

Increased Mortality and Comorbidity Associated With Leber's Hereditary Optic Neuropathy: A Nationwide Cohort Study

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PURPOSE. Leber's hereditary optic neuropathy (LHON) is a mitochondrial genetic disease in which optic neuropathy is considered a key feature. Several other manifestations of LHON have been reported; however, only little is known of their incidence and the life expectancy in LHON patients.

METHODS. This study, based on Danish nationwide health registries, included 141 patients diagnosed with LHON and 297 unaffected family members in the maternal line. The incidence of comorbidities and mortality for patients with LHON and unaffected family members was compared with that in the general population.

RESULTS. Having LHON was associated with an almost 2-fold risk of mortality with a rate ratio (RR) of 1.95 (95% confidence interval [CI]: 1.47-2.59; $P < 0.001$). The incidence of several diseases was increased for LHON patients, but not for family members. The incidence of stroke was 5.73 per 1000 patient-years for LHON patients compared to 2.33 for the general population, and the RR was 2.38 (95% CI: 1.58-3.58; $P < 0.001$). The incidence of demyelinating disorders was 2.24 compared to 0.21 for the general population; RR was 12.89 (95% CI: 6.70-24.77; $P < 0.001$). A 4-fold risk of dementia was seen for LHON patients (RR: 4.26, 95% CI: 1.91-9.48; $P < 0.001$), incidence 1.45 for LHON and 0.37 for the general population. Moreover, LHON patients had an increased risk of epilepsy, atherosclerosis, nerve symptoms, neuropathy, and alcohol-related disorders.

CONCLUSIONS. The manifestation of LHON was associated with increased mortality and increased incidence of several disorders including stroke, demyelinating disorder, dementia, and epilepsy.

Keywords: Leber's hereditary optic neuropathy, mitochondria, optic neuropathy, mortality, comorbidities

Leber's hereditary optic neuropathy (LHON) is a mitochondrial genetic disease resulting in acute or subacute loss of vision, affecting mostly men in their second or third decade.¹ As a consequence, LHON has a strong negative impact on quality of life.² It results from a point mutation in the mitochondrial DNA and is therefore maternally inherited. Although several point mutations have been shown to potentially cause LHON, more than 90% of cases are caused by one of three primary mutations (G3460A, G11778A, or T14484C).¹ LHON is generally accepted as the most prevalent mitochondrial disease,³ with an average European prevalence of 1:45,000.⁴ LHON has an incomplete penetrance,⁵ which is assumed to be caused by both genetic and environment factors.⁶

The loss of vision observed in LHON is caused by degeneration of the retinal ganglion cells. However, the biochemical mechanism is largely unknown. The mutations in mitochondrial DNA alter the function of the mitochondria

leading to multiple possible causative effects, including decreased ATP production as well as increased production of reactive oxygen species.^{1,7} The high metabolic demands of the retinal ganglion cells are thought to make them especially vulnerable to decreased mitochondrial function,⁸ and in consequence other high-energy tissues may be affected, possibly subclinically.

Although optic neuropathy is considered characteristic for the disease, several other manifestations of LHON have been reported, including neurologic and cardiac abnormalities, sometimes referred to as Leber's plus.⁹⁻¹² Unfortunately, these studies tend to include only small cohorts and investigate a limited number of additional manifestations. Likewise, few studies on mortality have been published. In fact, little is known of life expectancy and cause of death in LHON patients.

With a thorough characterization of a large cohort, the present study aimed to investigate the overall survival and comorbidities of individuals affected by LHON and unaffected



family members, whether obligate or proven to harbor a pathogenic mitochondrial mutation or not, compared to healthy controls.

METHODS

This registry-based study comprised data from nationwide Danish health registries. The incidence of comorbidities and mortality for patients with LHON and healthy family members was compared to that of the general population.

Registers

Since 1968, every Danish citizen has been assigned a unique, permanent civil registration number by the Civil Population Register, making linkage of individuals among nationwide registries possible.

The national Danish Registry of Families with Hereditary Eye Disorders includes patients and families with any diagnosed genetic disorder affecting the eye. The registry was founded in 1985 and is curated at the Department of Ophthalmology, Rigshospitalet, University of Copenhagen, the former National Eye Clinic for the Visually Impaired. The register is considered almost complete due to a highly centralized national molecular diagnostic and rehabilitation service for the whole Danish population.

The Danish National Hospital Register holds information of all hospital admissions in Denmark, including date of admission and all relevant diagnoses at discharge classified according to the International Classification of Diseases 8th and 10th revisions (ICD-8 and ICD-10) since 1976. Combined, these registries provide information on all diagnoses given at a hospital for all patients known with LHON and their relatives.

Study Population

The study cohort was identified in the Danish Family Registry. The clinical diagnosis is based on symptoms and signs characteristic for LHON, the family history, and since 1989 also molecular genetic analyses. As a result, a full characterization of the nation-based LHON cohort including diagnosed cases and family members was obtained.¹³

All identified patients and their family members assigned a Civil Registration number are included. Individuals were registered as either (1) subjects with LHON or (2) their brothers and sisters and first-degree relatives in the ascending maternal line without reported manifest LHON. More distant relatives in side branches of the genealogy without any manifestation of LHON are not included. As controls, the general Danish population apart from LHON patients and their family members was included. Hence, the study population comprised individuals included in one of three groups: (1) LHON, (2) family members, (3) general population. All the involved individuals were included and started follow-up at the age of 30, as the age of onset for LHON was not known for all LHON patients. Inclusion started at year 1960 and continued onward. Prior to the analyses, individuals with an endpoint diagnosis before inclusion were excluded. Individuals were followed up until the first occurrence of one of the following: death, emigration, end of follow-up (December, 31, 2014), or presence of one of the endpoint diseases listed below. Vital status was obtained from the Central Population Register.

Outcomes and Endpoints

Diseases previously described to coexist with one of the three primary LHON mutations were identified through a systematic

TABLE 1. List of Diagnostic Categories Included as Endpoints in the Study, With Matching ICD-8 and ICD-10 Codes

Diagnostic Category	ICD-8	ICD-10
Heart disease		
All heart disease	393-399, 40-45	DI
Atherosclerosis	440	DI70
Arrhythmia		DI44, DI45, DI47-49
Ischemic heart disease	411-414	DI20-25
Heart failure	425, 4270-71	DI42, DI50, DI110
Stroke	433-435	DI60-64, DG45-46
Neurologic disorders		
Demyelination disorders	340-41	DG35-37
Neuropathy		DG5-6
Nerve symptoms		DR20, DR25-27, DR29
Epilepsy	345	DG40-41
Migraine and other headache disorder	346	DG43-44
Alcohol-related disorders		
Dementia	290	DF00-DF03
Deafness	389	DH90-91

literature search in PubMed and Embase using the search term LHON and nine synonyms, resulting in 2169 articles after duplicates were removed. After screening for articles on comorbidities, a total of 160 articles proved relevant and ultimately resulted in a list of the diseases previously published as coexisting with LHON (see Supplementary Table S1). From this list, diseases with no available data in the registries or with a numerically insignificant number of observations among LHON patients and family members (<7) were excluded. Included diagnoses were classified according to ICD-10. Included comorbidities were grouped into diagnostic categories to increase the power of the study. Diagnostic categories are presented in Table 1 with matching ICD-8 and ICD-10 codes.

Statistics

The rate ratios (RR) of mortality and comorbidities among individuals with LHON or family members compared to the general population were analyzed via a time-dependent approach by using multivariate Poisson regression models.¹⁴ Separate Poisson regression analyses were performed for each comorbidity. All individuals entered the study at the age of 30, starting from January 1960. Individuals were followed up until the appearance of a comorbidity of interest, death, or the end of 2014. For Poisson regression, all individuals were split into separate records according to two time scales using the Lexis macro (<http://publicifsv.sund.ku.dk/~pka/epidata/Lexis.sas>; in the public domain; last accessed February 20, 2017). Calendar time was split by the years 1985, 1995, 2000, and 2005. Age was split according to 5-year increments. Variables were determined at the start of each time band for analyses. Testing showed that shorter time bands did not change the results. Poisson regression was performed with PROC GENMOD from the SAS Institute (Cary, NC, USA). From inclusion, individuals with LHON contributed with person years to disease exposure time for LHON patients while unaffected family members contributed to exposure time for unaffected family members. RR were expressed with 95% confidence interval (95% CI). A *P* value less than 0.05 was considered significant.

Descriptive data were reported as percentages. For the comorbidities and mortality, incidence ratios were expressed as the number of events per 1000 patient-years.

TABLE 2. Characteristics of the Study Population

Characteristic	LHON 141	Family Members 297	General Population 3,753,935
Males (%)	103 (73)	122 (41)	1,896,503 (51)
Mutation (%)			
11778G>A	103 (73)	168 (57)	-
3460G>A	20 (14)	67 (23)	-
14484T>C	12 (9)	33 (11)	-
No mutation found	6 (4)	29 (9)	-

Overall mortality was expressed by Kaplan-Meier estimates. Comorbidities were expressed as cumulative incidence accounting for competing risks of death from other causes.

All statistical analyses were performed using Statistical Analysis System version 9.4 and R Statistics version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>; in the public domain).

Ethical Considerations

In Denmark, registry-based studies do not require ethical approval or patient consent. The Danish Data Protection Agency approved the design of the study (approval no. 2008-58-028), and the authors adhered to the tenets of the Declaration of Helsinki.

RESULTS

From the national registries, 236 patients with LHON and 590 unaffected family members were identified. After including only individuals at 30 years of age no earlier than 1960, the study population comprised 141 LHON patients, 297 unaffected family members, and 3,753,935 individuals from the general population. The male/female distributions are listed in Table 2.

For a subset of the comorbidities, cumulative incidences accounting for competing risk of death by other causes are illustrated in Figure 1 together with the 1-Kaplan-Meier curves for mortality. The incidence rates (IR), RR, and *P* values are presented in Figure 2. The RR are adjusted for age, calendar year, and sex.

The incidence of heart diseases for LHON patients was 20.54 compared to 14.35 per 1000 patient-years in the general population with a RR of 1.44 (95% CI: 1.14–1.81; *P* = 0.002). Atherosclerosis and stroke among LHON patients had a RR of 2.2 (95% CI: 1.10–4.40; *P* = 0.026) and 2.38 (95% CI: 1.58–3.58; *P* < 0.001) respectively.

The incidence of a number of neurologic diseases was higher among LHON patients; see Figure 2. The RR for dementia was 4.26 (95% CI: 1.91–9.48; *P* < 0.001), epilepsy RR 2.99 (95% CI: 1.56–5.75; *P* = 0.001), nerve symptoms RR 3.13 (95% CI: 1.78–5.51, *P* < 0.001), and neuropathy RR 1.75 (95% CI: 1.01–3.01; *P* = 0.044). The highest-incidence RR was for demyelinating disorders, 12.89 (95% CI: 6.70–24.77; *P* < 0.001).

The incidence of alcohol-related disorders was 11.30 for LHON patients compared to 1.41 for the general population. The RR was 7.53 (95% CI: 5.59–10.16; *P* < 0.001).

Having LHON was associated with an increased risk of death RR 1.95 (95% CI: 1.47–2.59; *P* < 0.001); see Figure 2. The risk of death for family members did not differ significantly from the general population.

No significant increases were observed for ischemic heart disease, heart failure, arrhythmia, migraine, or deafness. For all the comorbidities, no differences among unaffected family members and the general population were observed.

DISCUSSION

It is widely accepted that mitochondrial diseases predominantly manifest in tissues/organs with high energy requirements, such as the central and peripheral nervous system, eyes, inner ears, and heart.¹⁵ Our findings add to the existing knowledge by demonstrating that the manifestation of LHON is associated with a statistically increased risk of certain diseases of the nervous system and heart. However, the causality is uncertain. Furthermore, the present study indicates increased alcohol consumption or susceptibility to alcohol-related disorders among LHON patients, which could potentially contribute to the increased risk of other diseases.

It is noteworthy that unaffected family members did not show an increased risk of the disorders included in the study. This might suggest either common pathophysiological etiology for the manifestation of LHON and associated comorbidities, or that having LHON itself implies an increased risk of accompanying diseases.

Most of the existing literature on cardiovascular diseases and LHON concerns cardiomyopathy and arrhythmia. This study did not find the incidence of hospital-diagnosed arrhythmia or heart failure (including cardiomyopathy, see Table 1) to be increased among LHON patients. In contrast, this study found an increased incidence of atherosclerosis for LHON patients, which in turn might increase the risk of hypertension. Thus in female carriers without LHON, the mt14484 mutation has been shown to be a potential cause of essential hypertension.¹⁶ To our knowledge, few data exist on vascular diseases in LHON patients, although they have been found to have increased aortic stiffness.¹⁷ With regard to stroke, a correlation to secondary LHON mutations has been reported.¹⁸ The results of this study demonstrated a significantly higher risk of stroke among LHON patients, suggesting that there might be an association with primary LHON mutations.

It is well known that neurologic disorders are present in many LHON patients.⁹ Neuropathy has previously been found in a small cohort of LHON patients.¹⁹ However, another study found only 1 in 104 LHON patients to have neuropathy.²⁰ Supporting these findings, we found an association between LHON patients and an increased prevalence of neurologic symptoms and neuropathy. This correlates with the existing literature reporting a spectrum of neurologic symptoms among LHON patients.

Similarly, unaffected family members of LHON patients have previously been associated with an increased prevalence of neurologic abnormalities. This association was correlated to how closely they were related to the LHON patient.²¹ In the present study, unaffected family members were not associated with an increased incidence of neurologic symptoms or neuropathy. This could be caused by a lack of subdivision according to closeness of the relation to the LHON patient.

The neural abnormalities observed in some LHON patients have also been suggested to involve the central auditory pathways. However, to our knowledge only few studies have investigated this and with conflicting results.^{22–24} Our study did not find an increased risk of deafness for LHON patients.

Few studies on a limited number of families have reported coexistence of migraine and LHON.^{25,26} In this study no association between LHON and migraine was found.

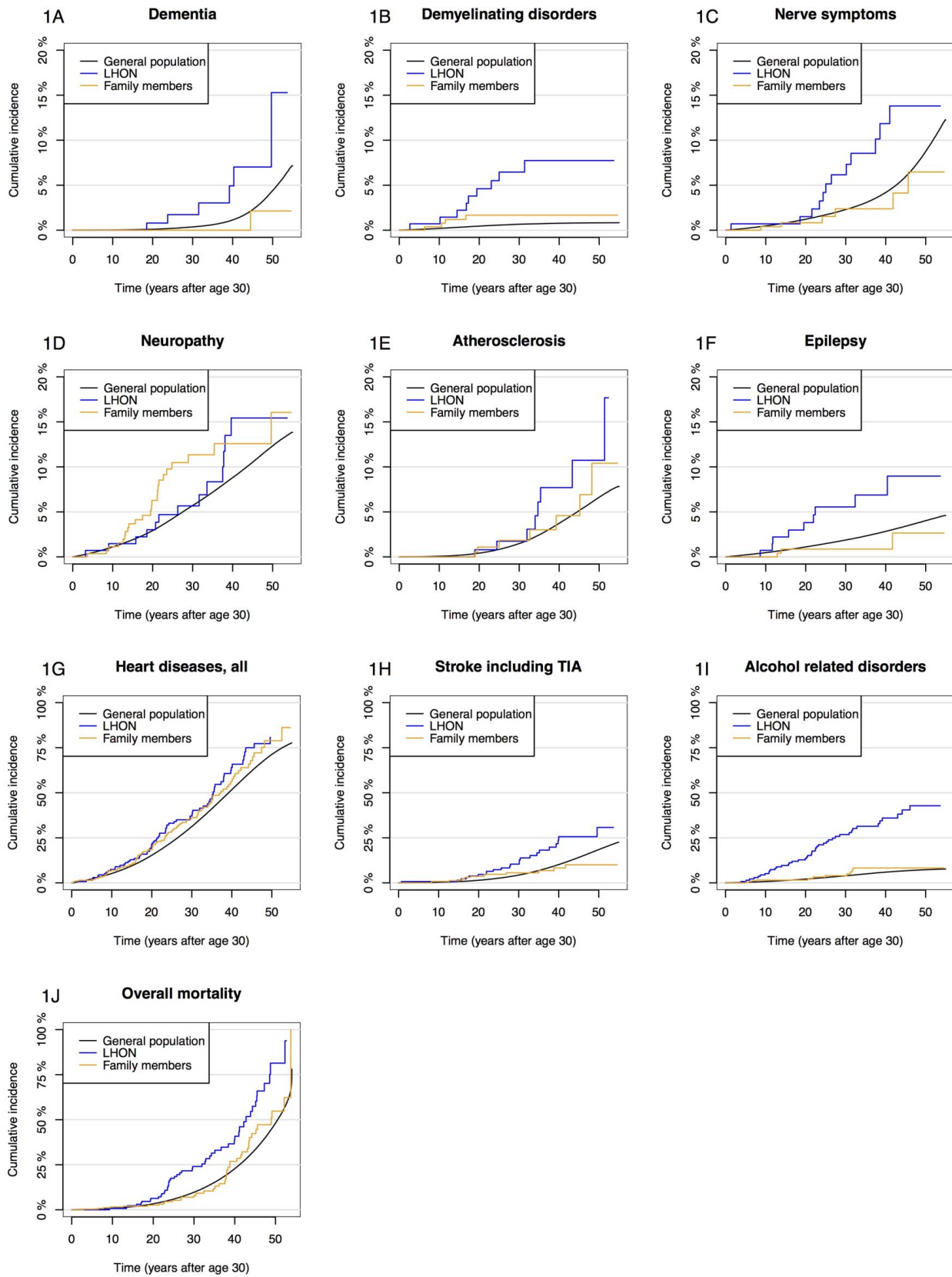


FIGURE 1. Cumulative incidences for comorbidities accounting for competing risk of death by other causes, and 1-Kaplan-Meier curves for overall mortality. The cumulative incidences are the risk of having the disease if being at risk (alive). For all the above comorbidities, rate ratios were significant for LHON patients but not for family members. TIA, transient ischemic attack.

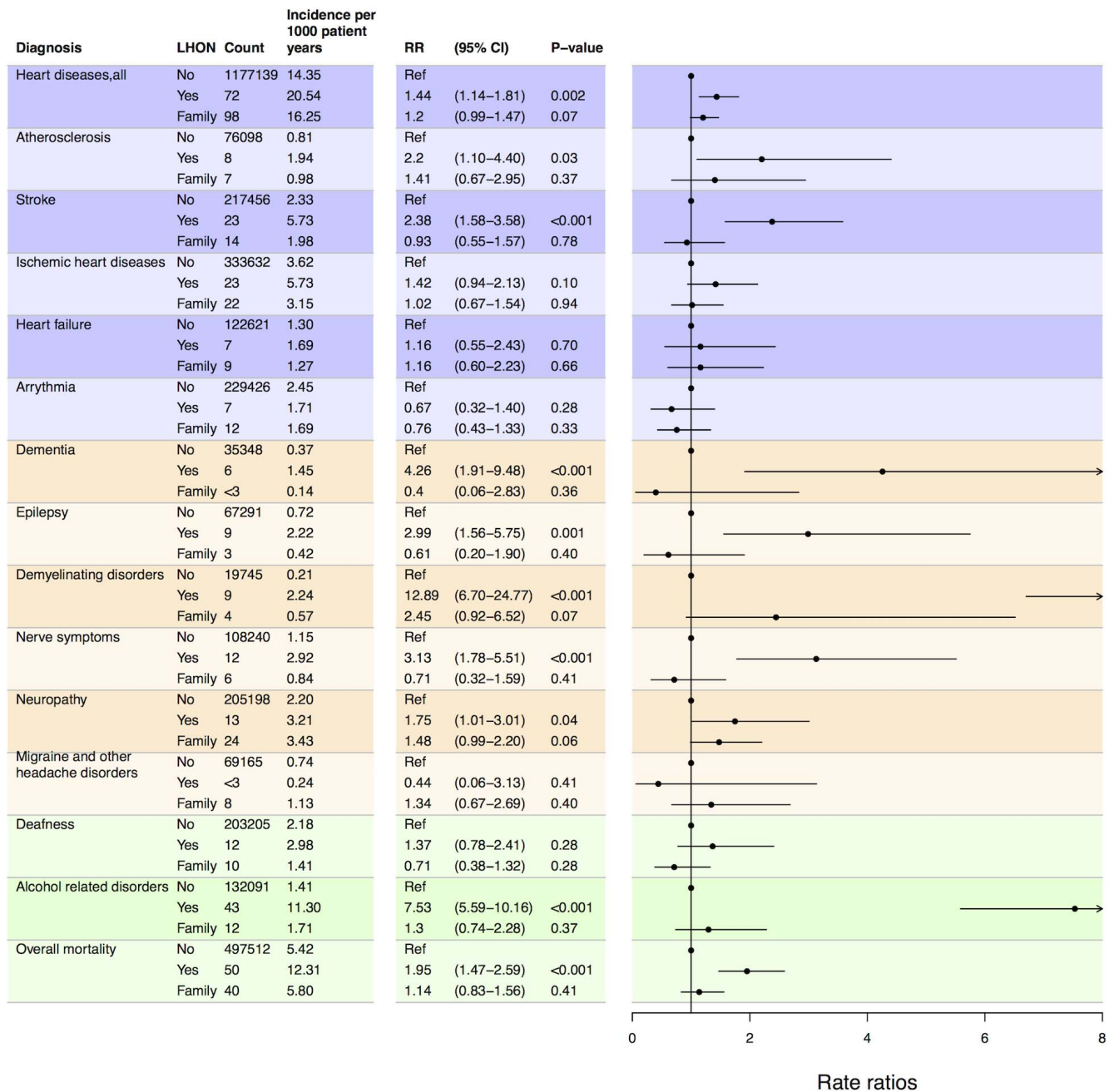


FIGURE 2. Incidences and rate ratios for comorbidities and mortality among LHON patients and unaffected family members compared to the general Danish population. RR were calculated by Poisson regression and adjusted for sex, age, and calendar year. Count, number of events; RR, rate ratios; 95% CI, 95% confidence interval.

Regarding dementia, the pathology of Alzheimer’s disease and Parkinson’s disease has been proposed to include mitochondrial DNA variations²⁷; however, only sparse data have linked LHON and dementia (see Supplementary Table S1). Our study adds to the existing evidence that there might be an association between dementia in general and mitochondrial DNA variations, more specifically LHON.

The relation between multiple sclerosis (MS) or MS-like disease and LHON has attracted special attention in the literature as it has previously been shown that primary LHON mutations increase the risk of MS.²⁸ This was confirmed by the present study. A recent study showed that cerebral magnetic resonance imaging (MRI) in MS-like LHON and MS was alike, providing support for a common pathophysiological mecha-

nism.²⁹ The pathophysiology of MS is still not fully understood, but mitochondrial mutations are presumed to play a role in the susceptibility to the disease, though studies on potential responsible genes are controversial.³⁰ Several studies in patients with MS have failed to demonstrate the primary LHON mutations among these.^{31–35} In conclusion, it would seem that LHON patients have increased risk of an MS-like disease, but that primary LHON mutations do not play a role in the majority of cases of MS.

The unknown burden of associated comorbidities could potentially negatively influence quality of life throughout the entire life span of individuals with LHON-associated mutations.² Alcohol consumption has previously been shown to be higher among some patients with LHON.³⁴ This study found an

increased risk of alcohol-related disorders such as alcohol abuse and dependence. It is uncertain whether alcohol consumption increases the risk of developing LHON or if having LHON evokes higher alcohol consumption.

While a recent study investigated the cause of death among patients with mitochondrial diseases,³⁵ there has been only limited evidence on life expectancy among LHON patients. In this study, increased mortality was found for LHON patients. Even though the causes remain unknown, the present study provides evidence of increased incidence of a number of comorbidities potentially contributing to increased mortality.

Strengths and Limitations

The multivariate analyses on incidence of comorbidities and mortality were adjusted for age, calendar year, and sex. Retrospective cohort studies based on registries have some built-in limitations; no data on smoking habits or body mass index were available, and hence the analysis could not be controlled for these confounding factors.

Additionally, the diagnosis of comorbidities relies on registered diagnosis at a hospital. Though the registries have been shown to be accurate regarding some diseases,³⁶ the sensitivity for other diagnoses could be questioned, especially coding on symptoms with no specific diagnostic criteria. For instance, alcohol-related conditions were included as an approximation for high alcohol consumption. However, there may be a proportion of patients with excessive alcohol consumption but without a hospital diagnosis. The same is true for nerve-related symptoms. As the diagnosis greatly relies on reporting from patients, it could be speculated that having a chronic disease, such as LHON, might affect the patient's likelihood of contacting a doctor and report other symptoms. This could potentially bias the results. In addition, the register for diagnoses holds only for information from year 1976 onward.

Furthermore, all individuals were included at age 30, and patients with LHON were regarded as such at inclusion irrespective of actual age at onset. The median age at onset in Denmark has previously been shown to be 25 for males and 33 for females.¹³ Therefore, individuals most likely at age 30 will be influenced by the genetic or environmental factors determining the penetrance for LHON mutations. All family members were relatives in the ascending female line and therefore probably harbored the mutation, however possibly with individual differences in mutational load, which was not accounted for.

Finally, this study included only disorders following hospital admission and therefore could not uncover the prevalence and risk of subclinically or less severe symptoms not resulting in hospital diagnoses. Moreover, the causality between LHON and other manifestations is still unsolved.

CONCLUSIONS

In this population-based study including 141 LHON patients, 297 unaffected family members, and the entire Danish population as a reference, the manifestation of LHON was association with an increased risk of heart diseases in general, atherosclerosis, stroke, dementia, epilepsy, demyelinating disorders, nerve symptoms, neuropathy, and alcohol-related disorders. Moreover, the risk of death was almost doubled for LHON patients compared to the general Danish population (RR 1.95).

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