Vision Loss in Leber Hereditary Optic Neuropathy

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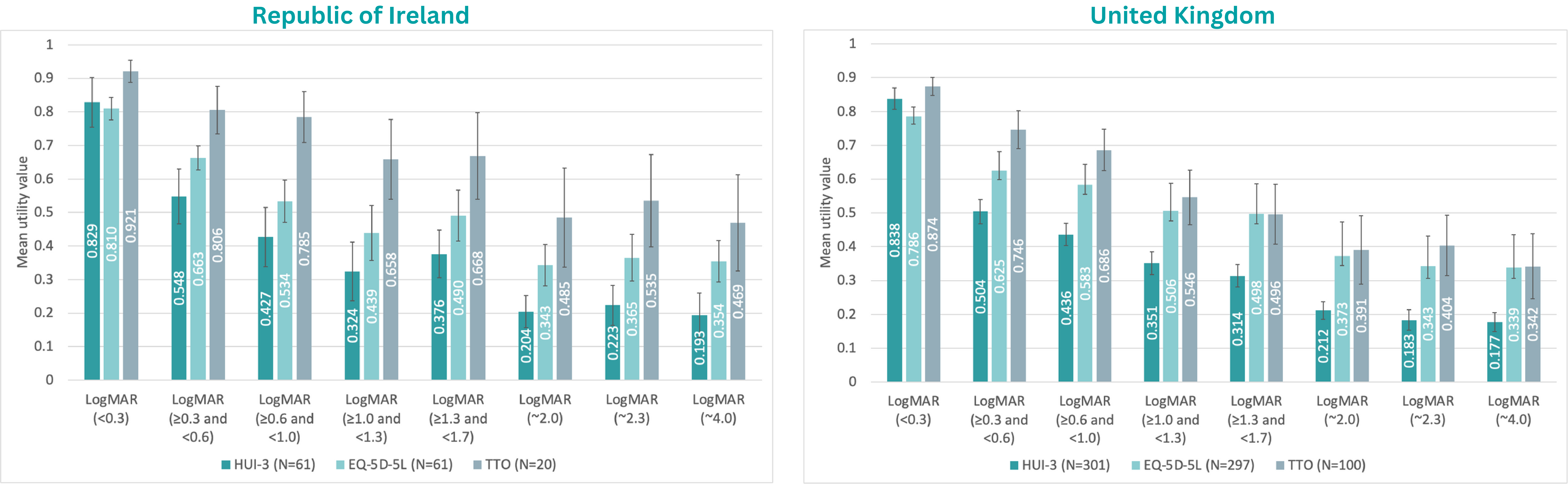

Republic of Ireland

United Kingdom

Figure 1. Health state utilities based on HUI-3, EQ-5D-5L and TTO valuations of health state vignettes in the ROI and UK. Error bars show confidence intervals 95%.