Poster

PCR 136

A Targeted Literature Review of Leber's Hereditary Optic Neuropathy Epidemiology and Burden of Illness in the United States

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Introduction

- Leber's Hereditary Optic Neuropathy (LHON) is a mitochondrial disease resulting in progressive and severe central vision loss[1]
- Though clinical course can vary by mutation type, onset typically occurs in early adulthood, beginning in one eye with the second eye following a similar course over subsequent weeks or months[2]
- Comprehensive studies assessing LHON epidemiology and burden of illness outside of Europe are limited

Objective

- A targeted literature review (TLR) to understand the epidemiology and humanistic, clinical, and economic burden of living with LHON, with a focus outside of Europe and special interest in the United States (US)

Methods

- A TLR was conducted in Embase and MEDLINE on May 24th, 2024, using PRISMA guidelines to identify full-text articles reporting on epidemiology and humanistic, clinical, and economic burden of LHON
- Database search strategies included but were not limited to the following terms:
  - **Epidemiology:** Incidence, prevalence
  - **Humanistic Burden:** QoL, PRO, patient experience, clinician-reported outcome, activities of daily life, psychological impact, care burden, mental health
  - **Clinical Burden:** Severity, complication, comorbidity, unmet medical need, patient acuity
  - **Economic Burden:** Direct costs, indirect costs, healthcare expenditure, financial burden
- Initial inclusion and exclusion criteria was as follows:
  - **Exclusion Criteria:** Non-English, non-human, other non-LHON visual impairment, case studies, case series with <10 patients, published ≥20 years ago
  - **Inclusion Criteria:** Observational studies, LHON population, relevant outcomes
- Following screening and eligibility assessments, selected records were supplemented with hand searching in Google Scholar, IPD, GlobalData, UpToDate, and EvaluatePharma
- Final studies were selected based on geography, relevance, timeliness, and quality to conduct a qualitative synthesis

Results

- Following screening and eligibility assessments, search methods yielded 22 unique publications (**Figure 1**)[1,3-23]
- Of the 22 selected studies, only five included US participants as part of a larger international cohort, and none focused solely on the US:[3-7]
  - The Impact of Inherited Retinal Diseases in the United States of America (US) and Canada from a Cost-of-Illness Perspective (**Gong et al., 2021**) – ***N=39 US patients***[3]
  - Natural history of patients with Leber hereditary optic neuropathy—results from the REALITY study (**Yu Wai Man et al., 2022**) – ***N=10 US patients***[4]
  - The Impact of Leber Hereditary Optic Neuropathy on the Quality of Life of Patients and Their Relatives: A Qualitative Study (**Chen et al., 2022**) – ***N=4 US patients, family, and caregivers***[5]
  - An International Study of Emotional Response to Bilateral Vision Loss Using a Novel Graphical Online Assessment Tool (**Gale et al., 2017**) – *US patient number not reported*[6]
  - Profound vision loss impairs psychological well-being in young and middle-aged individuals (**Garcia et al., 2017**) – *US patient number not reported*[7]

Figure 1. PRISMA Diagram

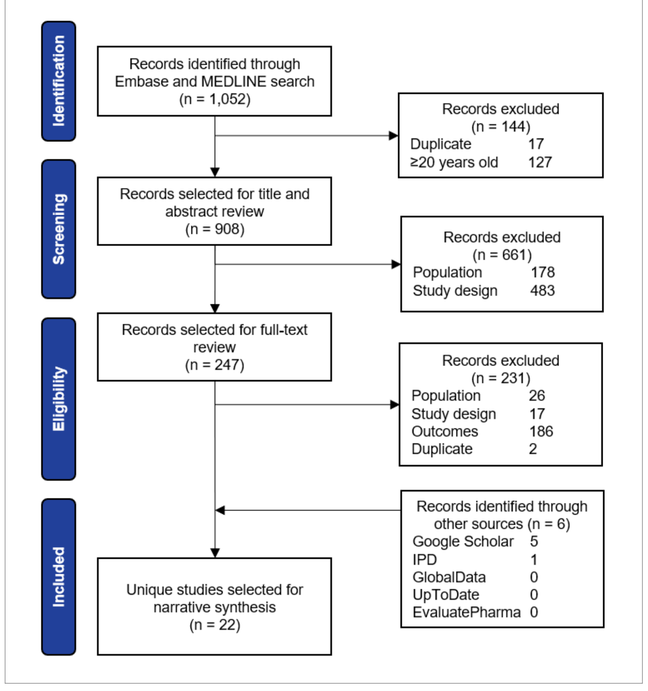
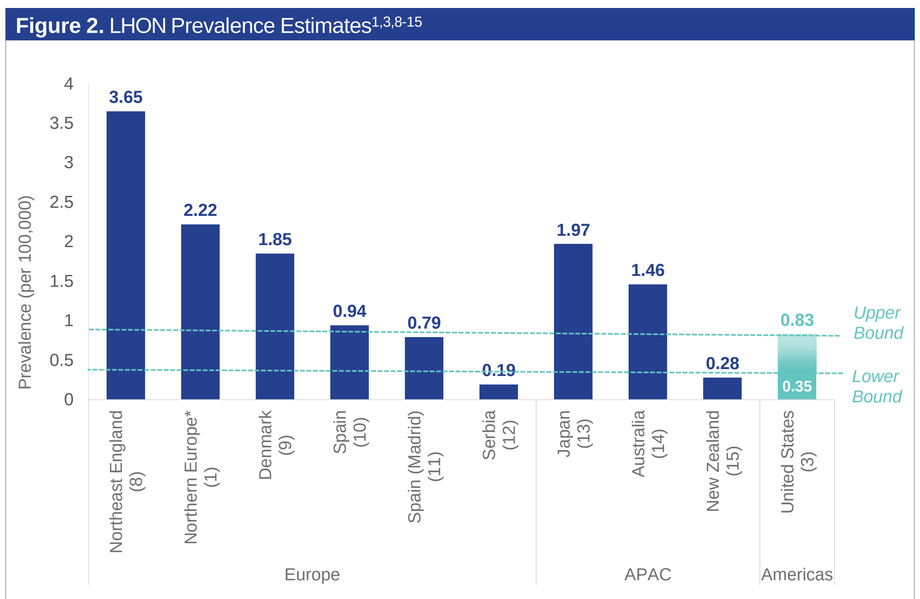
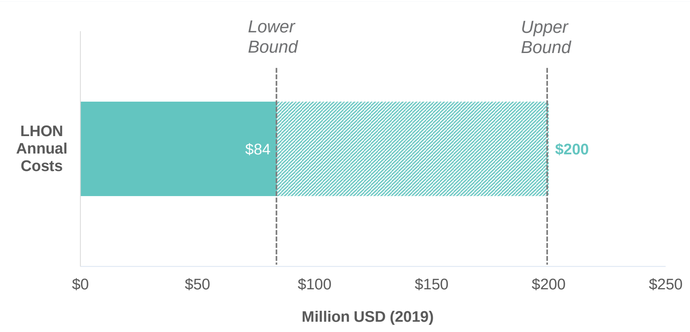


Figure 2. LHON Prevalence Estimates[1,3,8-15]



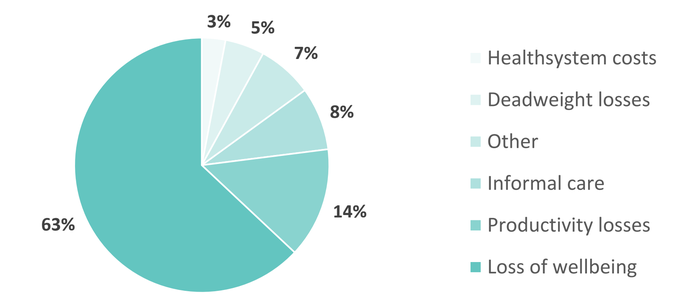
* Meta-analysis of n=5 studies covering Finland, Netherlands, UK (Northeast England), and UK (Cumbria).

Figure 3. Total annual costs attributable to LHON (US 2019)[3]



Adapted from: Gong et al., 2021

Figure 4. Breakdown of IRD Costs (US 2019)[3]



Adapted from: Gong et al., 2021

Humanistic Burden

- Humanistic patient, family, and caregiver burden was reported in seven key studies describing substantial physical, emotional, interpersonal, and professional impacts of vision loss[5-7,16-19]

Validated HRQoL Tools (n=4)

- On multiple validated HRQoL tools, affected LHON patients scored significantly lower than the general population[16-19]
  - **VF-14**: Affected LHON patients reported average scores between 20.7 (n=55)[16] and 25.1 (n=196)[17] out of a maximum score of 100, scoring lowest on reading small print, newspapers, or books. This deficit was not seen in unaffected LHON carriers, for whom the average score was 97.3 (n=206)[17]
  - **VFQ-25**: Adult patients (n=21) averaged a score of 43.47 out of a maximum score of 100. Lowest scores were reported for near activities, general vision, distance activities, and social functioning[18]
  - **PedEyeQ**: Pediatric patients (n=6) reported mean scores (out of a maximum score of 100) of 37.5 (functional vision), 52.5 (social), 52.5 (frustration/worry), and 62.5 (impact on parent and family)[18]
  - **SF-12v2**: Male patients (n=28) scored significantly lower on the PCS versus the general male population (47.3 v. 50.6, p<0.015). No statistically significant differences versus the general population were found for female PCS, female MCS, or male MCS[19]

Other Tools (n=2)

- **Graphical mood assessment**: In qualitative analyses of the tool, extent and duration of sadness reported by LHON patients (n=50) was markedly worse when vision loss resulted in negative effects on relationships, independence, and work/schooling. Importantly, use of adaptive techniques and technologies was correlated with mood recovery[6]
- **21-point Likert-type scale**: 70.9% of LHON patients (n=103) reported both negative interpersonal and career impacts[7]

Qualitative Findings (n=1)

- In focus group interviews patients, families, and caregivers (n=17) described extensive and multidimensional impacts of LHON, including physical impacts, psychological impacts, impacts on relationships, impacts on work/studies, and impacts on recreation[5]

Epidemiology

- 10 international studies published provided LHON prevalence estimates, though figures varied considerably and primarily represented European and APAC populations (**Figure 2**)[1,3,8-15]
- Internationally, estimates ranged from 0.19 (Serbia) to 3.65 (UK) per 100,000
  - In addition to true international variance, e.g., due to founder's effects, it is possible that this variation was heavily influenced by non-epidemiologic factors such as availability of diagnostic and treatment services and study methodologies[8,12,15]
- In the US, **Gong et al., 2021** provided the only estimate at a range of 0.35 to 0.83 per 100,000, though methods incorporated data from Danish and UK cohorts[3]
- Analyses leveraged diverse data sources, including EHR data, HCP surveys, registries, discharge data, and genetic laboratory data, highlighting the feasibility of conducting comprehensive LHON epidemiological assessments across healthcare systems[3,8-15]

Economic Burden

- Of three selected studies, only **Gong et al., 2021** focused on the US, estimating total direct and indirect costs of LHON in the US (2019) to be between $84 million and $200 million **(Figure 3)**[3]
- Across all IRDs, costs primarily arise from wellbeing (63%) and productivity (14%) losses, which is assumed to be similar for LHON **(Figure 4)**[3]
  - Internationally, LHON-specific productivity losses were evaluated in Chechia and Slovakia, finding high rates of combined relative absenteeism and presenteeism for LHON patients and parents of patients (50% and 68%, respectively)[18]
- Qualitatively, patients, families, and caregivers describe substantial financial impact from expenses for medications and visual aids and reduced personal income[5]

Clinical Burden

- Five studies reporting on clinical burden described high frequency of severe vision impairment and heightened non-vision morbidity and mortality risks among affected LHON patients[4,20-23]

Vision Impairment (n=4)

- In two studies assessing vision impairment in LHON patients, over half of patients (56.8%[20] and 58%[21]) recorded better eye BCVA logMAR 1.0 or worse, meeting WHO criteria for severe vision impairment and US criteria for legal blindness
  - A third study using more restrictive severity criteria (better eye BCVA logMAR 1.3 or worse) found that 47.58% of patients ≤12 months into their disease course met criteria for severe impairment[22]
- Further, in **Yu Wai Man et al., 2022**, a registry analysis wherein authors included all eyes (n=72 eyes of patients aged at least 15 years at onset), 76% scored a BCVA logMAR 1.0 or worse[4]

Comorbidity and Mortality Risks (n=1)

- In a retrospective analysis of Danish registry data, affected LHON patients (n=141) showed significantly increased risk of mortality and multiple cardiac and neurologic conditions compared to the general population[23]
  - Statistically significant RRs (p<0.05) were found for: mortality (1.95), demyelinating disorders (12.89), alcohol-related disorders (7.53), dementia (4.26), nerve symptoms (3.13), epilepsy (2.99), stroke (2.38), atherosclerosis (2.2), and neuropathy (1.75) [23]
  - Notably, unaffected family members of affected LHON patients (n=297) did not exhibit increased risk for mortality or any indications evaluated in the study[23]

Conclusions

- **This TLR identified 22 globally-representative real-world publications describing LHON epidemiology and the substantial burden experienced by patients, family, and caregivers**
- **Only five studies included US patients, highlighting a clear, persistent paucity of US-focused literature**
- **Despite limited data and unique demographic dynamics in the US that may challenge generalization, many of the clinical and quality of life impacts described internationally likely hold true in the US**
- **Additional real-world studies and LHON-specific health economic evaluations are needed to support effective patient care, clinical development, and healthcare decision making**

Abbreviations

QoL, quality of life; PRO, patient-reported outcome; IPD, Incidence and Prevalence Database; APAC, Asia-Pacific; EHR, electronic health record; HCP, health care provider; WHO, World Health Organization; RR, rate ratio; HRQoL, health-related quality of life; PCS, physical component summary; MCS, mental component summary; IRD, inherited retinal disease.

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