Tampere University

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Social and Economic Impact of Glaucoma and Glaucoma Care in Ageing Population

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium F114
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 15 March 2024, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Finland

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The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-3289-1 (print)
ISBN 978-952-03-3290-7 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-3290-7

Carbon dioxide emissions from printing Tampere University dissertations have been compensated.

PunaMusta Oy – Yliopistopaino
Joensuu 2024

ACKNOWLEDGEMENTS

The studies presented in this doctoral thesis were conducted in the Eye and Vision Research Study Group at the Faculty of Medicine and Health Technology, Tampere University, between the years 2020 and 2023. First, for funding and for making this thesis project possible, I would like to thank the Doctoral Programme in Medicine, Biosciences and Biomedical Engineering of the Tampere University, the Elsemay Björn Fund, the Finnish Federation of the Visually Impaired, Glaukooma Tukisäätiö Lux, the Juho Vainio Foundation, the Päivikki and Sakari Sohlberg Foundation, Sokeain Ystävät r.y., and Tampereen seudun Näkövammaisten tukisäätiö.

I want to express my deepest gratitude to my supervisors, Professor Emeritus Hannu Uusitalo and Janika Nättinen, PhD, for supporting me and this thesis work from start to finish with your expertise and endless enthusiasm. Hannu, you introduced me to the field of ophthalmology and the world of epidemiology. I admire your deep and profound expertise in both clinical and scientific issues, and I appreciate your friendly guidance in researching, presenting, and publishing results, working in multi-disciplinary environments, and establishing professional networks. Janika, you have supported me in your expertise field of biostatistics, and you have always been willing to help and give supportive hands-on guidance in statistical issues. I highly admire your remarkably broad knowledge of bioinformatics.

I sincerely thank my pre-examiners, Professor Jost Jonas and Docent Olavi Pärssinen, for your thorough review and valuable comments to ensure the quality of this thesis. I owe my deep gratitude to Professor Rupert Bourne for kindly agreeing to be my opponent.

I warmly thank Research Professor Seppo Koskinen and Matti Ojamo, MPolSci, for being members of my official follow-up group of this thesis project and for your collaboration, which has given us an access to comprehensive, high-quality data on the Finnish population and a network of multi-disciplinary professionals. Seppo, you have provided invaluable data on the Finnish adult population in the Health 2000 and 2011 Surveys, and your expertise in the field of epidemiology is outstanding. Your comments concerning the studies and this thesis have always been constructive and friendly, and your thoughts have broadened my scientific way of thinking. Matti, you have kindly provided data from the Finnish Register of Visual Impairment, and you have generously shared your expertise in the field of register-based research. In our monthly meetings, you always gave insightful comments and provided fruitful discussion regarding my analyses and results.

In addition to Seppo Koskinen and Matti Ojamo, I would like to express my sincere appreciation for my co-authors, Mika Gissler, Mika Harju, Minna Parkkari, Harri Rissanen, Päivi Sainio, Joonas Taipale, Anu Vaajanen, and Saku Väätäinen. You have provided invaluable contribution to the sub-studies presented in this thesis. I would like to particularly thank Joonas Taipale for equal contribution to the third sub-study. I also thank Saku Väätäinen for providing highly needed guidance in the field of health economy and Mika Gissler for providing data from the Care Registers and for always providing fast responses to my questions and inquiries.

My special thanks go to the current Research Director of the Finnish Register of Visual Impairment, Laura Tolkkinen, and my co-worker, Paula Mosallaei.

I thank Ulla Aapola and the rest of the Eye and Vision Research Study Group for your encouraging support. Special thanks to Sanna Leinonen and other members of the PhD seminar course for providing insight on writing research articles and the dissertation.

Finally, I want to thank my family for valuable and tireless support for me and my studies.

Tampere, December 2023

ABSTRACT

Glaucoma is one of the leading causes of visual impairment and blindness worldwide. Vision loss is associated with worsened well-being, increased use of health care services, and loss of productivity due to increased difficulties in daily living, socialization, functional capacity, and work ability. Glaucoma is strongly associated with ageing, and both glaucoma and glaucoma-related vision loss are expected to rise globally along ageing populations. Therefore, there is a growing interest in evaluating the impact of glaucoma and glaucoma care on quality of life, mental health, visual function, and health care resource use, particularly at the population level. Glaucoma remains commonly undetected, and there are difficulties in glaucoma treatment in preventing the irreversible loss of vision. These challenges further underline the significance of this type of epidemiological study on glaucoma.

The aims of this thesis work were to investigate the social and economic impact of glaucoma and glaucoma care in Finland between the years 2000–2011. The thesis consists of four sub-studies. In **Study I**, the time trends in prevalence and incidence of glaucoma in comparison with two other major vision-threatening eye diseases, cataract and retinal degeneration, were investigated, and the impact of these diseases on generic health-related quality of life, mental health, and distance visual acuity were evaluated. **Study II** evaluated these associations with a focus on glaucoma and its treatment. The aim of **Study III** was to provide estimates on the health care resource use and the direct and indirect costs of glaucoma and glaucoma care. Finally, in **Study IV**, the aim was to investigate the time trends in glaucoma-related visual impairment in the past four decades.

The study populations in **Studies I**, **II**, and **III** consisted of participants aged 30 years or older from two nationally representative health examination surveys: Health 2000 and Health 2011. The surveys included cross-sectional data from 2000 and 2011 as well as longitudinal, 11-year follow-up data on participants who partook in both the surveys. In **Study IV**, the study population consisted of persons with visual impairment due to glaucoma registered in the Finnish Register of Visual Impairment between 1980 and 2019.

For **Studies I**, **II**, and **III**, the Health Surveys included an interview and questionnaires with self-reported questions on diseases (including glaucoma,

cataract, and retinal degeneration), socio-economic status, and use of health care services. Validated instruments on generic health-related quality of life and mental health were included. Bilateral, habitual distance visual acuity was measured at a health examination carried out in both the surveys. The survey data were complemented with register-based information from the Care Registers for Social Welfare and Health Care and the Social Insurance Institution of Finland, which included inpatient, outpatient, and glaucoma medication data on the survey participants. Glaucoma patients were selected based on the self-reported survey interviews and the register data. Continuous variables were analyzed with Mann–Whitney U-test, Wilcoxon's signed-rank test, or Kruskal–Wallis test. Discrete variables were analyzed with a chi-squared test. The impact of background factors and confounders, i.e., age, sex, visual impairment, and common co-morbidities was estimated and controlled by including them in regression models.

According to **Studies I** and **II**, the prevalence of glaucoma increased from 2.3% to 2.6% between 2000 and 2011 in Finland. The prevalence of cataract and retinal degeneration increased as well. Eye diseases and visual impairment were associated with significantly worsened health-related quality of life and mental health. However, glaucoma diagnosis and its treatment did not show direct impact on these factors. Rather, the detrimental impact of glaucoma and other vision-threatening eye diseases on these factors was primarily caused by the reduced visual acuity than the awareness of the disease itself. As a positive trend, the detrimental impact of eye diseases and visual impairment on these factors diminished between 2000 and 2011.

The results of **Study III** indicate that glaucoma patients use health care services more often and have greater productivity losses due to early retirement than persons without glaucoma even after adjusting for age and sex. Consequently, at 2019 cost level, glaucoma was associated with total additional direct and indirect costs of EUR 202 million and EUR 67 million per year in Finland, respectively, after adjusting for age and sex. The share of eye care of the total additional direct costs of glaucoma was only 13%. Most of these additional costs were linked to the reduced visual acuity caused by the disease as well as an increased number of co-morbidities due to the generally higher age of glaucoma patients.

Based on **Study I**, the prevalence of overall visual impairment decreased from 1.6% to 1.3% between 2000 and 2011 in Finland. Similarly, in **Study IV**, the incidence of reported glaucoma-related visual impairment per 10 000 treated glaucoma patients decreased from 32 to 21 between the 1980s and the 2010s, with a notable shift to older age groups. Glaucoma-related visual impairment has also mildened in the past four decades, and it occurs at a later age. These positive trends in visual impairment are likely explained by the improvements in diagnostics, therapies, and awareness of glaucoma and other vision-threatening eye diseases. Because vision loss significantly worsens the quality of life and work ability of glaucoma patients and increases their health care use as observed in **Studies I**, **II**, and **III**, maintaining the reduction of visual impairment and the improvement in the well-being of the visually impaired as the population keeps ageing will be crucial.

In conclusion, the information directed to the public about glaucoma and other eye diseases and their risks should be strengthened to promote early diagnosis and adherence to treatment. Doing this would consequently prevent or at least reduce the detrimental effects of declining vision on the patient and the society. In addition, the endorsement of equal and easy access to aids and rehabilitation of vision loss can equalize and milden the difficulties and problems caused by visual impairment. Further investigation in other countries and populations is required to address the social and economic implications of glaucoma at a larger scale and to confirm the validity and generalizability of the results of this thesis.

TIIVISTELMÄ

Glaukooma on vanhenevan väestön kansantauti ja yksi merkittävimmistä näkövammaisuuden ja sokeuden aiheuttajista maailmassa. Heikentynyt näkökyky aiheuttaa huomattavaa haittaa monilla elämän alueilla, kuten arkielämän rutiineissa, toiminta- ja työkyvyssä sekä sosiaalisissa vuorovaikutuksissa. Heikentynyt näkökyky on siten yhteydessä heikentyneeseen hyvinvointiin, terveydenhuoltopalveluiden kuormitukseen sekä menetettyyn tuottavuuteen. Glaukooman ja sen aiheuttaman näkövammaisuuden ennustetaan yleistyvän maailmanlaajuisesti väestön ikääntyessä. Glaukooman varhainen diagnosointi ja hoitoon sitoutuminen voivat olla haastavia, mikä vaikeuttaa glaukoomasta aiheutuvan näkövammautumisen estämistä tai hidastamista. Glaukooman kokonaisvaltaisen merkityksen ymmärtämiseksi tarvitaan enemmän väestöpohjaista tutkimusta glaukooman ja sen hoidon vaikutuksista elämänlaatuun, mielenterveyteen, näkökykyyn ja terveydenhuollon palvelujen käyttöön.

Tämän väitöskirjan tavoitteena oli tutkia glaukooman ja sen hoidon sosiaalisia ja ekonomisia vaikutuksia Suomessa vuosina 2000–2011. Väitöskirja koostuu neljästä osatyöstä. **Osatyössä I** arvioitiin glaukooman esiintyvyyttä ja kehitystrendejä Suomessa sekä verrattiin niitä kahteen muuhun näköä uhkaavaan silmäsairauteen: harmaakaihiin ja silmänpohjan rappeumaan. Tutkimuksessa lisäksi tarkasteltiin näiden kolmen silmäsairauden vaikutusta terveyteen liittyvään elämänlaatuun, mielenterveyteen ja kaukonäköön. **Osatyössä II** selvitettiin erikseen glaukooman ja sen hoidon vaikutuksia näihin osa-alueisiin. **Osatyön III** tavoitteena oli arvioida glaukooman ja sen hoidon vaikutusta terveydenhuollon palvelujen käyttömäärään ja ennenaikaiseen eläköitymiseen sekä näistä laskettuihin suoriin ja epäsuoriin kustannuksiin. **Osatyössä IV** tarkasteltiin glaukoomasta aiheutuneen näkövammaisuuden kehitystrendejä Suomessa viimeisen neljänkymmenen vuoden aikana.

Osatöiden I, **II** ja **III** tutkittavat otokset koostuivat valtakunnallisten Terveys 2000 ja 2011 -väestötutkimusten 30-vuotiaista ja sitä vanhemmista osallistujista. Väestötutkimukset sisälsivät kaksi poikkileikkausasetelmaa vuosilta 2000 ja 2011 sekä 11-vuotisen pitkittäisasetelman, joka koostui molempiin väestötutkimuksiin

osallistuneista henkilöistä. **Osatyössä IV** tutkimusotos koostui näkövammarekisterin glaukoomapotilaista aikaväliltä 1980–2019.

Osatöissä I, **II** ja **III** hyödynnettiin Terveystutkimuksiin sisältyneitä geneerisiä ja validoituja elämänlaadun ja mielenterveyden mittareita sekä haastattelukysymyksiä, joihin kuului itsearvoidut sairaudet (mm. glaukooma, harmaakaihi ja silmänpohjan rappeuma), sosioekonominen asema ja terveydenhuollon palvelujen käyttö. Kaukonäkö mitattiin molempiin Terveystutkimuksiin sisältyneissä terveystarkastuksissa. Terveystutkimusten tietoja täydennettiin Hoitoilmoitusrekisterin ja Kelan rekisteritiedoilla, joihin kuuluivat erikoissairaanhoidon sairaalahoidot ja avokäynnit sekä glaukoomalääkitykset. Glaukoomapotilaat valittiin Terveystutkimuksiin osallistuneista itsearvioitujen tietojen ja rekisteriaineistojen perusteella. Määrälliset muuttujat analysoitiin Mann–Whitneyn U-testillä, Wilcoxonin testillä tai Kruskal–Wallisin testillä. Luokittelevat muuttujat analysoitiin khiin neliö -testillä. Taustatekijöiden (ikä, sukupuoli, näkövammaisuus ja yleisimmät sairaudet) vaikutusta tutkittaviin muuttujiin arvioitiin ja kontrolloitiin lisäämällä ne regressiomalleihin.

Osatöiden I ja **II** perusteella glaukooman esiintyvyys kasvoi Suomessa 2,3 %:sta 2,6 %:iin vuosien 2000 ja 2011 välillä. Myös harmaakaihin ja silmänpohjan rappeuman esiintyvyydet kasvoivat. Glaukooma ja muut silmäsairaudet sekä näkövammaisuus olivat merkitsevästi yhteydessä heikentyneeseen elämänlaatuun ja mielenterveyteen. Glaukooman diagnoosilla ja hoitomuodoilla ei kuitenkaan ollut suoraa vaikutusta näihin tekijöihin. Elämänlaatua ja mielenterveyttä heikensikin ensisijaisesti silmäsairauksista johtuva näön heikkeneminen eikä sairauksien varsinainen toteaminen. Positiivisena kehityksenä silmäsairauksien ja näkövammaisuuden haitallinen vaikutus näihin tekijöihin väheni vuosien 2000 ja 2011 välisenä aikana.

Osatyön III mukaan glaukoomapotilaat käyttivät terveydenhuollon palveluja enemmän kuin ikä- ja sukupuolivakioidut verrokkihenkilöt, jotka eivät sairastaneet glaukoomaa. Glaukoomapotilailla oli myös suurempi riski jäädä ennenaikaiselle eläkkeelle. Siten glaukoomaan liittyy huomattavia suoria ja epäsuoria lisäkustannuksia: vuosittaiset suorat lisäkustannukset Suomessa olivat vuoden 2019 hintatason mukaisesti arviolta 202 miljoonaa euroa ja epäsuorat lisäkustannukset 67 miljoonaa euroa ikä- ja sukupuolivakioituina. Silmäterveydenhuoltoon liittyvien hoitojen osuus oli suorissa lisäkustannuksissa vain 13 %. Kustannuksia lisäsivät eniten glaukoomapotilaiden heikentynyt näkökyky sekä ikääntymisen tuomat muut sairaudet.

Osatyön I mukaan yleisen näkövammaisuuden esiintyvyys väheni Suomessa 1,6 %:sta 1,3 %:iin. **Osatyön IV** mukaan glaukooman aiheuttaman näkövammaisuuden ilmaantuvuus väheni 32:sta 21:een (per 10 000 hoidettua glaukoomapotilasta) 1980-luvulta 2010-luvulle sekä siirtyi vanhempiin ikäryhmiin. Lisäksi viimeisen neljän vuosikymmenen aikana glaukoomasta aiheutuneen näkövammaisuuden vaikeusaste on lieventynyt ja näkövammaisuuden alku on siirtynyt myöhempään ikään. Kehityksen syinä ovat todennäköisesti kehittynyt diagnostiikka ja hoitomenetelmät sekä parantunut tietoisuus glaukoomasta ja muista silmäsairauksista. **Osatöiden I**, **II** ja **III** tulosten perusteella heikentynyt näkökyky heikentää merkittävästi glaukoomapotilaiden elämänlaatua ja työkykyä sekä lisää merkittävästi terveydenhuollon palvelujen käyttöä. Siksi onkin tärkeää, että näkövammaisuuden vähentyminen ja näkövammaisten hyvinvoinnin parantuminen voidaan taata jatkossakin väestön ikääntymisestä huolimatta.

Tämän väitöstutkimuksen tulosten perusteella glaukoomasta ja muista silmäsairauksista sekä niiden riskeistä tiedottamista tulisi parantaa ja varhaisen diagnoosin ja hoitoon sitoutumisen merkitystä tehostaa. Lisäksi tulisi edistää näönkuntoutuksen sekä apuvälineiden käytön saatavuutta ja tasavertaisuutta. Näin heikentyvän näkökyvyn haitallisia vaikutuksia saataisiin ehkäistyä tai vähintään lievennettyä sekä potilaan että yhteiskunnan kannalta. Samantasoisia aineistoja hyödyntäville jatkotutkimuksille on tarvetta, jotta tuloksia voitaisiin verrata muihin maihin ja väestöihin.

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ABBREVIATIONS

15D	Generic, 15-dimensional, standardized, self-administered health-related quality of life questionnaire
ACG	Angle-closure glaucoma
AMD	Age-related macular degeneration
BDI	Beck Depression Inventory
CI	Confidence interval
DR	Diabetic retinopathy
EQ-5D	EuroQoL-5 Dimension health-related quality of life questionnaire
GHQ-12	General Health Questionnaire 12
Health 2000	The Health 2000 Survey
Health 2011	The Health 2011 Survey
HILMO	Care Registers for Social Welfare and Health Care (Sosiaali- ja terveydenhuollon hoitoilmoitusrekisteri)
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
IOP	Intraocular pressure
KELA	Social Insurance Institution of Finland (Kansaneläkelaitos)
NVREK	Finnish Register of Visual Impairment (Näkövammarekisteri)
OR	Odds Ratio
OAG	Open-angle glaucoma
PACG	Primary angle-closure glaucoma
POAG	Primary open-angle glaucoma
QoL	Quality of life
RD	Retinal degeneration
SD	Standard deviation
THL	National Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos)
VA	Visual acuity
VF	Visual field
VI	Visual impairment
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-IV):

Publication I	Purola PKM, Nättinen JE, Ojamo MUI, Koskinen SVP, Rissanen HA, Sainio PRJ, Uusitalo HMT. Prevalence and 11-year incidence of common eye diseases and their relation to health-related quality of life, mental health, and visual impairment. *Quality of Life Research* 2021;30(8):2311–2327. doi: 10.1007/s11136-021-02817-1
Publication II	Purola PKM, Nättinen JE, Parkkari MM, Ojamo MUI, Koskinen SVP, Rissanen HA, Sainio PRJ, Uusitalo HMT. Improving health-related quality of life and mental health in glaucoma during 11 years and their association with vision loss and treatment of the disease. *Acta Ophthalmologica* 2022;100(1):e221–e232. doi: 10.1111/aos.14883
Publication III	Purola PKM*, Taipale J*, Väätäinen S, Harju M, Koskinen SVP, Uusitalo HMT. Price tag of glaucoma care is minor compared with the total direct and indirect costs of glaucoma: Results from nationwide survey and register data. *PLOS ONE* 2023;18(12):e0295523. doi: 10.1371/journal.pone.0295523
Publication IV	Vaajanen A, Purola P, Ojamo M, Gissler M, Uusitalo H. Changes in incidence and severity of visual impairment due to glaucoma during 40 years – a register-based study in Finland. *Acta Ophthalmologica* 2022;100:534–540. doi: 10.1111/aos.15030

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AUTHOR'S CONTRIBUTION

In all four original studies, the author contributed to the planning of study design in collaboration with the supervisors and co-authors. The author actively participated in the designing and execution of the statistical analyses (**I**, **II**) as well as with the help of co-authors (**III**, **IV**). The author was responsible for the evaluation of the results with the assistance of his supervisors and other co-authors. The author wrote the first drafts of the manuscripts and was also responsible for editing and submitting the final papers.

1 INTRODUCTION

Glaucoma is one of the leading causes of irreversible loss of vision globally: there are more than 70 million glaucoma patients in the world (Tham et al., 2014), and approximately 7.7 million individuals are bilaterally blind or visually impaired due to the disease (Steinmetz et al., 2021). Glaucoma is strongly associated with ageing (Laitinen et al., 2010), and as populations age rapidly around the world, the number of glaucoma patients and patients with glaucoma-related vision loss are expected to rise accordingly (Tham et al., 2014). Nevertheless, it is possible to arrest or mitigate the glaucoma-caused deterioration of vision with early diagnosis and efficient treatment of the disease (Cohen and Pasquale, 2014; Heijl et al., 2002).

From epidemiological and societal viewpoint glaucoma carries unique challenges. In high-income countries, the prevalence of glaucoma is usually lower than that of the two other major vision-threatening diseases: cataract and age-related macular degeneration (Steinmetz et al., 2021). On the other hand, the visual deterioration in cataract is treatable with high success rates, whereas the treatment for age-related macular degeneration, even though very much developed in past years (Purola et al., 2023a), is still largely limited. As for glaucoma, there exists many treatment options, requiring the treatment of glaucoma to be personalized. Furthermore, to prevent the irreversible loss of vision due to glaucoma, the key issue of the lifelong therapy is the adherence to the treatment and follow-up. Glaucoma also remains commonly undetected due to its asymptomatic early phases, which can lead to unnoticeable deterioration of vision (Weinreb et al., 2014).

There is a growing interest in evaluating the impact of glaucoma and its treatment on well-being and health care resource use, but so far these relationships have remained unclear due to limitations in study samples and methodologies. Particularly, the role of visual functions among glaucoma patients on these factors remains uncertain at the population level. This ambiguity bears great relevance because vision loss is associated with worsened quality of life and mental health, increased use of health care services, and loss of productivity (Rein et al., 2022; Taipale et al., 2019).

The present study aimed to fill these unmet needs by providing nationwide, population-based data on glaucoma, glaucoma treatment, and glaucoma-related visual impairment, and their association with generic health-related quality of life, mental health, health care resource use, and productivity. Cataract and retinal degeneration were partially included in the analyses to extend the findings and conclusions to the most common vision-threatening eye diseases. The analyzed data were based on two comprehensive health examination surveys carried out in Finland in 2000 and 2011, which included two cross-sectional settings and an 11-year longitudinal setting. Furthermore, the time trends in glaucoma-related visual impairment were observed based on Finnish register data from 1980 to 2019. In summary, the thesis can provide much needed information on the causes, development, economic, and welfare consequences of glaucoma and reduced visual acuity both in the whole population and its subgroups. The results will provide valid and scientifically valuable new information for the design of glaucoma screening, treatment, rehabilitation, and related public health strategies. This knowledge will also be very useful for planning and directing social and health care to allocate resources efficiently in the context of rapidly ageing population.

2 REVIEW OF THE LITERATURE

2.1 Vision and visual acuity

2.1.1 Eye and visual function

According to the World Health Organization (WHO), visual function refers to a person's ability to perceive the surrounding world by sensing the presence of light and the form, size, shape, and color of visual stimuli (WHO, 2001). The human eye is a complex organ that enables and controls visual function. The basic anatomy of the eye is illustrated in Figure 1. The eye can be divided into three layers, anterior, middle, and interior, all of which facilitate the transfer of light into visual sensation (Kanski and Bowling, 2011; Seppänen et al., 2018; Willoughby et al., 2010).

In the most anterior layer of the eye lie the cornea and the lens. The cornea refracts and transmits the light to the lens, which focuses the light on the retina in the interior layer of the eye.

The middle layer of the eye consists of the iris, the ciliary body, and the choroid. The iris regulates the amount of light that reaches the retina by adjusting the size of the pupil. The ciliary body controls the shape and power of the lens. It is also the site of aqueous production. The choroid is a vascular structure that provides oxygen and nutrients to the retina.

The inner layer of the eye is the retina, a layered structure of multiple types of neurons wherein the light is captured and converted into an electrical signal by phototransduction. It is carried by photoreceptors: neurons that are classified into cone cells and rod cells. The cones dominate the bright light vision and allow the detection of color and fine details, whereas rods are less sensitive for color but dominate the dim-light vision. A central area of the retina is called macula. A specialized center in the macula is the fovea, which is responsible for sharp vision and contains only densely packed cones. The electric signal from the photoreceptors is then processed in bipolar, amacrine, horizontal, and ganglion cells. The electrical signal is translated into nerve impulses by ganglion cells whose axons form the optic nerve that sends the signal to the brain for further processing, ultimately producing visual sensation.

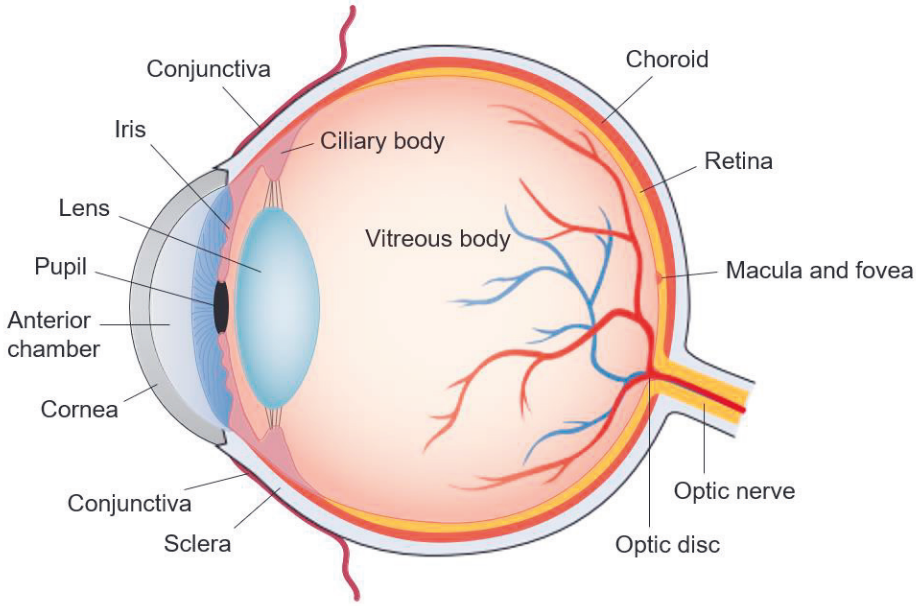


Figure 1. Basic anatomy of eye. The figure was modified from (Seppänen et al., 2022) and originally created by Helena Schmidt with permission of Duodecim Publishing Company Ltd.

2.1.2 Role of vision

Vision is a fundamental sense that influences an individual's ability to cope with different environments. Vision and visual function have an important role in orientation, balance, and gait. Vision also plays a major role in the independence of person by influencing mobility and self-care (Purola et al., 2023c; Taipale et al., 2019).

The role of vision at working places and in daily life has increased in recent decades due to technological evolution with a consequent increase in demand for precise vision. Furthermore, in societies with rapidly ageing population, delays in the retirement age are being considered given that elderly people are expected to be productive in work (Feng et al., 2019; Yeung and Lee, 2022). Essentially, there is an increasing need for maintaining good vision through the life.

Vision is also a very vulnerable sense, and the anatomy and function of the eye are highly complex. There is a wide range of diseases that can cause functional disturbances in the eye. The surface of the eye is directly exposed to many external threats such as pollution, injuries, and pathogens. Furthermore, there are many vision-threatening diseases that either are located directly in the eye or affect the eye via systemic pathways such as diabetes mellitus. A major risk factor for declining vision is high age with a consequently increased risk of vision-threatening diseases. Other risk factors for declining vision include genetic susceptibility, high-risk levels of diastolic blood pressure and low-density lipoprotein cholesterol, and debatably female sex (Cedrone et al., 2006; Steinman and Vasunilashorn, 2011; Taylor et al., 1997).

Vision loss has been associated with difficulties in mobility and activities of daily living, and it plays an important role in the development of disability. Even mild vision loss can significantly increase difficulties in daily functioning (Purola et al., 2023c; Taipale et al., 2019). The difficulties and consequent decrease in mobility and independence can lead to multiple adverse consequences such as social isolation and lack of physical activity, which in turn can increase risk for further disability, therefore leading to a vicious circle (Alma et al., 2011; Vu et al., 2005). Impaired vision is also associated with falls and injuries that can lead to substantial physical, psychological, and financial costs to both the individual and the community (Black and Wood, 2005; Marques et al., 2021; Rein et al., 2022). Therefore, loss of vision has a substantial impact on an individual by reducing personal quality of life and sense of independence as well as on the society by increasing the need for health and social services and institutionalization.

2.1.3 Definition of visual impairment

Visual impairment (VI) can be defined as a low vision or blindness. A person can be considered visually impaired when the loss of vision significantly impacts one's daily functioning (Ojamo and Tolkkinen, 2022). There exist multiple definitions for different classifications of VI. Visual function is generally assessed with the objective measurements of visual acuity (VA), visual field (VF), stereopsis, contrast sensitivity, dark adaptation, and glare. Self-reported visual function is also thought to provide additional information on the quality of visual function. In Finland, the definition by WHO from 1973 (WHO Study Group on the Prevention of Blindness, 1973) has been used, which includes five classifications based on the level of VI and utilizes both distance VA and VF (Table 1). In 2023, the new definitions of VI by WHO were established in Finland, which also includes near VA (WHO, 2023). The sub-studies of this thesis utilized the 1973 definitions, and near VA was also excluded in the sub-studies for showing poorer correlation with studied parameters than distance VA.

Table 1. Classification of visual impairment in Finland used up to 2023 based on the World Health Organization definitions and Snellen notation (WHO Study Group on the Prevention of Blindness, 1973)

Classification of visual impairment (VI)	Visual acuity (VA)	Visual field (VF) around central fixation
Mild VI	0.3 > VA ≥ 0.1	
Moderate VI	0.1 > VA ≥ 0.05	
Severe VI	0.05 > VA ≥ 0.02	10° > VF ≥ 5°
Nearly total blindness	0.02 > VA – 1/∞	VF < 5°
Total blindness	VA = 0, no sense of light	

The assessment of the VA and VF represents one of the most common visual function tests used in routine clinical ophthalmic practice because both measures are heavily affected by vision-threatening eye diseases. VA refers to the rating of a person's ability to recognize small details with precision, whereas VF (illustrated in Figure 2) can be defined as "that portion of space in which objects are visible at the same moment during steady fixation of the gaze in one direction" (Traquair, 1938). The defects and constriction of VF have been associated primarily with glaucoma (Drance, 1972) and (age-related) macular degeneration (Tolentino et al., 1994). The measurement of VF is considered the cornerstone of glaucoma management by influencing therapeutic decisions. The VF testing has three purposes: detection of early sensitivity deficits, determination of characteristic spatial patterns of sensitivity loss for differential diagnosis, and monitoring of patients for evidence of progression, stability, or improvement of VF deficits (Chauhan et al., 2008; Spry and Johnson, 2002).

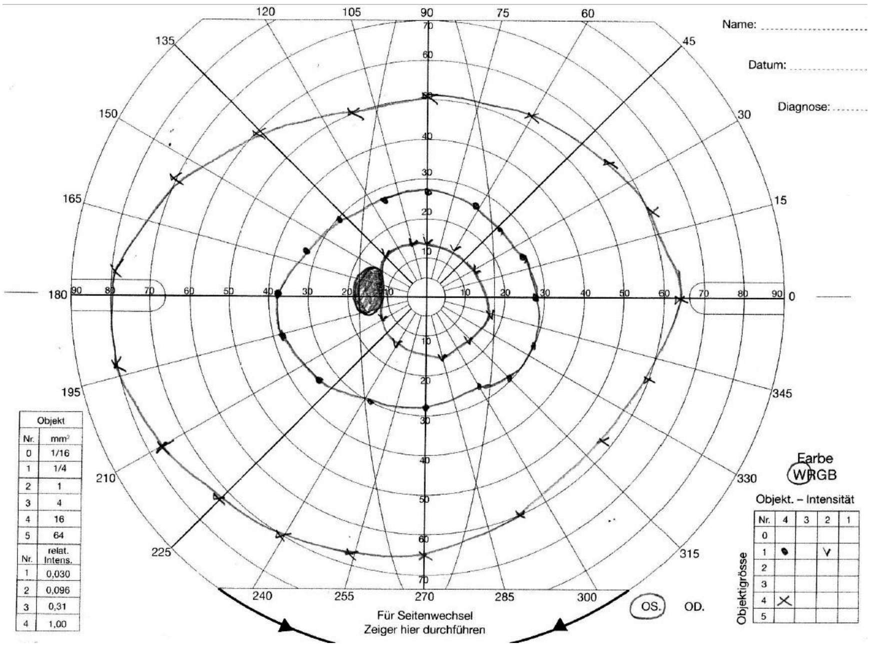


Figure 2. Illustration of visual field based on the Goldmann kinetic perimetry that allows the evaluation of the peripheral field as well. The three drawn circles were created based on the different size and intensity of the object. The figure was modified from (Seppänen et al., 2022) and originally from professor Eija Vesti with permission of her and Duodecim Publishing Company Ltd.

2.1.4 Epidemiology of visual impairment

VI is one of the most common disabilities in the world. In 2020, there were estimated to be 295 million people globally with moderate or severe VI (global prevalence 3.58%) and 43 million with blindness (global prevalence 0.53%; Bourne et al., 2021). Over the past few decades, several large population-based studies have been conducted to observe the distribution and prevalence of VI and blindness, for example, the Framingham Eye Study in 1973–1975 (Kahn et al., 1977; Leibowitz et al., 1980), the Beaver Dam Eye Study in 1988–1990 (Klein et al., 1991; Linton et al., 1991), the Blue Mountains Eye Study in 1991–1993 (Attebo et al., 1996), and the Ponza Study in 2000 (Cedrone et al., 2006). In Finland, the prevalence of VA and VI has been investigated in elder persons and in specific regions such as the city of Turku (Häkkinen, 1984) and the city of Oulu (Hirvelä and Laatikainen, 1995). Although these studies represent regional data well, estimates at the national level are in scarce. In prior to the sub-studies of this thesis, only two nationally representative population-based studies on vision and VI in Finland had been published (Laitinen et al., 2005; Taipale et al., 2019).

Overall, VI is strongly related to age. In the Framingham Eye Study, the prevalence of VI (VA ≤ 0.25) was 0.9% in the age group 52–85 years and 3.5% in the age group ≥ 75 years (Leibowitz et al., 1980). Based on the Turku Study, the prevalence of VI (VA ≤ 0.25) was 7.0% in the population aged 65 years or older, increasing to 13.9% among those aged 75 years or older (Häkkinen, 1984). According to the Blue Mountains Eye Study, the prevalence of VI (VA ≤ 0.25) was 1.3% in the population aged 49 years or older, increasing to 5.0% among those aged 75 years or older (Attebo et al., 1996). Based on a global estimation from 2015, approximately 86% of the persons who were blind (VA < 0.05) were aged 50 years or older (Bourne et al., 2017).

Most epidemiological studies have shown a higher rate of VI in females than in males, particularly in older age groups. For example, the sex difference was significant in the Beaver Dam Eye Study (Klein et al., 1991) and the Blue Mountains Eye Study (Attebo et al., 1996). On the other hand, no statistically significant differences in sex were observed in the Turku Study (Häkkinen, 1984) and the Ponza Study (Cedrone et al., 2006), for example.

Considering the heavy requirements for large-scale population-based surveys, most studies on VI have focused on measuring VA or assessing self-reported visual functions in clinical settings with limitations regarding age and population samples; hence, information on VA and the prevalence of VI and blindness in the general population is scarce. Longitudinal evaluation of both VI and overall vision is particularly absent. Furthermore, the definitions of VI and blindness vary between countries, which makes the comparisons between studies difficult. Due to the ageing of the populations and the increasing life expectancy, the number of visually impaired elderly persons is expected to increase worldwide over the decades to come (Bourne et al., 2021). Therefore, it would be vital to follow time trends in visual function and VA at the population level and the impact of interventions performed to prevent vision loss.

2.1.5 Causes of visual impairment

In 2020, the five leading causes of VI and blindness globally were estimated to be uncorrected refractive error, cataract, glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR; Flaxman et al., 2017; Steinmetz et al., 2021).

Assessing the prevalence and time trends of these causes is needed to plan the requirements for future health and eye care services.

There are major regional differences in the distribution of these diseases and disorders: in high-income countries, AMD exceeds as the main cause of blindness and VI followed by glaucoma and DR, whereas in low-income countries uncorrected refractive error and cataract are the leading causes of blindness and VI (Flaxman et al., 2017; Steinmetz et al., 2021). The deterioration of vision caused by cataract can usually be prevented with modern surgery, but the accessibility to cataract care can be inadequate particularly in low-income countries (Ramke et al., 2017). The limited access to eye care in low-income countries is also a likely explanation for the increased risk of VI due to uncorrected refractive error in these countries.

AMD is a class of retinal degeneration (RD) with a strong association with age. It affects the macular region of the retina, causing progressive loss of central vision (Mitchell et al., 2018). In 2020, the estimated number of people with AMD globally was approximately 200 million (Wong et al., 2014). AMD is clinically classified into early or late AMD. Early AMD includes such clinical findings as retinal drusen and/or pigment epithelial abnormalities. Late AMD is characterized by the signs of exudative AMD ("wet" form) or geographic atrophy ("dry" form). AMD-related VI is mainly caused by late AMD. The risk factors of AMD include high age, smoking, and family history (Klein et al., 2010; Seddon and Rosner, 2019). Currently, the treatment for AMD is limited. New therapies for the exudative form have been developed in the 2000s. Intravitreal anti-vascular endothelial growth factor therapy has been shown to be highly effective and has markedly decreased the prevalence of AMD-caused VI in populations worldwide (Colijn et al., 2017; Purola et al., 2023a). Treatments for geographic atrophy are still being investigated.

DR is the most common ocular complication of diabetes mellitus. In Finland, there are over 500 000 patients with diabetes mellitus and the incidence of insulin-dependent diabetes mellitus is the highest in the world (Parviainen et al., 2020). DR is categorized into non-proliferative DR and proliferative DR, latter being the more vision-threatening form of DR. Screening and early treatment of DR with laser therapy and surgery can reduce the risk of DR-related vision loss (Purola et al., 2022).

Glaucoma is discussed in more detail in Section 2.2.

The number of people with vision-threatening diseases is expected to increase in the future due to the ageing of the populations and rising life expectancy around the world as well as unfavorable changes in lifestyle, for example, unhealthy eating habits and decreased exercise in developed countries (Abarca-Gómez et al., 2017; Zhou et al., 2016, 2017). Still, in Finland, the VI caused by AMD and DR has started to decrease in the 2000s (Purola et al., 2022; Purola et al., 2023a), which highlights the importance of timely provision of vision examinations and treatment of eye diseases as well as the awareness of the eye diseases and their risks in preventing or postponing vision loss.

2.2 Glaucoma

2.2.1 Etiology of glaucoma

Glaucoma is a collection of progressive neurodegenerative diseases characterized by an irreversible progressive optic neuropathy that can lead to VI if not treated (Weinreb et al., 2014). Elevated intraocular pressure (IOP) is the leading risk factor of glaucoma. Risk factors for IOP include high body mass index and specific medications, particularly steroids and other glucocorticoids (Clark et al., 1995; Han et al., 2014). Risk factors for overall glaucoma besides IOP include old age, family history, myopia, and presence of exfoliative material (Brown and Congdon, 2006; "Glaucoma: Current Care Guidelines," 2023; Weinreb et al., 2014). Several genes have also been associated with IOP and different subtypes of glaucoma, including *ABCA1*, *AFAP1*, *ARHGEF12*, *ATXN2*, *CAV1*, *CDKN2B-AS1*, *FOXC1*, *GAS7*, *GMDS*, *MYOC*, *OPTN*, *SIX1/SIX6*, *TBK1*, *TMCO1*, and *TXNRD2* (Wiggs and Pasquale, 2017; Zukerman et al., 2020; Liuska et al. 2021).

Aqueous humor fills the anterior and posterior chambers of the eye and provides both nutrition and support to avascular cornea and lens. It is secreted from the ciliary epithelium, and the outflow occurs through the trabecular meshwork in the anterior chamber as well as via uveoscleral outflow. When normal aqueous outflow in the eye is decreased, it can cause an increase in IOP and lead to the development of glaucoma (Weinreb et al., 2014). The progression of glaucoma can result in death of retinal ganglion cells and axonal loss of the optic nerve, ultimately leading to loss of vision via reducing VF (Weinreb et al., 2014). The exact pathways that relate IOP to glaucomatous optic neuropathy and the associated VF defects have not yet been fully characterized (Nickells et al., 2012).

There exist many subtypes of glaucoma. The two main categories of glaucoma are open-angle glaucoma (OAG) and angle-closure glaucoma (ACG) depending on the mechanism of elevated IOP (illustrated in Figure 3). In OAG, there is an increased resistance to aqueous outflow through the trabecular meshwork, whereas in ACG the access to the drainage pathway is obstructed by either apposition of the peripheral iris to the trabecular meshwork or by a synechial closed angle (Sun et al., 2017). OAG can be subdivided into primary open-angle glaucoma (POAG), which is considered the most prevalent form of glaucoma (Quigley and Broman, 2006) and is associated with elevated IOP, and normal tension glaucoma, in which IOP by definition falls within a statistically normal range. In addition, a secondary OAG can result from multiple causes such as trauma, inflammation, pseudo-exfoliation, or corticosteroids. Primary angle-closure glaucoma (PACG) is less common than POAG, but it has been associated with a higher risk of VI and blindness (Quigley and Broman, 2006; Tham et al., 2014).

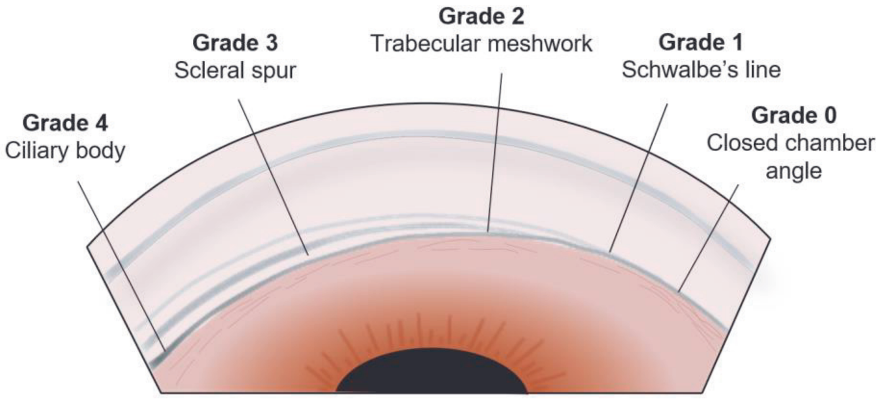


Figure 3. Illustration of the gonioscopy assessment of anterior chamber angle in determining the type of glaucoma. The angle opening is graded based on the Shaffer Grading System in which Grade 4 represents wide open angle and Grade 0 closed angle. The structures that are visible in each grade are illustrated. The figure was modified from (Seppänen et al., 2022) and originally created by Helena Schmidt with permission of Duodecim Publishing Company Ltd.

2.2.2 Epidemiology of glaucoma

In 2013, approximately 64.3 million people aged 40–80 were affected by glaucoma according to Tham and co-workers (Tham et al., 2014), and they estimated the number to increase to approximately 76.0 million by 2020. Similarly, Quigley and Broman estimated that 79.6 million people over 40 years of age worldwide will have glaucoma in 2020 (Quigley and Broman, 2006). The global prevalence of glaucoma in the population aged 40–80 years was estimated by Tham and co-workers as 3.54%

in 2013, and the estimated pooled global prevalence of POAG and PACG was 3.05% and 0.50%, respectively (Tham et al., 2014).

The prevalence of glaucoma increases with age. In Finland, the prevalence of glaucoma is approximately 4% among persons over 50 years according to the Social Insurance Institution of Finland (The Social Insurance Institution of Finland, 2021). Based on a Finnish population-based regional study from 1991–1992, the prevalence of glaucoma was estimated as 12% among persons over 70 years or older (Hirvelä et al., 1994). Based on nationwide Finnish data from 2000, Laitinen and co-workers reported that the prevalence of glaucoma increased from 2% in the population aged 30–64 years to 20% among those aged 85 years or older (Laitinen et al., 2010). Sex differences in the prevalence of glaucoma have remained inconclusive (Jonasson et al., 2003; Nizankowska and Kaczmarek, 2005; Weih et al., 2001).

An overview on the estimated prevalence of glaucoma in different countries is shown in Table 2. Accurate estimations of the current prevalence of glaucoma and future projections are critical for the design of adequate health policies tailored for the diverse populations worldwide. When comparing the prevalence of glaucoma in different population-based studies, it is important to consider the differences in demographic and genetic characteristics, the diagnostic methods employed, and the used terminological definitions. The age and percentage of the oldest participants may change the final results noticeably due to the high prevalence of glaucoma among the elderly. The diagnostic methods also affect the estimates of glaucoma prevalence. Particularly important is the definition of what constitutes a glaucomatous optic nerve change: the lack of well-defined, globally accepted criteria for glaucoma diagnosis makes interpretation of examination results challenging. Similar problems are associated with the assessment of abnormalities in VF. The time scale within the studies have taken place is also considerably wide, during which many improvements and changes in the diagnostics of glaucoma, particularly in measuring VF, have taken place.

There is substantial geographic variation in the prevalence of glaucoma subtypes. In 2013 according to Tham and co-workers, the prevalence of POAG in the population aged 40–80 years was highest in Africa (4.20%), while the prevalence of PACG was highest in Asia (1.09%; Tham et al., 2014). The prevalence of pseudo-exfoliation syndrome and subsequent capsular glaucoma has been reported particularly high in Finland and other Nordic countries (Arnarsson et al., 2007; Åström et al., 2007; Åström and Lindén, 2007; Krause et al., 1988).

Table 2. Examples of population-based studies reporting prevalence of glaucoma

Country	Population	Time	Glaucoma type	Prevalence, %	Reference
Netherlands	Inhabitants of Rotterdam aged ≥55 years	1990–1993	POAG	1.1	(Dielemans et al., 1994)
Finland	Inhabitants of Oulu aged ≥70 years	1991–1992	OAG	10.4	(Hirvelä et al., 1994)
Australia	Inhabitants aged ≥40 years	1992–1996	OAG	1.8	(Weih et al., 2001)
Iceland	Inhabitants of Reykjavik aged ≥50 years	1996	OAG	4.0	(Jonasson et al., 2003)
Japan	Inhabitants of Tajimi City aged ≥40 years	2000–2001	POAG	3.9	(Iwase et al., 2004)
Poland	Inhabitants aged 40–79 years	1999–2002	All	1.6	(Nizankowska and Kaczmarek, 2005)
Finland	Inhabitants aged ≥30 years	2000–2001	All	4.5	(Laitinen et al., 2010)
China	Inhabitants aged ≥40 years	2001	All	3.6	(Wang et al., 2010)
South Korea	Inhabitants in rural area aged ≥40 years	2007–2008	POAG	3.5	(Kim et al., 2011)
Japan	Inhabitants in rural area aged ≥40 years	2005–2006	PACG	2.0	(Sawaguchi et al., 2012)
US	Inhabitants aged ≥40 years	2005–2008	All	2.1	(Gupta et al., 2016)
Australia	Non-indigenous inhabitants aged 50–98 years	2015–2016	All	1.5	(Keel et al., 2019)

OAG, open-angle glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma.

It has been estimated that as much as 50% of all glaucoma cases in a population can be undiagnosed (Gupta et al., 2016; Keel et al., 2019; Leske, 2007; Weih et al., 2001), and the risk of undiagnosed glaucoma increases with age (Heijl et al., 2013). Approximately one third of patients with undetected glaucoma have advanced disease (Heijl et al., 2013). Therefore, the estimated prevalence rates of glaucoma and the number of glaucoma patients are likely to be higher. The underlying cause of underdiagnosis of glaucoma is likely the typically asymptomatic nature of its early phases (Leite et al., 2011; Weinreb et al., 2014). Furthermore, the knowledge and awareness of glaucoma and its risk factors in general populations have been regarded low (Celebi, 2018; Mansouri et al., 2006; Nduaguba and Lee, 2006), and the risk of undiagnosed glaucoma is higher among those who do not attend eye care regularly (Weih et al., 2001).

2.2.3 Treatment of glaucoma

Elevated IOP is considered one of the major risk factors of glaucoma. Because there is a lack of therapies at present that could directly prevent the death of retinal ganglion cells, the current management of glaucoma focuses heavily on lowering the IOP (Heijl et al., 2002). This outcome is achieved either by reducing the aqueous humor production or by enhancing the outflow of aqueous humor though trabecular meshwork or via uveoscleral outflow.

The reduction of IOP can be achieved via three treatment methods: medical treatment, laser therapy, and surgery (Cohen and Pasquale, 2014). Medical treatment is the most common form of glaucoma care, and it consists of topical medication administered as eye drops with aim to reduce the aqueous humor production and/or increase the fluid outflow. Prostaglandin analogues are primarily used, but alternative topical medications include beta-blockers and carbonic anhydrase inhibitors (Parkkari et al., 2020).

Due to the chronic nature of the disease, glaucoma patients usually require more than one topical drug for the successful control of IOP (Parkkari et al., 2020, 2022); hence, the medical treatment of glaucoma is highly personalized and requires life-long adherence. Worryingly, multiple studies have shown low compliance with glaucoma medication (Gurwitz et al., 1993; Reardon et al., 2011; Schwartz and Quigley, 2008; Yeaw et al., 2009). Patient satisfaction with their treatment is acknowledged to be an important factor in ensuring adherence with treatment regimens and cooperation with medical practitioners. Therefore, patients and family members need encouragement and information from their practitioner as well as efficient, convenient, and acceptable medications.

Glaucoma medications of the most recent generation have generally not been associated with significant systemic adverse effects. Still, the continuous use of topical medication among glaucoma patients has been associated with increasing prevalence of ocular surface problems (Ghosh et al., 2012; Leung et al., 2008; Parkkari et al., 2022). This phenomenon is often linked to both the active ingredient in the eye drops and the preservative frequently added to prevent bacterial contamination (Baudouin et al., 2010; Parkkari et al., 2022; Uusitalo et al., 2010). Therefore, special attention should be paid on patients having signs and symptom of ocular surface problems on what type of medicine is prescript. In case of multi-therapy, a switch to laser or surgical treatment instead of increasing topical medication may be viable.

If adequate IOP reduction cannot be achieved with medical treatment with acceptable adverse effects, laser therapies or incisional surgeries are indicated (Weinreb et al., 2014). Additionally, in poorly adherent patients, in patients with severe disease, or in patients with difficulties in administering topical medication, laser or surgery treatment can sometimes be offered as a first-line glaucoma therapy.

Laser trabeculoplasty lowers IOP by inducing biological changes in the trabecular meshwork that results in increased aqueous outflow (Gulati et al., 2017). The procedure is considered low-risk and can be performed during an office visit (Weinreb et al., 2014). It can result in a 6.9%–35.9% IOP reduction (Wong et al., 2015). The effect decreases gradually over time, and approximately 67% of the treated eyes can be managed without additional medication for 8 years (Odberg and Sandvik, 1999).

Glaucoma surgery can be divided into minimally invasive, filtering, and non-filtering types. Minimally invasive procedures include a placement of a stent to lower the outflow resistance through the trabecular meshwork (Lavia et al., 2017). Trabeculectomy is considered the reference standard for a filtering operation, in which an accessory pathway is created for the aqueous humor to flow out of the eye. Although minimally invasive glaucoma surgeries have been reported to have fewer side effects than a filtering procedure (Pillunat et al., 2017), they also lower the IOP by a lesser amount (Agrawal and Bradshaw, 2018). Examples of non-filtering types include deep sclerectomy and canaloplasty (Schuster et al., 2020).

2.2.4 Glaucoma-related visual impairment

The progressive loss of retinal ganglion cells leads to irreversible vision loss by reducing VF; hence, in addition to decreased VA, defective VF is a major cause of VI among glaucoma patients. Further functional disturbances include impaired contrast, impaired color perception, and difficulties in reading (Erb, 2015). Even though timely and effective treatment of glaucoma could prevent the deterioration of vision, glaucoma remains as one of the leading causes of VI and blindness worldwide (Flaxman et al., 2017; Steinmetz et al., 2021; Tham et al., 2014). In Finland

and other Western countries, glaucoma is the second leading cause of irreversible VI after AMD and before DR in the population aged 65 years or older (Ojamo and Tolkkinen, 2022).

According to global-based projections, in 2020, there were estimated to be at least 4.5 million glaucoma patients with moderate to severe VI (VA < 0.33 but ≥ 0.05) and 3.2 million glaucoma patients with blindness (VA < 0.05) worldwide (Flaxman et al., 2017). Based on clinical records, approximately 14–16% of all glaucoma patients are bilaterally blind (Forsman et al., 2007; Peters et al., 2013). In the Copenhagen City Eye Study, 40% of blindness (VA < 0.05) was caused by glaucoma in the population aged 60–80 years (Buch et al., 2001a, 2001b). Based on a population-based regional follow-up study during 1991–2011 with a mean follow-up time of 12 years, the incidence rate of glaucomatous VF loss in the population aged 55 years or older was 2.9 per 1000 person years, and the 12-year incidence was 3.5% (Springelkamp et al., 2017). With longer life expectancy, the lifetime risk of glaucoma-caused vision loss has been implied to increase even further (Peters et al., 2013).

There is a deficit of epidemiological studies on the vision loss due to glaucoma, particularly at the population level and in nationwide settings and with longitudinal design. Most of the previous studies have been based on clinical or regional settings. Furthermore, the common underdiagnosis of the disease due to its asymptomatic early stages can likely lead to underestimations of glaucoma-related vision loss similarly to the prevalence estimations of glaucoma (Weinreb et al., 2014). This factor along with the low public awareness of glaucoma and the non-adherence to prescribed therapy can lead to inadequate control of glaucoma with severe consequences for both the individual and the society.

2.2.5 Glaucoma care in Finland

The glaucoma care is usually initiated by private ophthalmologists. Alternatively, opticians or primary care physicians refer patients with high IOP and/or abnormal optic nerve head to undergo a complete ophthalmologic examination in either public or private ophthalmic units. Special attention should be given to individuals having glaucoma-related risk factors such as family history and myopia ("Glaucoma: Current Care Guidelines," 2023).

The treatment of glaucoma is initiated by establishing a target level for the IOP and the type of therapy. The target IOP is heavily individualized and depends on the initial IOP level and the severity of glaucoma ("Glaucoma: Current Care Guidelines," 2023). The initial therapy type is usually topical medication or laser therapy as described in Section 2.2.3. Prostaglandin analogues and beta-blockers are the first-line medical therapy. In comparison with prostaglandin analogues, other classes of topical medications are less effective in lowering IOP (Stewart et al., 2008), but they are used as second-line agents or when there is a contraindication or intolerance to the use of prostaglandin analogues. A fixed-combination glaucoma therapy is also an option, which can reduce the chemical burden on the surface of the eye and consequently lessen the adverse effects associated with topical medication (Parkkari et al., 2020, 2022; Radcliffe, 2014). In general, the target IOP should be achieved with the fewest medications and minimum adverse effects. In Finland, glaucoma medication is conditionally reimbursed by the Social Insurance Institution of Finland (KELA).

Personalized IOP-lowering treatment should be evaluated in regularly scheduled follow-up visits for assessment of possible changes in the structure and function of the optic nerve and adjusted as necessary to minimize the risk of progression. In Finland, the follow-up of glaucoma patients is assigned to the specialized health care either in public or private sector based on the patient's demand ("Glaucoma: Current Care Guidelines," 2023). For patients with poor adherence to medical treatment or for those with severe disease, surgery may sometimes be offered as a first-line therapy.

Finland has a health care guarantee that ensures the equal opportunity to get health care services, including glaucoma care, in the different regions of the country. The guarantee was legislated in 2005, and it has had a significant impact on the access to glaucoma care among glaucoma patients ("FINLEX ® - Säädökset alkuperäisinä," 2004).

2.3 Epidemiological research

Epidemiological research covers studies and analyses of the distributions, trends, and determinants of health and disease conditions in defined populations (Miettinen, 2011). Epidemiological research can be considered as one of the bases for public health and health management by identifying risk factors for diseases and targets for preventive health care (Savitz et al., 1999). The results from epidemiological studies can aid decision making and can be applied to policy makers and communities who can implement appropriate policies or disease control measures to protect or improve the health of a population. In addition to current population health issues, the information from these studies can be used to guide how a health system can be managed to better respond to future potential population health issues.

Epidemiological research faces many challenges. High participation rates are important to reduce potential biases caused by non-participation; yet, despite the concept of participation rate differing from study to study, the declining of participation rates for epidemiological studies during the past 40 years is well acknowledged. Galea and Tracy (Galea and Tracy, 2007) listed four potential reasons for this trend: the proliferation of research studies; the general decrease in volunteerism; the lacking salience of study topics to participants' lives; and the increasingly demanding nature of surveys on participants. The demographic characteristics of study participants are a particular concern for epidemiologists. For example, there is clear evidence that women are more likely to participate in surveys and other forms of epidemiological studies than men (Dunn et al., 2004). Previous research also suggests that persons with higher socio-economic status such as good education and income are more likely to participate in epidemiological studies (Galea and Tracy, 2007). These issues can lead to under-representation of population subgroups and biased generalization at the overall population level.

The role and guidance of epidemiological research in the allocation of health care resources are expected to increase due to the ageing of populations and the consequent burden on health care; hence, the importance of population-representative samples remains high. To sustain the acquisition of such data in the future, epidemiologic studies require innovation involving both the development of creative recruitment and retention techniques that optimize participation as much as possible along with the application of statistical methods for adjustment of potential bias introduced by non-participation (Galea and Tracy, 2007).

2.4 Health-related quality of life and mental health

2.4.1 Definition of health-related quality of life and mental health

According to the WHO, "health" can be defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO, 1948). This definition is commonly used and highlights the multidimensional aspects of health, which is influenced by determination of quality of life (QoL) as a multidimensional and predominantly subjective concept. QoL can be defined as the person's own evaluation of his or her well-being and functioning in different life domains in the context of the culture and value systems in which the person lives. It reflects a person's physical, material, social, and emotional well-being along with development and activity in one's everyday life.

In recent decades there has been a paradigm shift from measuring clinical outcomes to patient-reported outcomes such as QoL (Fayers and Machin, 2013; Haas, 1999). This concept also represents a change in the approach to treatment of health disorders, given that it shifts its focus from removal of the symptom to the maintenance of functioning. There is a particularly growing interest towards health-related quality of life (HRQoL): an evolving, multidimensional construct of physical, psychological, and functional well-being that aims to capture the aspects of QoL that can be influenced by health and health care (Staquet et al., 1998).

The WHO has defined mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" (WHO, 2004). Impairment of any of these areas increase risk for mental disorders or illnesses, which are a component of mental health (Galderisi et al., 2015; Manwell et al., 2015). Nevertheless, this definition has been criticized as potentially misleading, and there has been a lack of consensus on the characterization of mental health. A recently proposed definition specifies mental health as "a dynamic state of internal equilibrium", which reflects the fact that different life epochs, e.g., adolescence and parenthood, require an active search for a new mental equilibrium (Galderisi et al., 2015). This definition also includes and acknowledges the reality that mentally healthy people may experience appropriate human emotions such as grief and anger whilst at the same time possessing sufficient resilience to restore the dynamic state of internal equilibrium. Ultimately, this concept "enables individuals to use their abilities in harmony with universal values of society". The definition also includes multiple important components of mental health, including basic cognitive and social skills, the ability to regulate one's own emotions, and the flexibility and ability to cope with adverse events.

2.4.2 Instruments of health-related quality of life and mental health

As a relatively new field of science, QoL research is still developing; hence, there are few well-validated instruments, and there is a lack of largely accepted gold standards

(Lohr, 2002). For HRQoL, there are few validated questionnaires and semi-structural interviews available that account the multidimension nature of QoL. The instruments of HRQoL are either generic or specific for a disease or condition. These instruments are known to provide different estimates for HRQoL (Whitehurst and Bryan, 2011). Considering that HRQoL instruments usually lack a spectrum of mental health, it is useful to utilize mental health instruments alongside to allow thorough evaluation of one's well-being.

Although the sensitivity of generic HRQoL instruments can be lesser compared with disease-specific instruments, the use of generic HRQoL instruments allows comparisons within generic populations without limiting to one specific disease or condition. Furthermore, generic HRQoL instruments can be useful when weighing where to direct limited health care resources and comparing the additional health benefits produced by different health care methods, considering as the resources are always restricted and the health gained is expected to be lost elsewhere (Drummond et al., 2015).

HRQoL and mental health instruments can produce both individual dimension scores and index scores. Index score summarizes different subdimensions of the specific instrument into single value that is easily comparable with other diseases, populations, and studies; yet the subdimensions are needed to be complementarily analyzed to find the specific factors affecting HRQoL, which index score alone fails to do. This evaluation of subdimensions is also important because some diseases and symptoms do not affect the patient's general well-being.

Because a statistically significant change or difference can be easily achieved in large samples, the clinical and practical meaningfulness of changes or differences in HRQoL and mental health can be evaluated using minimal important difference or change. In general, it defines the smallest change in well-being that is significant from the patient's perspective and would justify a change in the patient's care (Jaeschke et al., 1989). Minimal important difference or change can be used both at the personal level and in population-based settings, and there are validated values available for multitude of HRQoL and mental health instruments (Alanne et al., 2015; Beck et al., 1988).

Two commonly used HRQoL instruments are EuroQoL-5 Dimension (Brooks, 1996) and 15D (Sintonen, 2001), and two commonly used mental health instruments are Beck Depression Inventory (Beck and Beck, 1972) and General Health Questionnaire 12 (Goldberg, 1972; Pevalin, 2000). These are described more in detail in Section 4.2.2.

2.4.3 Health-related quality of life and mental health in impaired vision

Vision loss has been associated with a detrimental impact on generic HRQoL and mental health (Park et al., 2015; Taipale et al., 2019; Wu et al., 2021). As discussed in Section 2.1.2, vision loss increases difficulties particularly in daily functioning and mobility tasks, and it has been suggested that impaired vision affects HRQoL mostly through loss of independence and increased social isolation (Kempen et al., 2012; Purola et al., 2023c; Vu et al., 2005). Even mild vision loss, which may easily remain undetected such as in the case of glaucoma, can have a clinically meaningful effect on both generic HRQoL and mental health before the individual has become visually impaired (Purola et al., 2023c; Taipale et al., 2019). This outcome underlines the importance of evaluation of visual functions among those who are not classified as visually impaired. In general, prevention, early detection, treatment, and rehabilitation of decreased visual functions are fundamental ways of reducing disability and consequent effects on the person's QoL and mental health.

There is a paucity of population-based data on the relation between vision in vision-threatening eye diseases such as glaucoma and both generic HRQoL and mental health. Even though many vision-specific QoL instruments have been applied to evaluate the relation of vision and eye conditions to QoL, the obtained results may not be generalizable to non-eye-related diseases and other factors (Jones et al., 2017; Misajon et al., 2005; Nickels et al., 2017; Seland et al., 2011; Trillo and Dickinson, 2012; Vashist et al., 2016). In addition, generic HRQoL instruments have been shown insensitive to visual factors in various clinical settings (Browne et al., 2012; Datta et al., 2008). On the contrast, in population-based settings, generic HRQoL instruments have displayed adequate sensitivity to vision (Purola et al., 2023c), which should encourage the use of both generic HRQoL instruments and population-based data in the evaluation of trends and effects of vision-threatening eye diseases and VI.

2.4.4 Health-related quality of life and mental health in glaucoma

The awareness of an eye disease such as glaucoma is thought to reduce HRQoL and mental health due to fear of future blindness, in other words, through the fear of declining vision before the loss of VA affects the patient's life (Brown et al., 2018; Jampel et al., 2007; Nutheti et al., 2006; Wang et al., 2012; Ye et al., 2015). But it is not known what the scale of this fear is in comparison with other factors of glaucoma that can also detrimentally impact one's well-being. The role of reduced visual functioning among glaucoma patients has particularly remained uncertain.

As in the case of vision loss, most of the conducted research on the connection between QoL and glaucoma and other eye diseases has been based on relatively small study samples that may not be representative on larger populations (Holló et al., 2021; Machado et al., 2019; Wolfram et al., 2013). Furthermore, many studies have measured HRQoL among glaucoma patients using vision-related assessments (Freeman et al., 2008; Jones et al., 2017; Lisboa et al., 2013; Medeiros et al., 2015; Riva et al., 2019), but more generic instruments could allow better generalization and comparison with other diseases and defects.

All in all, there is a need to improve the understanding of causes that lead to reduced HRQoL and mental health among glaucoma patients. The determination of factors influencing well-being in glaucoma and VI is crucial for public health to aid in the prioritization and allocation of health care resources as well as for individuals to help reduce and prevent the burden of the disease on one's life. In addition, addressing this issue in different countries, cultures, and populations is important because different social and economic conditions, values, and norms of local populations are all factors playing a role in the impact of disease and health problems on an individual's QoL (Schalock et al., 2005; Smith, 2004).

2.5 Cost-of-illness

2.5.1 Definition of cost-of-illness

Cost-of-illness studies aim to evaluate the financial aspects of an illness by identifying and measuring the direct and indirect costs associated with it in a descriptive manner (Jo, 2014). These studies are particularly useful for chronic diseases with a strong impact on health expenditures in formulating and prioritizing health care policies and interventions to achieve policy efficiency and effective allocation of health care resources (Clabaugh and Ward, 2008; Jefferson et al., 2000; Rice, 2000). The costs can be evaluated from multiple perspectives, for example, societal, health system, industry, and individual perspective. The perspective of the cost analysis indicates who bears the costs, which in turn determines the costs to be included in the analysis.

Direct costs are those directly related to a disease and are divided into medical and non-medical costs. Direct medical costs cover the field of health care, including consultations, hospitalizations, medications, diagnostic tests, and accident and emergency services. Direct non-medical costs can be defined as costs and resources used in connection with the health service but are not health sector costs, for example, transportation, household expenditures, relocating, and property losses. Resource estimation for the calculation of direct costs can be achieved via top-down approach or bottom-up approach. In top-down approach, the proportion of cost attributed to a disease is measured from aggregate figures, i.e., the analysis is directed from total to lower levels. Bottom-up approach is based on actual consumption of resources by referring to records of patients, i.e., the analysis is directed from individual levels to the total. Bottom-up approach is more commonly used in cost-of-illness studies (Clabaugh and Ward, 2008; Jo, 2014).

Indirect costs can be defined as costs due to lost or reduced productivity caused by a disease. Precisely, these cover absenteeism, presenteeism, and early retirement. Indirect costs are usually summarized by the human capital method, in which productivity losses are approximated by the value of the individual's earnings under the condition that the person would have continued to work in full health (Jo, 2014). Alternatively, indirect costs can include or be based on friction costs from the friction period, which is the time until another individual from the unemployment pool replaces the worker who is absent due to sickness (Jo, 2014). The value of productivity losses is then estimated based on the individual's earnings over the friction period.

An additional third type of cost are the intangible costs, which refer to functional limitations, pain, psychological distress, reduced social interactions, and other sufferings due to a disease beyond the monetary costs of goods and services. Although it is important to recognize all consequences of a disease to establish the total burden of the individual, the inclusion of intangible costs in cost-of-illness studies is uncommon due to measurement difficulties and related controversies (Jo, 2014).

2.5.2 Costs of impaired vision

The economic effects of vision loss have been extensively studied worldwide, although in most cases the focus has been put solely on VI and blindness (Chakravarthy et al., 2017; Frick et al., 2010; Gordois et al., 2012; Green et al., 2016; Köberlein et al., 2013; Morse et al., 2019, 1999; Rein et al., 2022). Both VI and blindness are associated with an increased use of health care resources that manifests specifically as greater hospital costs and prolonged hospitalization among older adults. Most of the hospitalizations among visually impaired elder persons are caused by falls, accidents, and injuries such as hip fractures (Black and Wood, 2005; Mikhailova et al., 2018; Rau et al., 2014). The severity and progression of vision loss increase these costs even further (Javitt et al., 2007).

VI and blindness are also associated with productivity losses and other non-medical resources (Marques et al., 2021). In fact, the indirect costs of VI and blindness are considered as the main contributor to the overall economic burden of vision loss (Köberlein et al., 2013). For example, in Europe, the annual economic loss due to reduced productivity from blindness and moderate to severe VI was estimated as EUR 56.5 billion in the population aged 50 years or older during 2010–2015 (Chakravarthy et al., 2017).

2.5.3 Costs of glaucoma

Given the limited resources available to health care providers, it is crucial to provide appropriate information to facilitate the decision making and the allocation of health care resources regarding glaucoma; yet there is a severe paucity of knowledge of the effects of glaucoma on total direct and indirect costs at the population level. Glaucoma-related publications have mostly focused on comparing different glaucoma treatments in clinical settings (Calissendorff, 2001; Cantor et al., 2008; Lindblom et al., 2006; Olsen et al., 2013). Few studies have estimated direct costs of glaucoma and its treatment in nationwide settings (Quigley et al., 2013; Rein et al., 2006; Taylor et al., 2006; Traverso et al., 2005), and indirect cost data are particularly lacking (Coyle and Drummond, 1995). In addition, the costs of glaucoma are often considered underestimated due to the high percentage of undiagnosed glaucoma (Wong et al., 2004; Heijl et al., 2013).

Based on population-level data in 2004, the direct medical costs of glaucoma corresponded to 8% of total medical costs of visual disorders in Australia and 17.8% of total medical costs of visual disorders in the US (Rein et al., 2006; Taylor et al., 2006). Approximately half of the total costs of glaucoma treatment is covered by medication costs (Lindblom et al., 2006). The high costs of glaucoma medicine are likely caused by the increased consumption of anti-glaucoma drugs in recent decades as well as the use of more expensive novel drugs (Dirani et al., 2011). Furthermore, the severity of glaucoma has been associated with increasing treatment costs (Schlenker et al., 2015; Shih et al., 2021). There has not been definitive conclusion on which form of treatment of glaucoma is the most cost-effective (Lindblom et al., 2006).

All things considered, there is a need for a comprehensive overview on the total economic burden of glaucoma, which would include all eye- and non-eye-related direct and indirect costs associated with the disease. Likewise, the utilization of multiple data sources, national surveys and registers in particular, is uncommon, even though such practice could provide more accurate estimates on the use of health care services and both direct and indirect costs.

3 AIMS OF THE STUDY

The main aims of the present study were to evaluate the social and economic impact of glaucoma and glaucoma care, the time trends in glaucoma and glaucoma-related VI, and the role of reduced VA among glaucoma patients.

The specific aims were:

1. To evaluate the prevalence and incidence of common vision-threatening eye diseases and impaired distance VA and their impact on an individual's HRQoL and mental health (**I**).
2. To evaluate the impact of glaucoma and glaucoma treatment on an individual’s HRQoL and mental health and the role of impaired distance VA among glaucoma patients (**I**, **II**).
3. To estimate the economic impact of glaucoma and glaucoma care (**III**).
4. To observe the time trends in VI due to glaucoma in Finland during 1980–2019 (**IV**).

4 MATERIALS AND METHODS

4.1 Study designs and populations

An overview of the structure of the population-based data and the variables used in the sub-studies is provided in Figure 4.

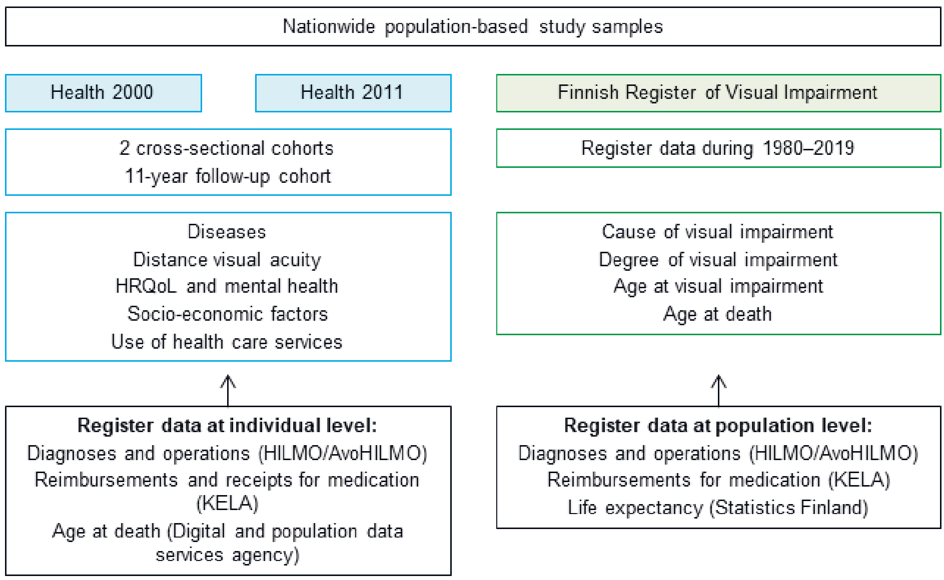


Figure 4. Overview of the used data from the Health Surveys and the Finnish Register of Visual Impairment. Health 2000, The Health 2000 Survey; Health 2011, The Health 2011 Survey; HILMO/AvoHILMO, inpatient/outpatient visits in the Care Registers for Social Welfare and Health Care; HRQoL, health-related quality of life; KELA, Social Insurance Institution of Finland.

4.1.1 Health 2000 and 2011 Surveys (I, II, III)

Studies I, **II**, and **III** were based on a nationally representative sample of Finnish adults from two cross-sectional nationwide health examination surveys, the Health

2000 Survey (Aromaa and Koskinen, 2004) and its follow-up, the Health 2011 Survey (Koskinen et al., 2012), both of which were conducted by the Finnish Institute for Health and Welfare (THL) and its co-operators. The aim of the surveys was to collect comprehensive, up-to-date overview on health, functional capacity, and welfare. Both the surveys included identical self-reported assessments in form of questionnaires and a home-visit interview. The participants who dropped out of these stages of the study were first approached by phone and then by letter to retrieve key health information. An identical health examination was conducted at a nearby screening center in both the surveys. If the invited participants did not attend the examination, an abridged examination was conducted at home or in an institution.

The Health 2000 Survey (Health 2000) was carried out in Finland in 2000–2001, and the study sample consisted of 9873 adults aged 18 years or older living in Finland. A representative sample of the Finnish adult population was selected by utilizing a probability-clustered sampling and weighting scheme. The sample was drawn by a two-stage stratified cluster sampling: five university hospital districts of mainland Finland were used as strata and health centers as clusters. The health centers in the fifteen most populous cities were chosen followed by a random selection of 65 health centers with a consequent 80 health centers in total. To match the population sizes in different clusters and to form representative data, the participants were weighted using inverse probability weighting, which is a statistical technique for calculating statistics standardized to a population different from that in which the data were collected. Additionally, persons aged 80 or older were oversampled by doubling the sampling fraction. To account for non-response and missing data, the sample weights were calibrated by post-stratification, defined by age, sex, region, and native language. The participation rate for any part of the survey was 93% and for the health examination 85%.

The Health 2011 Survey (Health 2011) was carried out in 2011–2012, and it included all living members of Health 2000 sample who had not refused further contact as well as a new sample of young adults. The total sample included 8550 adults aged 18 years or older living in Finland, and the participation rate for any part of the survey was 73% and for the health examination 59%. The weights were updated for all the participants in Health 2011.

The details of the design and sampling of Health 2000 and 2011 have been described previously (Heistaro, 2008; Lundqvist and Mäki-Opas, 2016).

For the sub-studies, we included participants aged 30 years or older representing the Finnish adult population at the two time points. Separate weights were applied for the surveys to produce results representing the Finnish population at each time point. In addition, the participants who partook at both time points allowed for an 11-year longitudinal follow-up. More details of the eligible samples are provided in Section 5.1. Both cross-sectional and longitudinal data of Health 2000 and 2011 were used in **Studies I** and **II**, whereas in **Study III** only participants of Health 2000 were analyzed.

4.1.2 Finnish Register of Visual Impairment (IV)

Study IV was based on data from the Finnish Register of Visual Impairment (NVREK) of The Finnish Federation of the Visually Impaired. NVREK is a national register that was established in 1983 by the National Board of Health. Its operations are regulated by the Act (556/89) and Decree (774/89) on National Personal Records kept under the Health Care System. Health care providers, specialists in ophthalmology, and the ophthalmological units of hospitals are, under the above-mentioned Act, responsible to submit information on people with irreversible VI to the register without need for permission from the patients. Between 1980 and 2019, the register included data on 58 822 patients with VI. The data represent the visually impaired persons living in Finland, and it includes eye diagnoses, home region, date of birth and death, year of VI onset, and classification of VI. The time at the onset of VI is determined based on the notification data, and if it is not available, the date of registration is used instead.

In NVREK, the VI is classified according to the examination of ophthalmologists and the Finnish definitions of VI using VA and VF from central fixation (Ojamo and Tolkkinen, 2022). Up to 2023, the Finnish definitions were based on the definitions of WHO (WHO Study Group on the Prevention of Blindness, 1973) with a modification of the nomenclature of the names of the VI classes (see Table 1 in Section 2.1.3). The classification of VI is updated if any further information is notified.

4.2 Survey data

The survey data are not openly available. The permissions for use in the sub-studies were evaluated and granted through THL.

4.2.1 Self-reported diseases (I, II, III)

Information on eye diseases and co-morbidities was collected in both the surveys via identical face-to-face interviews with a question "Has a doctor diagnosed one of the following diseases?". Data on these diseases were available from 7390 and 5725 participants aged 30 years or older in 2000 and 2011, respectively, and the information was used in **Studies I**, **II**, and **III**.

The list of eye diseases consisted of glaucoma, cataract, RD, and other visual defect or eye trauma. Previously performed cataract operations were also asked. We excluded operated cataract patients from the analyses because cataract surgeries improve VA and have been demonstrated to improve QoL as well (Lamoureux et al., 2011). In **Study I**, the participants who had replied "yes" or "no" to at least one of these eye disease questions were chosen for further analyses, classified as "eye disease status known". In **Studies II** and **III**, participants who had glaucoma-related register-based data were also included, which is described more in detail in Sections 4.3 and 4.4. Participants who had only answered "no" to the set of eye disease questions were classified as "no eye diseases", a comparison group for glaucoma, cataract, and RD in **Study I**.

We selected and classified the co-morbidities according to a previous publication on the same dataset (Taipale et al., 2019) into following groups: heart diseases (myocardial infarction, angina pectoris, heart failure, arrhythmias, and "other heart disorders"); respiratory diseases (asthma, chronic obstructive pulmonary disease, chronic bronchitis, and "other pulmonary disease"); vascular diseases (stroke and varicose veins in lower limbs); musculoskeletal conditions (rheumatoid arthritis, osteoarthrosis, fractures, and osteoporosis); psychiatric conditions (psychotic disorders, depression, anxiety, psychoactive substance abuse, and "other psychiatric disease"). Furthermore, hypertension, diabetes, Parkinson's disease, and unspecified cancer were each classified as a separate group.

Co-morbidity status was determined according to the previous publication (Taipale et al., 2019) so that a participant was considered to have a co-morbidity if they reported any of the conditions included in the co-morbidity group. When analyzing new incident diagnoses during the follow-up period, each condition was scrutinized in the 2000 baseline and in the 2011 follow-up. If the participant reported at least one new condition included in the co-morbidity group in 2011, they were classified as having incident co-morbidity regardless of the presence of other conditions of that specific co-morbidity group in the baseline.

4.2.2 Self-reported health-related quality of life and mental health (I, II)

The assessment of generic HRQoL and mental health in **Studies I** and **II** was based on self-administered questionnaires included in both the surveys.

The EuroQoL-5 Dimension (EQ-5D) was developed by the EuroQol Group (Brooks, 1996). It evaluates generic HRQoL across five dimensions: mobility (i.e., walking), self-care (e.g., washing and dressing), usual activities (performing, e.g., work, study, housework, and leisure activities), pain or discomfort, and anxiety or depression. Each dimension contains three levels (EQ-5D-3L, referred to hereafter as "EQ-5D") that answer to "no problems", "moderate problems", and "extreme problems". The maximum index score of the EQ-5D is 1, which represents the best possible HRQoL. The minimum score depends on the valuation algorithm used, for example, the commonly used UK time-trade-off tariff as used in the Health surveys produces a minimum score of -0.594, with 0 representing HRQoL equal to being dead. The clinical meaningfulness of the EQ-5D index score can be based on the minimal important difference or change, which has been estimated to be ≥ 0.07 (Walters and Brazier, 2005).

The 15D is a generic HRQoL instrument developed in Finland (Sintonen, 2001). It consists of 15 dimensions: mobility (i.e., walking), vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities (performing, e.g., work, studying, housework, and free-time activities), mental function (thinking clearly and logically; memory functioning), discomfort or symptoms (physical, e.g., pain, ache, nausea, and itching), depression, distress, vitality (healthy and energetic feeling), and sexual activity. Each dimension includes five levels from 1 (no problems) to 5 (extreme problems). Finnish preference weights with a scale between 0 (representing HRQoL equal to being dead) and 1 (representing the best possible HRQoL) were used in the Health Surveys. The estimated minimal important difference or change for the 15D index score is ≥ 0.015 (Alanne et al., 2015).

In Health 2000, a version of Beck Depression Inventory (BDI) that encompasses 21 questions was used to evaluate depression, whereas in the follow-up survey a shorter version, BDI-13 containing 13 questions, was used (Aalto et al., 2012; Beck and Beck, 1972). A total score was calculated for both questionnaires with a scale of 0–63 for BDI-21 and 0–39 for BDI-13, where higher points indicate a major depression. Total scores of ≥ 10 for BDI-21 and ≥ 5 for BDI-13 were used as cut-off points to categorize a participant as having depressive symptoms (Beck et al., 1988).

General Health Questionnaire 12 (GHQ-12) is a questionnaire containing 12 questions that assess different dimensions of psychological distress, including symptoms of anxiety and depression, social dysfunction, and loss of confidence (Goldberg, 1972; Pevalin, 2000). The answers were dichotomized based on whether difficulties were presented or not (0 = no, 1 = yes). A total score with a scale of 0–12 was calculated using the dichotomized points, with 12 representing the highest psychological distress. A total score of > 3 was used as a cut-off point indicative of psychological distress (Aromaa and Koskinen, 2004; Koskinen et al., 2012).

4.2.3 Self-reported health care resource use and retirement (III)

Information on the use of outpatient health care services, employment status, and the time of retirement was collected in the interview of Health 2000 and was used in **Study III**. The data on outpatient health care services consisted of private, occupational, health center, and other doctor visits, and the number of occupational, home care, and outpatient nurse visits during the preceding 12 months. Employment status consisted of employed, unemployed, retired, and others outside the labor force. We complemented the employment and retirement data with identical information from Health 2011 based on participants who partook in both the surveys to improve the quality of the data. The data on outpatient health care services were not complemented because the response rate for the corresponding questions was low in Health 2011.

4.2.4 Examination of visual acuity (I, II, III)

The bilateral distance VA examined in **Studies I**, **II**, and **III** was measured in the health examination included in both the surveys by a specially trained study nurse with current visual correction. We found the bilateral evaluation of VA important considering that the relation between vision and HRQoL and mental health was studied. Illumination was set to ≥ 350 lx on the modified logMAR letter chart (Ferris et al., 1982). Distance VA was measured at 4 m. All measurements were standardized and identical in both the surveys. The result was entered as the lowest line on which the participant correctly identified at least four letters. All VA values are presented as Snellen notation equivalents. Low VA values outside the modified logMAR letter chart that could not be determined were reported as 0.01. Based on the previous study (Taipale et al., 2019) on the same dataset, we classified distance VA values into following categories: VA ≥ 1.0 (good vision), VA 0.63–0.8 (adequate vision), VA 0.32–0.5 (weak vision), and VA ≤ 0.25 (VI / impaired vision or worse). The VI (VA ≤ 0.25) category also included those with severe VI or blindness (VA < 0.1) and was included as one of the studied subgroups with good vision (VA ≥ 1.0) category acting as a comparison group.

4.3 Complementary register data

In **Studies I**, **II**, and **III**, Health 2000 and 2011 samples were linked to the KELA registers to obtain data on the special reimbursement for glaucoma medication (1965–2011) and the number of glaucoma medication prescriptions (ATC S01E; 1999–2011). Data on glaucoma diagnoses and operations and other eye- and non-eye related diagnoses and operations were obtained from the Care Registers for Social Welfare and Health Care (HILMO). These data included inpatient care (HILMO; 1968–2011) and specialized health care outpatient visits (AvoHILMO; 1997–2011). HILMO data also covered the number and length of hospitalizations. The HILMO and AvoHILMO data are collected automatically from health care service providers' patient management systems and delivered to the THL.

In **Study III**, we calculated a follow-up time for each participant separately using register data from 1.1.1999 to 31.12.2011 to represent the average annual use of healthcare resources more accurately. The follow-up durations were corrected for participants who had died during the follow-up (n = 1279) with a range of 1.2–13.0 years. We included all eye- and non-eye-related hospitalizations and outpatient visits. Eye-related hospitalizations and visits consisted of main diagnoses with International Classification of Diseases (ICD) diagnosis codes H00–H59 for version 10. We analyzed participants who had either survey visits available or both survey and HILMO/AvoHILMO visits available.

For **Study IV**, the estimated total number of treated glaucoma patients in Finland was obtained from the KELA registers based on the number of persons with special reimbursement for glaucoma medication (1986–2019). Using data from the NVREK and KELA, we estimated the incidence of glaucoma-related VI among treated glaucoma patients in Finland. We also calculated the expected number of years with glaucoma-related VI using the age at the onset of reported VI from the NVREK data and the age at death acquired from the Digital and population data services agency. These numbers were compared with the age-specific life expectancies in the general population provided by Statistics Finland (Statistics Finland, 2023).

4.4 Selection of glaucoma patients

In **Studies II** and **III**, we classified survey participants into five glaucoma positive groups according to Table 3. The first group, "self-reported glaucoma", included participants who reported having glaucoma in the survey questionnaire. The second group, "verified glaucoma", included participants that fell into one of the register-based conditions shown in Table 3. One condition included high number of glaucoma medication prescriptions since some participants had prescriptions only for a short duration, indicating they were suffering from another disease than chronic glaucoma. The third group, "self-suspected glaucoma", consisted of participants who had self-reported glaucoma but not verified glaucoma. The fourth group, "glaucoma medication", included all glaucoma patients with glaucoma medication prescriptions. The fifth group, "glaucoma operated", included all verified glaucoma patients that had undergone at least one of the listed eye operations in Table 3 footnote or had self-reported glaucoma operation in the survey questionnaire. A comparison group, "glaucoma negative", included participants with a known eye disease status but did not belong to any of the above-mentioned five glaucoma positive groups. In **Study III**, self-reported glaucoma group was excluded because the focus was on real glaucoma cases. In **Study I**, only self-reported glaucoma group was included because the focus was to evaluate the effects of the patients' awareness of the condition.

In **Study IV**, glaucoma patients were selected from the NVREK data based on their main diagnosis for VI (ICD diagnosis code 365 for version 9).

Table 3. Glaucoma group classification in Studies I, II, and III

	Classification conditions in 2000	Classification conditions in 2011
Glaucoma, self-reported	Reported glaucoma in the questionnaire (Health 2000)	Reported glaucoma in the questionnaire (Health 2011)
Glaucoma, verified	Entitlement to special reimbursement for glaucoma medication between 1965–2000 (KELA) OR High number (> 10) of glaucoma medication prescriptions between 1999–2000 (KELA) OR Glaucoma diagnosis[1] between 1968–2000 (HILMO/AvoHILMO) OR Eye operation[2] due to glaucoma between 1997–2000 (HILMO/AvoHILMO)	Entitlement to special reimbursement for glaucoma medication between 1965–2011 (KELA) OR High number (> 10) of glaucoma medication prescriptions between 1999–2011 (KELA) OR Glaucoma diagnosis[1] between 1968–2011 (HILMO/AvoHILMO) OR Eye operation[2] due to glaucoma between 1997–2011 (HILMO/AvoHILMO) OR Glaucoma medication prescriptions since 2011 (KELA)
Glaucoma, self-suspected	Self-reported glaucoma but not verified glaucoma	Self-reported glaucoma but not verified glaucoma
Glaucoma, medication	Self-reported, verified, or self-suspected glaucoma and glaucoma medication prescriptions between 1999–2000 (KELA)	Self-reported, verified, or self-suspected glaucoma and glaucoma medication prescriptions between 1999–2011 (KELA)
Glaucoma, operated	Eye operation[2] due to glaucoma between 1997–2000 (HILMO/AvoHILMO) OR Verified glaucoma and self-reported glaucoma operation (Health 2000)	Eye operation[2] due to glaucoma between 1997–2011 (HILMO/AvoHILMO) OR Verified glaucoma and self-reported glaucoma operation (Health 2011)
Glaucoma, negative	Eye disease status known but not included in above glaucoma groups	Eye disease status known but not included in above glaucoma groups

Health 2000, The Health 2000 Survey; Health 2011, The Health 2011 Survey; HILMO/AvoHILMO, inpatient/outpatient visits in the Care Registers for Social Welfare and Health Care; KELA, Social Insurance Institution of Finland; [1] International Classification of Diseases diagnosis codes 37500–37520 and 37598–37599 for version 8; 3651–3659 for version 9; H40 and H40.1–H40.9 for version 10; [2] At least one of the following: trabeculectomy and iridectomy, glaucoma shunt operation, non-penetrating glaucoma surgery, other filtering operation, and transscleral laser coagulation of ciliary body.

4.5 Cost analyses

The economic evaluation in **Study III** was performed in accordance with the CHEERS 2022 guidelines (Husereau et al., 2022). We utilized a prevalence-based bottom-up approach to evaluate the direct and indirect costs associated with glaucoma. The direct costs covered self-reported outpatient health care services, registered hospitalizations and outpatient visits, and travel costs for outpatient visits during 1999–2011. Unit costs were first calculated using 2011 level and then converted to 2019 level (Table 4) based on the most recent data available on health expenditure and financing in Finland (Kapiainen et al., 2014; Matveinen and THL, 2023; Väätäinen et al., 2019). The calculation and application of public health care and private practitioner costs, and the proportions of emergency and non-emergency visits for the unit costs are described in more detail in the sub-study. Drug costs and direct non-health care costs were not included in the economic evaluation because appropriate data were not available. We calculated the travel costs for outpatient visits based on a previous publication (Väätäinen et al., 2019).

The indirect costs covered early retirement and consequent productivity losses. The number of early retirement years was calculated for each participant with time of retirement available, starting from the age of 30 years up to 64 years. If the participant had retired but the time of retirement was not available, the average retirement age of the respective population was used. More details regarding the calculation of early retirement years are provided in the sub-study. Productivity losses were calculated using early retirement years. The annual indirect costs were estimated by dividing the total costs by the mean duration of working career in Finland, which was 32.6 years in 2011 (Järnefelt et al., 2013). The indirect costs were also converted to 2019 euros (Table 4). Intangible costs were not included in the economic evaluation.

Table 4. Direct and indirect costs in Finland in 2011 and 2019

Health care resource	Cost per person (EUR)		Reference
	2011	2019	
Secondary / tertiary hospital ward day	737	905	(Kapiainen et al., 2014)
Secondary / tertiary hospital ophthalmic ward day	873	1072	(Kapiainen et al., 2014)
Secondary / tertiary care ambulatory visit to doctor	264	324	(Kapiainen et al., 2014)
Secondary / tertiary care ambulatory visit to eye clinic	199	244	(Kapiainen et al., 2014)
Primary health care doctor visit (including collateral costs, e.g., laboratory, imaging, and general costs)			(Kapiainen et al., 2014)
during office hours	110	135	
on emergency duty	96	118	
Private practitioner visit (administrative payment added)	66	81	(Kapiainen et al., 2014)
Occupational doctor visit	77	95	(Kapiainen et al., 2014)
Occupational nurse visit	28	34	(Kapiainen et al., 2014)
Home care nurse visit	110	135	(Kapiainen et al., 2014)
Outpatient nurse visit	48	59	(Kapiainen et al., 2014)
Travel cost per outpatient visit			(Väätäinen et al., 2019)
Southern Finland		19	
Western Finland		23	
Central Finland		25	
Eastern Finland		32	
Northern Finland		44	
Annual pension	16 428	20 178	Finnish Centre for Pensions
Annual gross domestic product	36 746	45 133	Statistics Finland

4.6 Statistical methods

All analyses were performed using R software version 3.5.1 or newer (R Core Team, R Foundation for Statistical Computing, Austria). The sampling design of the surveys was accounted for by using the Survey Package (Lumley, 2004) and weighting scheme calculated by THL (**I**, **II**, **III**). Participants with missing data in relevant variables were excluded. In **Study I**, data were compared within two groups:

participants with eye diseases versus those with no eye diseases, and participants with impaired distance VA versus those with good distance VA. In **Studies II** and **III**, data were compared between glaucoma positive groups and glaucoma negatives.

In all sub-studies, the results were expressed as means, standard deviations (SDs), standard errors of the means, and 95% confidence intervals (CIs). Population estimates and prevalence and incidence rates were calculated using the Survey package (**I**, **II**, **III**). For data with skewed distribution, statistical analyses were carried out by using Mann–Whitney U test for between-group comparisons, Wilcoxon's signed-rank test to compare the matched pairs, and Kruskal–Wallis test for multiple group comparisons adjusted with the Dunn–Bonferroni correction from package DescTools (Signorell et al., 2019). A chi-squared test was used for categorical variables when appropriate. Pearson correlation coefficients were calculated using package jtools (Long, 2019), which is an increment to the Survey package that accounts for the sampling design in the surveys (**III**).

Multivariable linear regression and Odds Ratios (ORs) were used to evaluate the association of co-variates with HRQoL, mental health, and costs (**I**, **II**, **III**). These co-variates consisted of self-reported co-morbidities, age, sex, and impaired distance VA. Standardized regression coefficients were calculated using package lm.beta (Vittinghoff, 2012). The collinearity of the co-variates was assessed using generalized variance inflation factor using package car (Fox and Monette, 1992; Fox and Weisberg, 2018). All co-variates resulted in values below 2, therefore showing no indication of collinearity. Because the cost data in **Study III** were right-skewed and the proportion of participants with zero costs was under 20% (Kurz, 2017), a Tweedie distribution was applied using gamma with log link scale response using package statmod (Giner and Smyth, 2016). Marginal means and contrasts were calculated using package emmeans (Lenth et al., 2018).

For all analyses, a two-tailed p-value of < 0.05 was considered as the cut-off for statistical significance.

4.7 Ethical considerations

The current study was conducted in line with the tenets of the Helsinki Declaration. All procedures in Health 2000 and 2011 involving human participants were performed in accordance with the ethical standards of the institutional and national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (**I**, **II**, **III**). Health 2000 was approved by the Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa. Health 2011 was approved by the Coordinating Ethics Committee at the Hospital District of Helsinki and Uusimaa. All the participants received an information letter regarding the study beforehand. Written informed consent was obtained from everyone. The ethical approval process details are discussed in previous publications (Heistaro, 2008; Lundqvist and Mäki-Opas, 2016). Regarding the NVREK data, according to the Finnish legislation, ethical committee approval is not required for register-based studies (**IV**). The personal data and identity of the subjects in the survey and register data have not been revealed to the researchers.

5 RESULTS

5.1 Survey samples and studied subgroups (I, II, III)

A demographic summary of the studied subgroups from the survey data (**I**, **II**, **III**) is presented in Table 5. The flowchart of the glaucoma positive group selection is illustrated in Figure 5. A total of 158 participants belonged to both verified and self-reported glaucoma groups in 2000 and 119 participants respectively in 2011. A total of 34 participants had a verified glaucoma without self-report in 2000 and 83 participants respectively in 2011. And a total of 39 participants belonged to both medicated and operated glaucoma treatment groups in 2000 and 36 participants respectively in 2011.

Table 5. Descriptive statistics of participants aged 30 years or older in studied subgroups and with measured parameters

	Health 2000 Survey			Health 2011 Survey			11-year follow-up in 2011		
	n	Mean age (SD)	% females	n	Mean age (SD)	% females	n	Mean age (SD)	% females
Eligible sample	7977	54 (16)	55	7964	55 (16)	53	6360	61 (13)	56
Eye disease status	7380	54 (16)	55	5774	56 (15)	56	4683	60 (12)	56
No eye diseases	4793	52 (16)	52	4067	53 (14)	53	3122	58 (12)	53
Glaucoma, self-reported	258	71 (14)	75	160	72 (11)	67	159	72 (11)	67
Glaucoma, verified	192	74 (11)	71	202	75 (11)	68	201	75 (11)	68
Glaucoma, self-suspected	100	67 (16)	81	41	65 (14)	81	40	66 (13)	80
Glaucoma, medication	143	74 (13)	73	186	76 (12)	6	185	76 (12)	67
Glaucoma, operated	59	75 (12)	68	38	75 (11)	55	38	75 (11)	55
Glaucoma negative	7088	54 (16)	54	5531	55 (14)	55	4442	60 (12)	55
Cataract, all	740	77 (10)	74	663	74 (10)	64	654	74 (10)	64
Cataract, unoperated	291	74 (10)	75	273	71 (9)	65	268	71 (9)	65
Cataract, operated	449	78 (10)	73	390	76 (11)	62	386	76 (10)	63
RD	291	74 (12)	68	216	73 (12)	62	211	74 (11)	62
Distance VA	6644	54 (16)	55	4554	57 (14)	56	3804	60 (12)	56
VA ≥ 1.0	4943	49 (12)	54	3678	54 (13)	56	3002	57 (10)	55
VA ≤ 0.25	147	80 (12)	74	52	77 (14)	62	45	78 (13)	62
EQ-5D	6131	54 (16)	56	4024	56 (14)	56	3082	59 (12)	57
15D	6149	53 (15)	56	4212	56 (14)	56	3460	60 (12)	56
BDI	6297	53 (15)	55	4300	56 (14)	56	3562	60 (12)	56
GHQ-12	6530	53 (15)	55	4445	56 (14)	56	3685	60 (12)	56
Direct and indirect costs	7368[1]	54 (16)	55						

The 11-year follow-up group includes the 2011 status of participants who partook in both the surveys (age ≥ 30 years). BDI, Beck Depression Inventory; GHQ-12, General Health Questionnaire 12; RD, retinal degeneration; SD, standard deviation; VA, visual acuity; [1] Four persons had missing data on employment/retirement status.

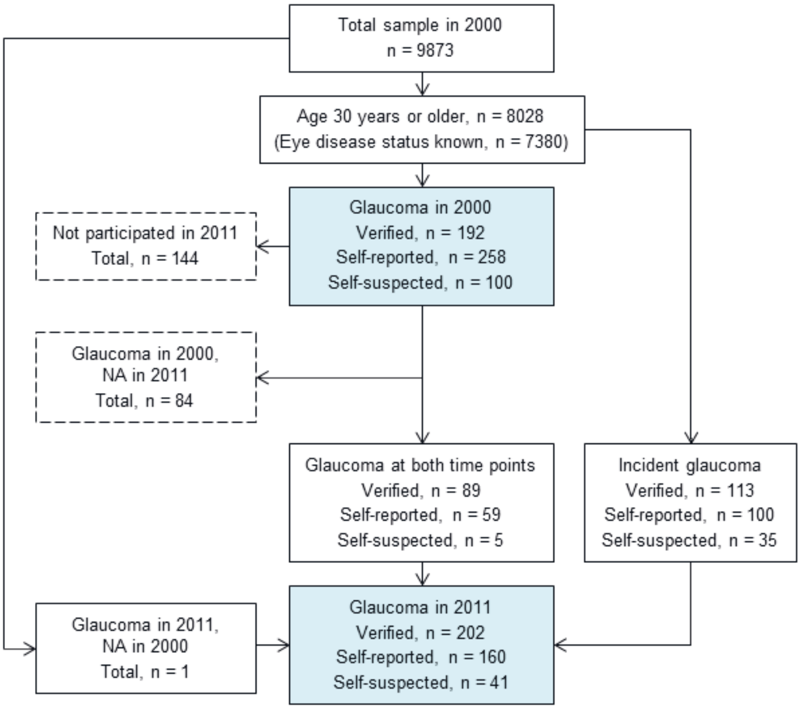


Figure 5. Flowchart of the selection of glaucoma positive groups in 2000 and 2011. NA, not applicable.

5.2 Trends in prevalence and incidence of common vision-threatening eye diseases and visual impairment in Finland (I, II)

The prevalence and incidence of glaucoma, cataract, RD, and VI in the Finnish population aged 30 years or older in 2000 and 2011 were estimated in **Studies I** and **II**, and the results are summarized in Table 6. Between 2000 and 2011, the prevalence of verified glaucoma, cataract, and RD increased while the prevalence of self-suspected glaucoma, self-reported glaucoma, and VI decreased.

Table 6. Estimated prevalence and incidence with 95% confidence intervals (CIs) of eye diseases and visual impairment (VI) in the Finnish population aged 30 years or older in 2000 and 2011

	2000		2011		Incidence 2000–2011	
	N (95% CI)	Prevalence % (95% CI)	N (95% CI)	Prevalence % (95% CI)	N (95% CI)	N/year/10 000 persons (95% CI)
Glaucoma, self-reported	100 517 (76 226–124 808)	3.10 (2.95–3.26)	83 453 (64 288–102 618)	2.70 (2.47–2.93)	52 026 (40 359–63 693)	22 (20–23)
Glaucoma, verified	75 683 (57 534–93 832)	2.33 (2.19–2.48)	79 758 (60 199–99 317)	2.57 (2.30–2.85)	45 325 (34 490–56 160)	19 (17–20)
Glaucoma, self-suspected	37 349 (27 648–47 050)	1.15 (1.06–1.25)	21 455 (16 245–26 665)	0.69 (0.61–0.77)	18 233 (13 851–22 615)	7 (6–8)
Cataract, all	262 927 (200 002–325 852)	8.11 (7.76–8.48)	353 082 (270 532–435 632)	11.41 (10.88–11.94)	257 658 (196 158–319 158)	109 (104–114)
Cataract, unoperated	107 955 (79 476–136 434)	3.50 (3.23–3.77)	140 120 (108 073–172 167)	4.86 (4.60–5.12)	122 239 (93 419–151 059)	55 (52–59)
RD	111 652 (87 115–136 189)	3.45 (3.29–3.61)	118 285 (88 207–148 363)	3.83 (3.46–4.20)	83 843 (61 808–105 878)	35 (31–38)
VI (distance VA ≤ 0.25)	48 405 (34 479–62 331)	1.58 (1.40–1.76)	31 275 (23 799–38 751)	1.27 (1.13–1.41)	21 134 (15 506–26 762)	10 (8–12)

RD, retinal degeneration; VA, visual acuity.

The prevalence and incidence of all eye diseases and VI increased with age, which is illustrated in Figure 6 with verified glaucoma and VI. Although the prevalence and incidence of eye diseases and VI were somewhat higher among females than males, this difference between sexes varied greatly between these conditions and the difference diminished between 2000 and 2011 (Figure 6).

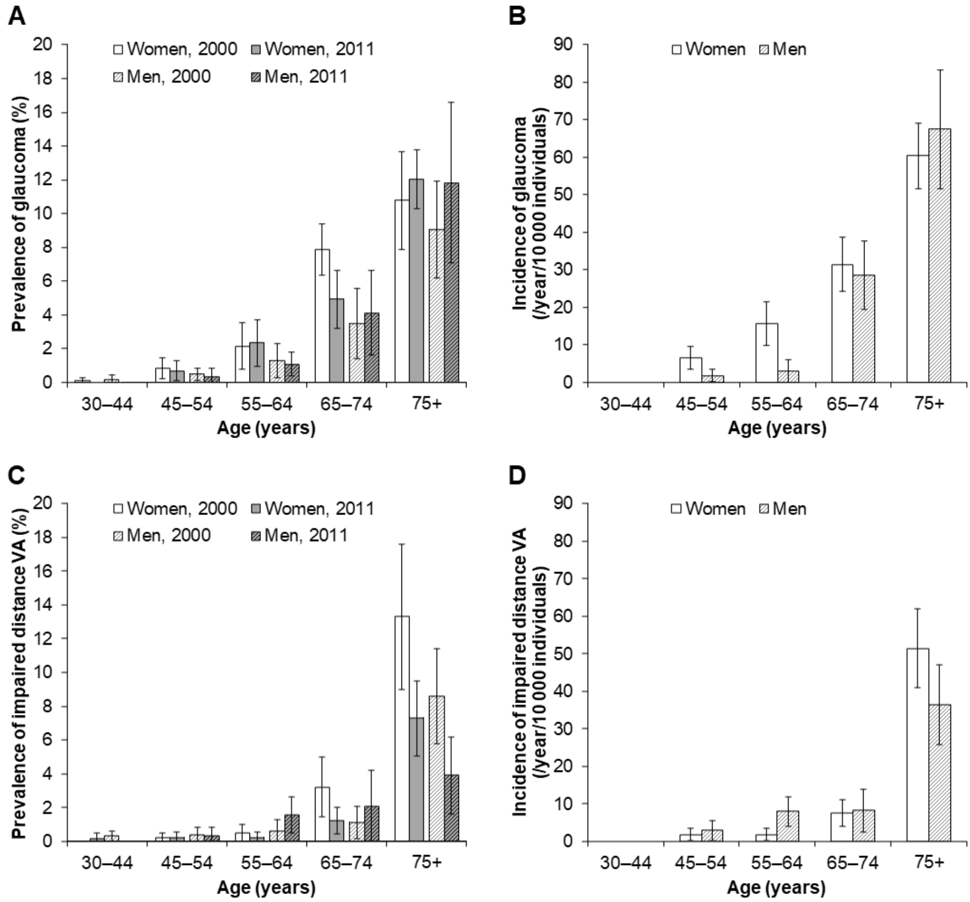


Figure 6. Estimated prevalence (with 95% confidence intervals) of verified glaucoma in 2000 and 2011 (A), incidence of verified glaucoma in 2000–2011 (B), prevalence of impaired distance visual acuity (VA ≤ 0.25) in 2000 and 2011 (C), and incidence of impaired distance visual acuity in 2000–2011 (D) in the Finnish population aged 30 years or older by age and sex

5.3 Health-related quality of life and mental health in common vision-threatening eye diseases and visual impairment (I, II)

The mean HRQoL index scores were evaluated in the studied subgroups in **Studies I** and **II**, and they are visualized in Figure 7. Persons with eye diseases (all glaucoma positive groups, unoperated cataract, and RD) and those with VI reported significantly worse EQ-5D and 15D index scores compared with their respective comparison group (those with no eye disease, with no glaucoma, or with good distance VA) in 2000 and 2011. This difference was also clinically meaningful at both the time points. Persons with VI had the poorest HRQoL compared with all the other groups. Neither statistically significant nor clinically meaningful differences in HRQoL were observed between verified, self-reported, and self-suspected glaucoma groups as well as between medicated and operated glaucoma.

The mean HRQoL index scores were significantly better in 2011 than in 2000 among all eye disease groups and persons with VI (Figure 7). This improvement in HRQoL was also clinically meaningful between the two time points. Persons with no eye diseases and those with good distance VA showed significant improvement between the two time points only regarding 15D, whereas glaucoma negatives showed significant improvement in both EQ-5D and 15D, but these improvements were not clinically meaningful.

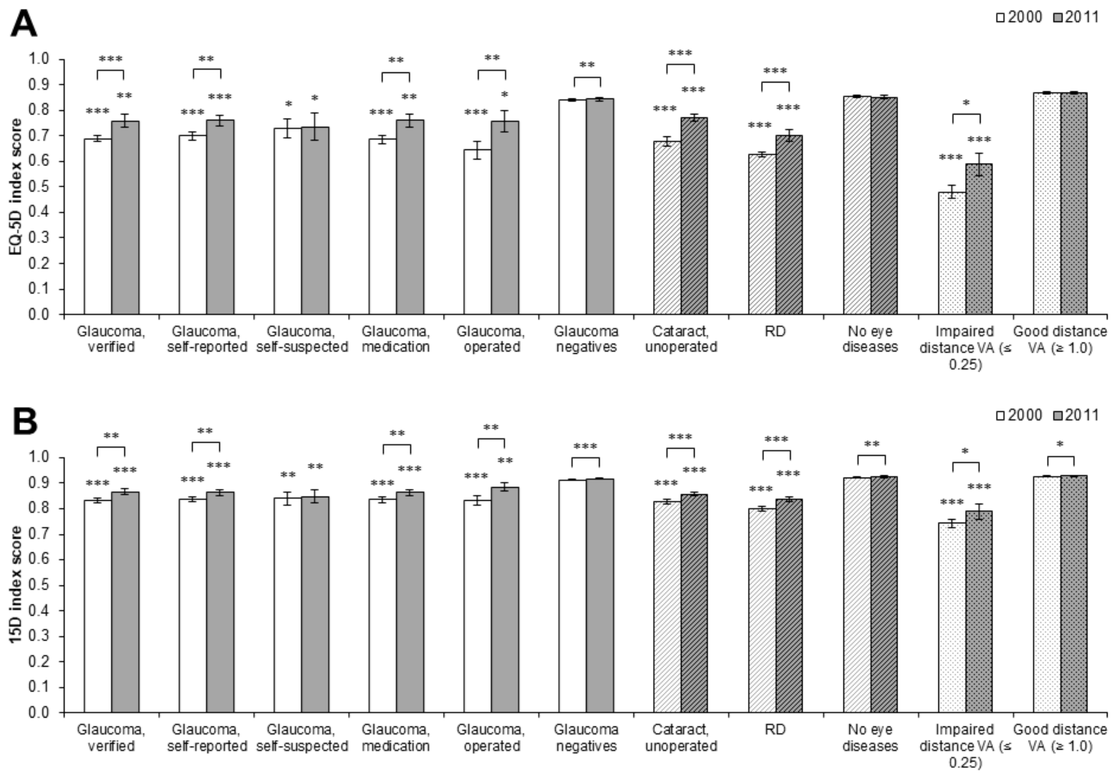
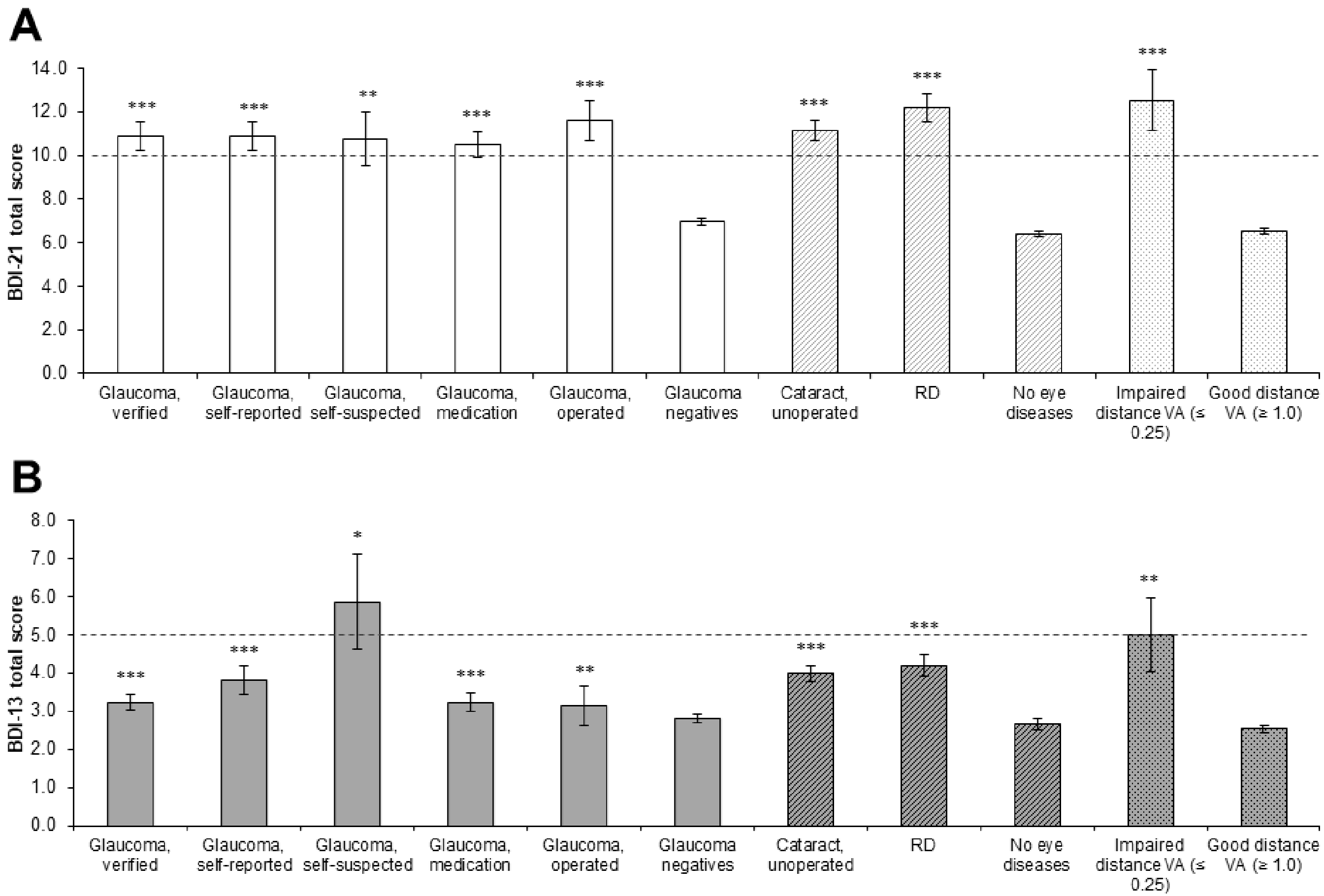


Figure 7. Mean values of EQ-5D (A) and 15D (B) index scores in 2000 and 2011 in glaucoma groups (solid color), other eye disease groups (diagonal stripes), and vision groups (dotted). When calculating statistical significance, glaucoma positive groups were tested against glaucoma negatives, cataract/retinal degeneration (RD) against persons with no eye diseases, and persons with impaired distance visual acuity (VA) against those with good distance VA within the same year. In addition, mean values were compared between the two time points within each group. Error bars represent standard errors of the means. *$p < 0.05$. **$p < 0.01$. ***$p < 0.0001$.

The mean mental health total scores in the studied subgroups (**Studies I**, **II**) are visualized in Figure 8. All eye disease groups and persons with VI had significantly worse BDI-21 and BDI-13 total scores compared with their respective comparison group. Furthermore, in 2000, the mean BDI-21 total scores were above the cut-off value among persons with eye disease and those with VI, indicating clinically meaningful level of depression. Regarding BDI-13 in 2011, the mean score was above the cut-off value only among persons with self-suspected glaucoma and those with VI. Because the scales of the BDI questionnaires between the two time points were not equal, the mean change between 2000 and 2011 was not assessed.

The impact on GHQ-12 varied between eye diseases: it was most severe in RD and least severe in glaucoma (Figure 8). Persons with RD had the mean GHQ-12 total score above the cut-off value in 2000 and those with VI at both the time points, indicating clinically meaningful level of psychological distress. Persons with VI had the poorest GHQ-12 total score compared with all the other groups at both the time points. Verified glaucoma, treated glaucoma groups, RD, and all the comparison groups showed significantly better GHQ-12 scores in 2011 than in 2000. Neither statistically significant nor clinically meaningful differences in BDI and GHQ-12 total scores were observed between verified, self-reported, and self-suspected glaucoma groups as well as between medicated and operated glaucoma.


A
BDI-21 total score
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
***
**
Glaucoma, verified
Glaucoma, self-reported
Glaucoma, self-suspected
Glaucoma, medication
Glaucoma, operated
Glaucoma negatives
Cataract, unoperated
RD
No eye diseases
Impaired distance VA (≤ 0.25)
Good distance VA (≥ 1.0)
B
BDI-13 total score
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
*

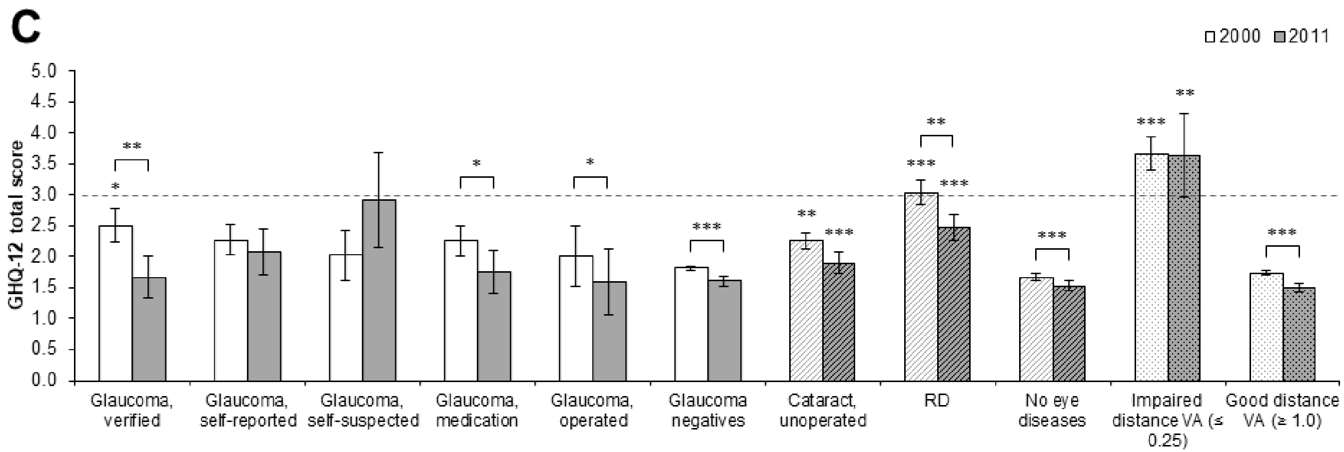


Figure 8. Mean values of BDI-21 (A), BDI-13 (B), and GHQ-12 (C) total scores in 2000 and 2011 in glaucoma groups (solid color), other eye disease groups (diagonal stripes), and vision groups (dotted). When calculating statistical significance, glaucoma positive groups were tested against glaucoma negatives, cataract/retinal degeneration (RD) against persons with no eye diseases, and persons with impaired distance visual acuity (VA) against those with good distance VA within the same year. In addition, mean values of GHQ-12 were compared between the two time points within each group. Error bars represent standard errors of the means. Dashed lines represent clinically meaningful cut-off values for BDI-21 (≥ 10), BDI-13 (≥ 5), and GHQ-12 (> 3). $^*p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.0001$.

5.4 Dimensions of health-related quality of life and mental health in glaucoma and visual impairment (II)

The association between glaucoma and the dimensions of EQ-5D and 15D (difficulties versus no difficulties) and the cut-off points of BDI and GHQ-12 in 2000 and 2011 were assessed using ORs in two settings: glaucoma positive group versus glaucoma negative and glaucoma treatment group versus untreated glaucoma patient in **Study II**, adjusted for age, sex, and co-morbidities (Table 7 and Table 8). As a comparison, the ORs for persons with VI versus persons with good VA were included.

Regarding EQ-5D, in 2000, self-reported glaucoma group showed significant odds for having difficulties in usual activities, and operated glaucoma group in usual activities and pain/discomfort (Table 7). In 2011, verified and self-reported glaucoma groups showed significant odds for having difficulties in mobility, and self-suspected glaucoma group in self-care (Table 8). VI was associated with increased odds for mobility, self-care, usual activities, and anxiety/depression at both the time points.

When assessing the five most affected 15D dimensions, verified and self-reported glaucoma groups showed significant odds for having difficulties in vision and usual activities, and self-suspected glaucoma group in mobility in 2000 (Table 7). In 2011, verified and self-reported glaucoma groups showed significant odds for having difficulties in usual activities and mental function, and self-suspected glaucoma group in vision (Table 8). VI was associated with increased odds for vision, usual activities, mobility, and vitality in 2000, and vision and usual activities in 2011.

When evaluating the odds for mental health, verified glaucoma group showed increased odds for psychological distress (GHQ-12) in 2000 (Table 7). VI showed increased odds for psychological distress at both the time points. No group showed significant association with BDI-21 or BDI-13.

Table 7. Odds Ratios (ORs) for EQ-5D dimensions, five most affected 15D dimensions, and mental health total scores indicative of having difficulties in a specific dimension, depression, or psychological distress in glaucoma positive groups and persons with visual impairment in 2000

	EQ-5D dimensions (95% CI)					Five most affected 15D dimensions (95% CI)					Mental health (95% CI)	
2000	Mobility	Self-care	Usual activities	Pain / discomfort	Anxiety / depression	Vision	Usual activities	Mobility	Vitality	Mental function	BDI-21 sum ≥ 10	GHQ-12 sum > 3
Glaucoma, verified	1.37 (0.97-1.92)	0.94 (0.60-1.47)	1.33 (0.92-1.92)	1.04 (0.82-1.34)	1.21 (0.71-2.07)	**2.26 (1.68-3.06)**	**1.80 (1.18-2.75)**	1.27 (0.85-1.92)	1.07 (0.78-1.47)	0.89 (0.60-1.32)	1.15 (0.83-1.60)	**1.37 (1.06-1.76)**
Glaucoma, self-reported	1.42 (0.90-2.23)	1.02 (0.71-1.46)	**1.60 (1.10-2.33)**	1.09 (0.86-1.36)	1.05 (0.65-1.69)	**1.83 (1.34-2.50)**	**1.64 (1.13-2.37)**	1.62 (1.05-2.52)	1.18 (0.82-1.70)	0.97 (0.67-1.40)	1.27 (0.91-1.76)	1.07 (0.80-1.45)
Glaucoma, self-suspected	1.72 (0.81-3.65)	1.34 (0.60-2.96)	1.82 (0.88-3.74)	1.36 (0.82-2.24)	0.79 (0.34-1.79)	1.34 (0.78-2.28)	1.41 (0.61-3.23)	**2.71 (1.40-5.25)**	1.28 (0.65-2.55)	1.06 (0.56-2.00)	1.23 (0.73-2.09)	0.72 (0.39-1.34)
Glaucoma, medication	0.71 (0.36-1.39)	1.08 (0.49-2.39)	0.71 (0.30-1.69)	0.82 (0.49-1.36)	0.82 (0.38-1.77)	1.18 (0.80-1.74)	1.11 (0.50-2.45)	0.66 (0.28-1.56)	0.76 (0.30-1.94)	0.87 (0.44-1.72)	0.76 (0.38-1.50)	0.63 (0.36-1.12)
Glaucoma, operated	1.28 (0.43-3.79)	1.22 (0.61-2.43)	**3.14 (1.46-6.75)**	**2.91 (1.53-5.53)**	1.34 (0.53-3.42)	1.37 (0.68-2.71)	1.23 (0.37-4.13)	0.83 (0.31-2.19)	0.92 (0.31-2.72)	0.58 (0.23-1.46)	1.50 (0.85-2.66)	0.74 (0.38-1.45)
Impaired distance VA (≤ 0.25)	**2.70 (1.60-4.55)**	**6.54 (4.05-10.6)**	**8.44 (4.90-14.5)**	1.11 (0.66-1.90)	**3.72 (1.85-7.48)**	**22.2 (14.6-33.8)**	**2.65 (1.37-5.14)**	**2.77 (1.99-3.86)**	**2.51 (1.51-4.17)**	0.90 (0.55-1.46)	1.49 (0.83-2.71)	**2.90 (2.18-3.86)**

The ORs and 95% confidence intervals (CIs) were estimated through logistic regression analysis corrected for age, sex, and the most common co-morbidities. Bolded values denote statistically significant ($p < 0.05$) ORs. Glaucoma negatives acted as a reference (OR = 1.0) for verified, self-reported, and self-suspected glaucoma groups. All glaucoma positives without glaucoma medication acted as a reference for glaucoma medication group. Verified glaucoma patients without operated glaucoma acted as a reference for glaucoma operated group. Good distance visual acuity (VA) group acted as a reference for impaired distance VA group.

Table 8. Odds Ratios (ORs) for EQ-5D dimensions, five most affected 15D dimensions, and mental health total scores indicative of having difficulties in a specific dimension, depression, or psychological distress in glaucoma positive groups and persons with visual impairment in 2011

	EQ-5D dimensions (95% CI)					Five most affected 15D dimensions (95% CI)					Mental health (95% CI)	
2011	Mobility	Self-care	Usual activities	Pain / discomfort	Anxiety / depression	Vision	Usual activities	Mobility	Vitality	Mental function	BDI-13 sum ≥ 5	GHQ-12 sum > 3
Glaucoma, verified	**1.73** **(1.18-2.54)**	1.00 (0.57-1.75)	1.21 (0.71-2.07)	1.02 (0.64-1.62)	0.66 (0.31-1.42)	1.25 (0.65-2.43)	**1.85** **(1.30-2.63)**	1.39 (0.96-2.02)	1.42 (0.97-2.08)	**1.45** **(1.05-1.99)**	1.25 (0.79-1.96)	1.21 (0.61-2.41)
Glaucoma, self-reported	**1.50** **(1.11-2.03)**	1.30 (0.89-1.89)	1.16 (0.65-2.10)	1.06 (0.68-1.64)	0.83 (0.48-1.47)	1.47 (0.83-2.62)	**1.64** **(1.12-2.40)**	1.21 (0.95-1.54)	1.56 (1.05-2.31)	**1.49** **(1.07-2.08)**	1.26 (0.75-2.10)	1.23 (0.69-2.17)
Glaucoma, self-suspected	1.14 (0.47-2.78)	**2.86** **(1.52-5.39)**	1.66 (0.60-4.64)	1.22 (0.64-2.34)	1.51 (0.75-3.04)	**2.78** **(1.20-6.43)**	1.47 (0.77-2.82)	1.05 (0.50-2.17)	2.84 (1.17-6.91)	1.43 (0.77-2.65)	1.85 (0.75-4.57)	1.09 (0.55-2.18)
Glaucoma, medication	1.26 (0.36-4.49)	0.50 (0.17-1.49)	0.84 (0.25-2.81)	0.47 (0.20-1.16)	0.44 (0.11-1.81)	0.62 (0.17-2.28)	0.98 (0.42-2.29)	0.85 (0.30-2.40)	0.46 (0.16-1.35)	0.90 (0.31-2.58)	0.53 (0.20-1.38)	1.52 (0.50-4.59)
Glaucoma, operated	0.42 (0.16-1.12)	0.15 (0.02-1.09)	0.53 (0.19-1.48)	2.06 (0.44-9.59)	0.10 (0.01-1.65)	0.83 (0.29-2.36)	0.48 (0.23-1.04)	0.40 (0.10-1.55)	0.64 (0.17-2.38)	0.61 (0.22-1.67)	0.68 (0.19-2.42)	0.82 (0.18-3.73)
Impaired distance VA (≤ 0.25)	**2.24** **(1.15-4.37)**	**6.13** **(3.23-11.6)**	**4.64** **(2.18-9.88)**	0.90 (0.44-1.81)	**2.91** **(1.44-5.88)**	**44.5** **(16.9-117.1)**	**3.28** **(1.53-7.04)**	2.04 (0.86-4.84)	2.31 (0.97-5.52)	1.51 (0.67-3.42)	1.65 (0.87-2.51)	**3.23** **(1.88-5.54)**

The ORs and 95% confidence intervals (CIs) were estimated through logistic regression analysis corrected for age, sex, and the most common co-morbidities. Bolded values denote statistically significant ($p < 0.05$) ORs. Glaucoma negatives acted as a reference (OR = 1.0) for verified, self-reported, and self-suspected glaucoma groups. All glaucoma positives without glaucoma medication acted as a reference for glaucoma medication group. Verified glaucoma patients without operated glaucoma acted as a reference for glaucoma operated group. Good distance visual acuity (VA) group acted as a reference for impaired distance VA group.

5.5 Distance visual acuity in common vision-threatening eye diseases (I, II)

The mean distance VA was evaluated in all studied subgroups in **Studies I** and **II**. All eye disease groups had significantly worse distance VA compared with those with no eye diseases in 2000 and 2011 (Figure 9). All groups showed significantly better mean distance VA in 2011 than in 2000, excluding self-suspected glaucoma group. In 2000, a significant ($p = 0.0002$) difference between the verified, self-reported, and self-suspected glaucoma groups was observed, in which the verified group had the worst value and the self-suspected group the highest.

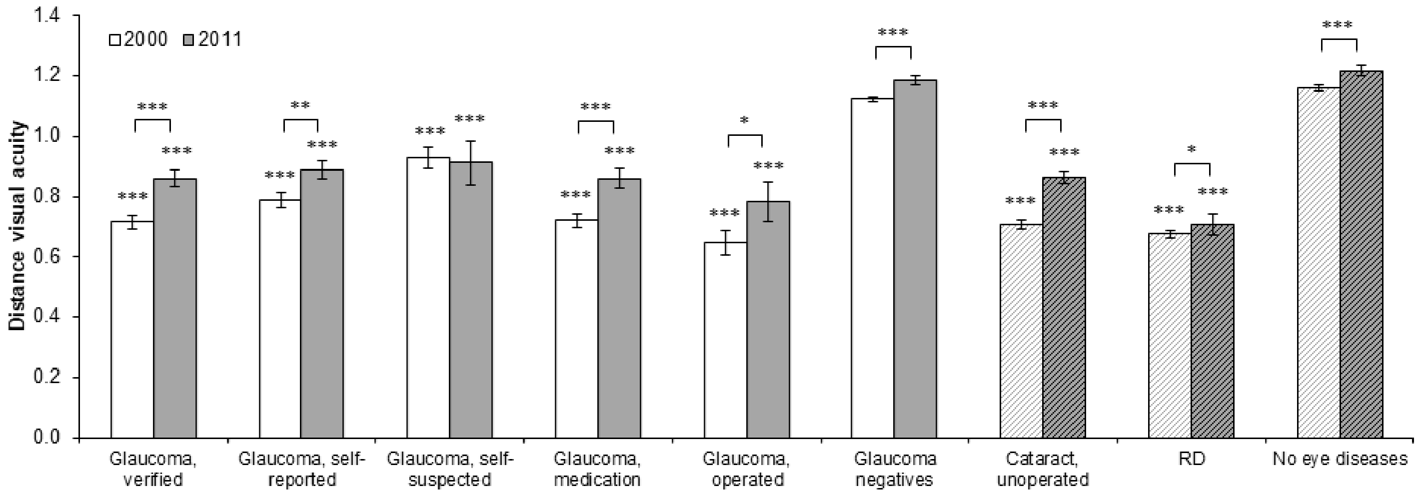


Figure 9. Mean values of distance visual acuity in 2000 and 2011 in glaucoma groups (solid color) and other eye disease groups (diagonal stripes). When calculating statistical significance, glaucoma positive groups were tested against glaucoma negatives, and cataract/retinal degeneration (RD) against persons with no eye diseases within the same year. Means were also compared between the two time points within each group. Error bars represent standard errors of the means. $^{*}p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.0001$.

5.6 Distance visual acuity in glaucoma and its impact on health-related quality of life and mental health (I, II)

As shown in previous Section 5.5, all glaucoma positive groups showed significantly worse distance VA compared with glaucoma negatives at both the time points (Figure 9). There was no significant difference in the association between glaucoma and VA when cataract and RD were included as co-variates (see Table S2 in **Study II**).

The impact of distance VA on HRQoL and mental health among glaucoma positive groups and glaucoma negatives was observed in 2000 and 2011 (**Study II**), which is illustrated in Figure 10. Self-suspected and operated glaucoma groups were not included because the number of persons with impaired distance VA within these groups was low. In summary, a positive association between distance VA and both HRQoL and mental health was observed regardless of whether a person had glaucoma or not.

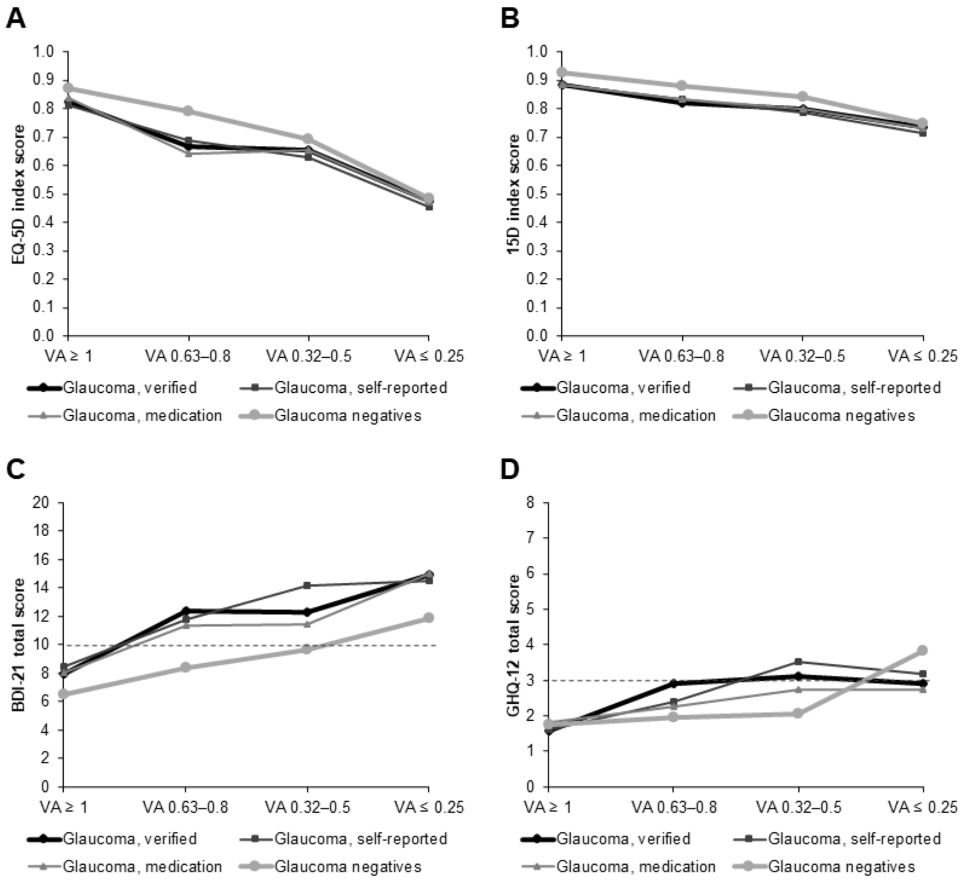


Figure 10. Association between health-related quality of life (A, B) and mental health (C, D) with distance visual acuity (VA) in glaucoma groups in 2000. Dashed lines represent clinically meaningful cut-off values for BDI-21 (≥ 10) and GHQ-12 (> 3).

The association between individual HRQoL dimensions and distance VA was observed based on data from 2000, and a summary is illustrated in Figure 11 (**Study II**). Of all the subdimensions, usual activities, self-care, and mobility of both EQ-5D and 15D as well as vision of 15D showed a noticeable positive association with distance VA regardless of whether a person had glaucoma or not.

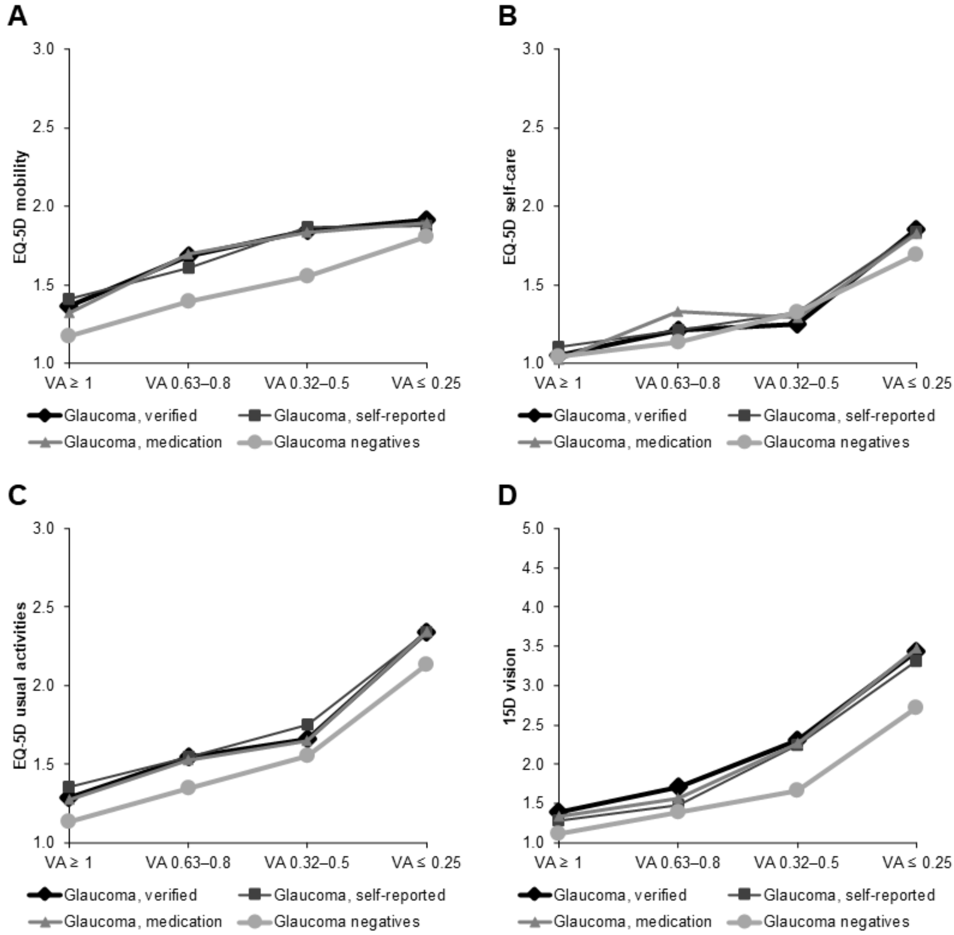


Figure 11. Examples of individual EQ-5D (A–C) and 15D (D) dimensions and their association with distance visual acuity (VA) in glaucoma groups in 2000. Higher scores indicate more difficulties in the corresponding subdimension.

The impact of the awareness of glaucoma on HRQoL and mental health was evaluated using linear regression analysis with the self-reported glaucoma group adjusted for co-variates, which is shown in Table 9 based on the year 2000 data (**Study I**). After these corrections, the impact of self-reported glaucoma became insignificant on both HRQoL and mental health. VI, psychiatric disorders, and Parkinson's disease showed the strongest detrimental impact on EQ-5D, 15D, and GHQ-12. On the other hand, the overall effect and/or association of all the co-variates on HRQoL and mental health were lesser in 2011 than in 2000 (see Table 5 in **Study I**). No significant difference was observed in the outcome when only statistically significant ($p < 0.05$) factors were included as explanatory variables in a stepwise-insertion analysis.

Table 9. Multivariable linear regression analysis examining the impact of self-reported glaucoma, self-reported co-morbidities, visual impairment, age, and gender on EQ-5D and 15D index values, and GHQ-12 and BDI-21 total scores in 2000

	Change in EQ-5D (n = 5643)		Change in 15D (n= 5777)		Change in GHQ-12 (n = 6064)		Change in BDI-21 (n = 5886)	
	B coefficients	Beta coefficients	B coefficients	Beta coefficients	B coefficients	Beta coefficients	B coefficients	Beta coefficients
Age	-0.003 ***	-0.213 ***	-0.002 ***	-0.259 ***	-0.008	-0.039	0.058 **	0.115 **
Male gender	0.012 **	0.031 **	-0.0004	-0.002	-0.148	-0.025	-1.23 ***	-0.087 ***
Glaucoma	-0.007	-0.005	-0.008	-0.013	-0.021	-0.001	0.428	0.009
Cataract, unoperated	-0.013	-0.012	**-0.017**	-0.034	-0.135	-0.009	0.844	0.022
RD	-0.047 *	-0.038 *	**-0.033 ***	-0.057 *	0.654 *	0.036 *	1.713 *	0.038 *
Impaired distance VA (≤ 0.25)	**-0.210 *****	-0.125 ***	**-0.083 *****	-0.099 **	1.464 *	0.055 *	1.091	0.016
Heart disease	-0.041 **	-0.069 **	**-0.032 *******	-0.112 ***	0.256 *	0.029 *	0.804 *	0.037 *
Pulmonary disease	-0.022 *	-0.044 *	**-0.024 *****	-0.103 **	0.305 *	0.042 *	1.081 **	0.062 **
Vascular disease	-0.025 *	-0.047 *	-0.007	-0.028	0.269 *	0.035 *	0.476	0.025
Musculoskeletal condition	-0.059 ***	-0.148 ***	**-0.017 *****	-0.093 **	0.361 *	0.062 *	1.167 **	0.083 **
Hypertension	-0.011 *	-0.024 *	-0.007 *	-0.036 *	0.145	0.023	0.488	0.032
Diabetes	**-0.073 *****	-0.081 **	**-0.033 *****	-0.077 **	0.327	0.025	1.577 *	0.049 *
Psychiatric disorder	**-0.129 *******	-0.219 ***	**-0.068 *******	-0.247 ***	2.118 ***	0.246 ***	6.635 ***	0.319 ***
Parkinson's disease	**-0.195 ***	-0.059 *	**-0.072 *****	-0.041 **	2.153 *	0.044 *	3.194	0.026
Cancer	-0.013	-0.013	**-0.018**	-0.042	0.352	0.025	1.240	0.037

The unstandardized B coefficients show the magnitude of the impact on health-related quality of life and mental health, while the standardized Beta coefficients allow the comparison of the explanatory variables with each other. Clinically meaningful B coefficients are bolded (≥ 0.07 for EQ-5D and ≥ 0.015 for 15D). The respective B coefficient constants for change in EQ-5D, 15D, GHQ-12, and BDI-21 are 1.062***, 1.035***, 1.605*, and 2.437**, and the respective adjusted R^2 0.281***, 0.358***, 0.086***, and 0.198***. RD retinal degeneration; VA visual acuity. *p < 0.05. **p < 0.01. ***p < 0.0001.

5.7 Impact of glaucoma on health-related quality of life, mental health, and distance visual acuity during the 11-year follow-up (II)

The impact of glaucoma on HRQoL and GHQ-12 during the 11-year follow-up was observed in **Study II** amongst participants who had partook in both the surveys, which is illustrated in Figure 12. The self-suspected glaucoma group was excluded from the longitudinal analyses because the number of persons within the group was low.

Among the participants who belonged to the same glaucoma group at both the time points, verified and self-reported glaucoma showed significant ($p = 0.024$ and $p = 0.036$, respectively) and clinically meaningful decline in 15D between the two time points (Figure 12). Glaucoma negatives showed significant ($p < 0.0001$) decline in EQ-5D and 15D, but it was not clinically meaningful. Glaucoma negatives showed significant ($p < 0.0001$) improvement in GHQ-12. Verified ($p = 0.0006$) and self-reported ($p = 0.035$) glaucoma positives and glaucoma negatives ($p < 0.0001$) showed significant decline in distance VA (Figure 12).

Among the newly diagnosed glaucoma patients, i.e., the participants who were glaucoma negative in 2000 but belonged to the verified or self-reported glaucoma group in 2011, the newly diagnosed verified glaucoma patients showed a significant decline in EQ-5D ($p = 0.002$) and 15D ($p = 0.006$), but it was clinically meaningful only in 15D (Figure 12). Distance VA had declined significantly among the newly diagnosed verified ($p = 0.011$) and self-reported ($p = 0.047$) glaucoma patients (Figure 12). Additionally, based on a multivariable regression analysis that included incidental self-reported glaucoma and incidental co-morbidities during the 11-year follow-up, newly diagnosed self-reported glaucoma showed neither significant nor clinically meaningful impact on HRQoL and GHQ-12 after adjusting for the co-variates (see Online Resource 1 in **Study I**).

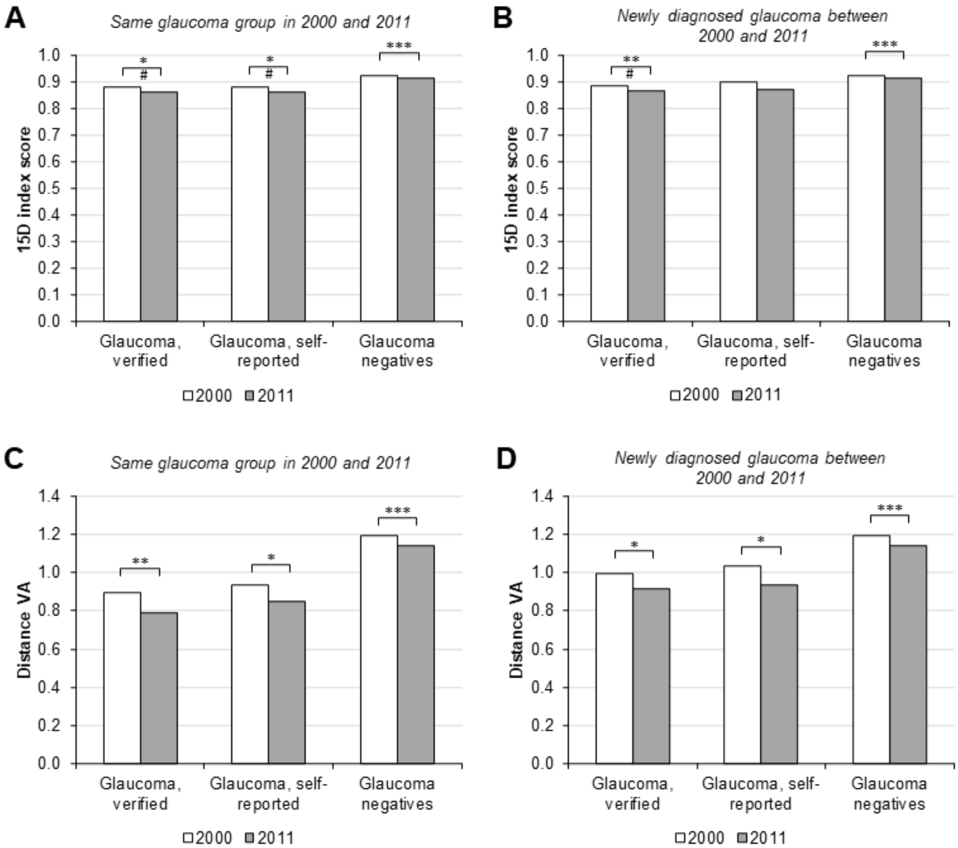


Figure 12. Change in health-related quality of life (A, B) and distance visual acuity (VA; C, D) in persons within the same glaucoma group at both the time points (A, C) and in persons with newly diagnosed glaucoma during the 11-year follow-up in 2000–2011 (B, D). Persons within glaucoma negative group at both the time points are shown as reference in each graph. *p < 0.05. **p < 0.01. ***p < 0.0001. # indicates clinically meaningful change.

In **Study I**, the association between age and HRQoL, GHQ-12, and distance VA was observed among the participants who partook in both the surveys. Regardless of whether a person had an eye disease or not, age showed noticeable negative association with EQ-5D, 15D, GHQ-12, and distance VA (see Figure 5 in **Study I**).

5.8 Utilization of health care services in glaucoma (III)

The use of health care services based on HILMO data was observed in **Study III** among three glaucoma positive groups: verified, medicated, and operated. Glaucoma negatives were included as a comparison group. The results are summarized in Table 10. All the three glaucoma positive groups were associated with a significantly ($p < 0.001$) higher number of eye-related and non-eye-related hospitalizations and outpatient visits than glaucoma negatives even after adjusting for age and sex. Additionally, the annual average time spent hospitalized due to eye- or non-eye-related diagnosis and the travel costs of eye- and non-eye-related outpatient visits were significantly ($p < 0.001$) higher among the three glaucoma groups compared with glaucoma negatives even after adjusting for age and sex. The self-reported use of outpatient health care services was also significantly ($p < 0.001$) higher among the three glaucoma positives groups than glaucoma negatives even after adjusting for age and sex. No statistically significant differences were observed between the three glaucoma positive groups in any of the previously described parameters.

Table 10. Mean annual visits to eye- and non-eye related hospital and outpatient care in glaucoma groups based on 13-year follow-up data in 1999–2011 adjusted for age and sex with 95% confidence intervals

	Annual hospitalizations per 100 persons		Annual outpatient visits per 100 persons	
	Eye	Non-eye	Eye	Non-eye
Glaucoma, verified	8 (7–9)	51 (44–58)	86 (74–98)	188 (161–214)
Glaucoma, medication	8 (7–9)	45 (38–53)	85 (71–100)	123 (103–144)
Glaucoma, operated	7 (5–8)	81 (60–102)	72 (54–91)	331 (246–415)
Glaucoma negatives	2 (2–2)	41 (40–42)	7 (7–7)	117 (114–119)

5.9 Direct and indirect costs associated with glaucoma and glaucoma care (III)

The additional direct health care costs in the total Finnish glaucomatous population were estimated to be approximately EUR 202 million after adjusting for age and sex, and EUR 886 million without adjustment compared with the expected level based on average costs per person in the non-glaucomatous population (**Study III**). The additional age- and sex-adjusted direct costs were approximately EUR 100 million (non-adjusted EUR 521 million) in the glaucomatous population treated with medication and EUR 91 million (non-adjusted EUR 345 million) in the operated glaucomatous population.

The shares of eye-and non-related expenses are illustrated in Figure 13. Majority of the direct expenditures came from hospitalizations: 83.4% of age- and sex-adjusted costs (non-adjusted 82.3%) among glaucoma negatives, 78.9% (non-adjusted 91.2%) in the verified glaucoma group, 81.5% (non-adjusted 89.5%) in the medicated group, and 73.9% (non-adjusted 90.9%) in the operated group. Importantly, the share of eye care was only 12.8% of the age- and sex-adjusted additional direct costs associated with the glaucomatous population. The share of adjusted additional eye-related expenses was 20.9% (non-adjusted 4.1%) in the glaucomatous population treated with medication and 7.8% (non-adjusted 2.9%) in the operated glaucomatous population. All in all, most of the additional direct health care costs among the three glaucoma positive groups came from non-eye-related hospitalizations.

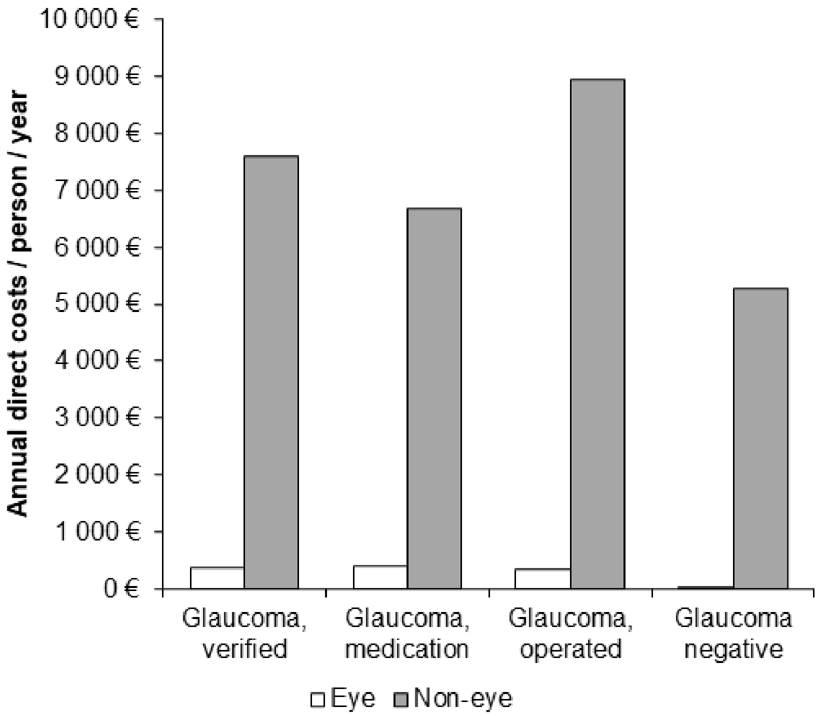


Figure 13. Mean annual direct health care costs in glaucoma groups at the 2019 cost level based on 13-year follow-up data in 1999–2011 adjusted for age and sex. Eye costs consist of eye-related hospitalizations, outpatient visits, and outpatient travels. Non-eye costs consist of non-eye-related hospitalizations, outpatient visits, outpatient travels, and all outpatient health care services.

Among the study participants aged 30–64 years, early retirement was granted to 85.3% (n = 29) persons in the verified glaucoma group, 80.8% (n = 21) in the medicated group, 70.0% (n = 7) in the operated group, and 29.8% (n = 1572) without glaucoma by 2011.

Glaucomatous population was associated with total additional indirect costs of EUR 67 million per year compared with the non-glaucomatous population. The additional expenditures were EUR 38 million in the glaucomatous population treated with medication and EUR 59 million in the operated glaucomatous population. The sources of indirect costs are illustrated in Figure 14. Productivity losses contributed to the majority (69.1%) of the total indirect expenditures among the three glaucoma positive groups and glaucoma negatives.

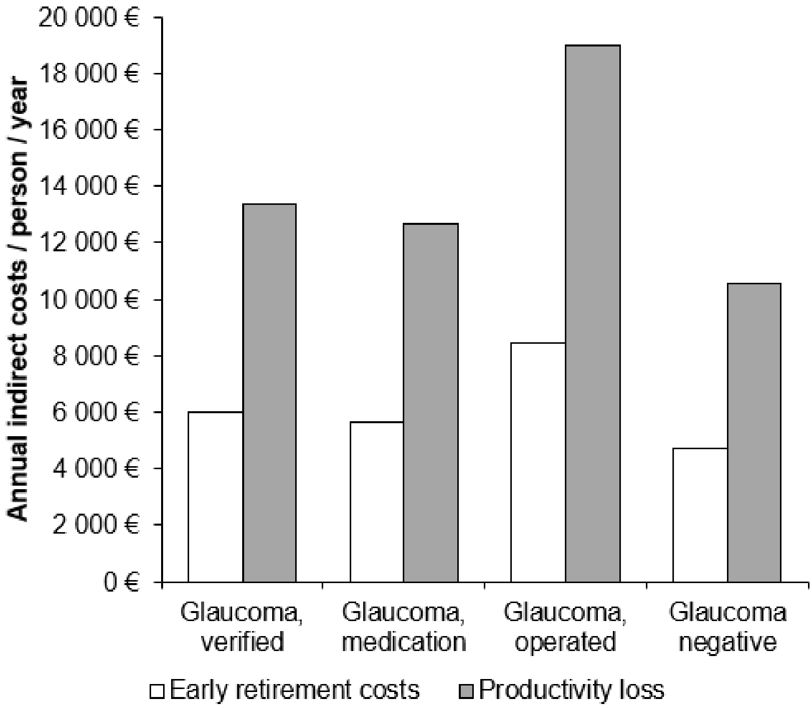


Figure 14. Mean annual indirect costs in persons aged 30–64 years within glaucoma groups at the 2019 cost level

5.10 Relation of distance visual acuity and glaucoma costs (III)

As observed in previous Section 5.9, glaucoma was associated with substantial additional direct and indirect costs. However, based on a multivariable model that included age and sex as well as VI and co-morbidities, neither glaucoma nor its treatment showed statistically significant association with the total direct costs compared with glaucoma negatives (see Table S3 in **Study III**), and only operated glaucoma showed significant association with the total indirect costs (see Table 6 in **Study III**). In the multivariable model, VI showed the third strongest impact on the total direct costs after Parkinson's disease and psychiatric disorders. On the total indirect costs VI showed the strongest impact.

We further examined the association between distance VA and both direct and indirect costs. A strong negative association between distance VA and the costs was observed regardless of whether a person had glaucoma or not: correlation coefficients among the verified, treated, and operated glaucoma groups and glaucoma negatives ranged from -0.24 to -0.36 regarding direct costs and from -0.16 to -0.58 regarding indirect costs (see Figure 3 in **Study III**).

5.11 Trends in incidence and severity of glaucoma-related visual impairment in Finland (IV)

In **Study IV**, between 1980 and 2019 a total of 5819 persons (60.7% females) had been registered in NVREK with glaucoma as the main diagnosis of VI. The total number of registered persons per decade (1980–1989, 1990–1999, 2000–2009, 2010–2019) was 1104, 1476, 1357, and 1882, and the respective share of females was 59.9%, 61.2%, 62.2%, and 59.8%. The cause of VI was in most cases either solely decreased VA or both decreased VA and defective VF; only 5.9% (345/5819) were visually impaired solely due to VF defects. When comparing data between Health 2000 and NVREK, the risk of VI was highest in exfoliative glaucoma, followed by ACG, POAG, and normal-tension glaucoma. Based on the KELA data, the estimated mean annual number of glaucoma patients entitled to special reimbursement for glaucoma medication, i.e., treated glaucoma patients in Finland, was 37 475, 51 339, 69 405, and 88 217 per decade (1986–1989, 1990–1999, 2000–2009, 2010–2019), and the respective share of females was 68.8%, 68.9%, 67.1%, and 63.3%.

The trends in incidence of reported VI due to glaucoma in the Finnish population are shown in Table 11. The mean annual incidence of reported VI per 100 000 persons increased significantly ($p < 0.0001$) from 2.3 to 3.4 between the 1980s and the 2010s with a noticeable increase in reported cases in the age group of 85 years or older. The incidence of VI due to glaucoma remained significantly ($p < 0.05$) higher among females from the 1990s to the 2010s even after stratifying for age.

Table 11. Mean annual incidence of reported visual impairment due to glaucoma per 100 000 persons in the Finnish population by sex, age group, and decade

	Incidence per 100 000 females			
	1980–1989	1990–1999	2000–2009	2010–2019
0–54	0.1	0.1	0.1	0.1
55–59	0.9	0.8	0.7	0.7
60–64	1.6	1.4	0.8	1.2
65–69	4.9	2.9	3.2	1.9
70–74	10.1	10.0	5.6	4.4
75–79	21.0	23.3	15.8	10.8
80–84	32.4	39.1	28.3	28.5
85–	30.8	44.6	44.2	61.3
All	2.6	3.5	3.1	4.0
	Incidence per 100 000 males			
	1980–1989	1990–1999	2000–2009	2010–2019
0–54	0.1	0.1	0.1	0.2
55–59	1.2	1.1	0.6	1.1
60–64	2.6	2.0	1.0	1.9
65–69	5.4	5.3	2.6	2.7
70–74	13.1	12.5	8.1	7.1
75–79	27.0	27.3	14.9	13.6
80–84	39.5	51.4	33.4	31.0
85–	54.1	57.8	57.1	59.5
All	1.9	2.3	2.0	2.8

The trends in incidence of reported VI due to glaucoma among treated glaucoma patients are shown in Table 12. Contrarywise to the incidence in the total Finnish population, the mean annual incidence of reported VI per 10 000 treated glaucoma patients decreased significantly ($p < 0.0001$) from 32 to 21 between the 1980s and the 2010s. This decrease occurred mostly in the 2000s and 2010s. Although the incidence of reported VI among treated glaucoma patients was noticeably higher among males in every decade, this sex difference was not statistically significant.

Table 12. Mean annual incidence of reported visual impairment due to glaucoma per 10 000 treated glaucoma patients by sex, age group, and decade

	Incidence per 10 000 treated female glaucoma patients			
	1986–1989	1990–1999	2000–2009	2010–2019
0–54	8.5	7.6	5.3	9.3
55–59	10.4	7.6	5.8	6.7
60–64	10.2	8.1	3.6	6.3
65–69	18.1	9.4	8.8	5.4
70–74	23.6	19.7	9.9	7.9
75–79	31.9	30.9	19.0	12.9
80–84	38.3	39.5	26.2	26.0
85–	31.4	39.0	32.0	43.8
All	25.5	25.5	18.1	20.2
	Incidence per 10 000 treated male glaucoma patients			
	1986–1989	1990–1999	2000–2009	2010–2019
0–54	13.1	10.1	8.3	12.6
55–59	16.7	13.8	7.3	10.7
60–64	20.5	14.8	6.7	11.7
65–69	27.0	24.0	10.5	10.5
70–74	44.9	34.7	20.3	17.6
75–79	55.4	50.0	25.3	21.7
80–84	59.8	68.6	41.0	36.9
85–	62.7	61.0	53.0	54.3
All	37.9	35.9	22.5	23.7

Between 1980 and 2019, the mean age at the onset of reported VI due to glaucoma increased significantly from 76.0 years to 82.6 years among females and from 73.9 years to 77.5 years among males ($p < 0.0001$). The mean onset age was also significantly higher in females than in males in every decade ($p < 0.0001$). The expected number of years with VI decreased significantly ($p < 0.0001$) among females from 10.1 years in the 1980s to 7.0 years in the 2010s despite the longer life expectancy. Among males, the respective change was from 9.6 years to 8.7 years, but this change was not statistically significant.

The percentage of mild VI among newly diagnosed VI increased significantly ($p < 0.0001$) from 40% to 51% between the 1980s and the 2010s. No statistically significant differences were observed in the distribution of VI classes between sexes.

6 DISCUSSION

6.1 Trends in glaucoma and glaucoma-related visual impairment

Prior to this study, population-based estimates on the longitudinal trends in glaucoma and glaucoma-related VI have been few and far between. There has not been clear evidence on whether the prevalence of glaucoma has changed since the first large population-based studies were published on the subject (Bankes et al., 1968; Kahn et al., 1977). The primary issue in this matter is the difficulty in acquiring comprehensive and representative data. Population-based surveys that include multiple parameters and types of examinations are uncommon due to their high costs and need of resources. Furthermore, nationwide register-based data are in deficit because national registers are rare. To tackle these challenges in this thesis, we utilized both population-based survey data and nationwide register data that were complemented with each other.

Based on **Studies I** and **II**, there were estimated to be over 80 000 glaucoma patients in Finland in 2011, with an estimated prevalence ranging from 2.6% among register-based verified glaucoma to 2.7% among self-reported glaucoma. These national estimates compare well to the estimates in other countries as seen in Table 2 in Section 2.2.2. Between 2000 and 2011, the number of glaucoma patients and the prevalence of glaucoma increased slightly. The access to health care services improved during these years (Pentala-Nikulainen et al., 2018), which may explain this trend. Both figures are likely to continue growing due to the age shift in population and the increasing life expectancy. Likewise, according to the KELA data used in **Study IV**, the number of treated glaucoma patients has almost tripled in the past 40 years in Finland. The decline in the prevalence of self-suspected glaucoma during 2000–2011 is likely a consequence of improved knowledge of glaucoma in the general population. However, the incoherence between register-based verified glaucoma and self-reported glaucoma remained rather noticeable at both the time points, indicating that there is room for improvement in the awareness of glaucoma.

According to **Study IV**, in 2019, approximately 1.5% of the Finnish treated glaucoma patients were visually impaired with VA lower than 0.3 and/or diameter of VF less than 10 degrees. Although the overall incidence of VI due to glaucoma has increased in Finland since the 1980s, the incidence of glaucoma-related VI among treated glaucoma patients has steadily decreased and shifted to older age groups since the beginning of the new millennium. At the same time, the severity of glaucoma-related VI has mildened. Glaucoma-related VI also occurs at older age, which manifests as shorter lifetime living visually impaired. Similar positive trends in the incidence and severity of VI due to glaucoma have been reported at the global level (Flaxman et al., 2017; Steinmetz et al., 2021). These positive developments suggest that the risk of VI for a glaucoma patient has decreased, likely due to the improved therapeutic options and their availability, and the earlier diagnosis of glaucoma.

Based on **Studies II** and **IV**, both glaucoma and glaucoma-related VI were somewhat more common among females even after accounting for age. On the other hand, the onset of glaucoma-related VI occurred significantly earlier in males even in recent decades. This difference between sexes might indicate that the diagnosis of glaucoma and onset of therapeutic measures are happening later in the course of the disease for males. Furthermore, there are indications of sex differences in general health behavior, including health awareness, health seeking, health care utilization, and adherence to therapies (Gender Equality, Norms, and Health Steering Committee, 2019; Koponen et al., 2018; Mahalik et al., 2006). Females have been reported having better health awareness, which may cause more health seeking behavior and health care utilization than males (Galdas et al., 2005). Consequently, glaucoma and glaucoma-related vision loss may be detected at an earlier age in females than in males. These outcomes suggest that more attention should be given to the male population to promote healthier lifestyle and active participation in eye examinations.

Based on **Studies I** and **II**, the prevalence of overall VI has decreased in Finland between 2000 and 2011. There are multiple potential explanations for this positive trend. Most importantly, besides glaucoma-related VI, the incidence of VI due to AMD and DR has also been reported to have decreased between the 1980s and the 2010s in Finland (Purola et al., 2022; Purola et al., 2023a). The positive developments in VI due to AMD have occurred in the 2010s when the treatment for the exudative form of the disease became more widely available (Purola et al., 2023a). The VI due to DR decreased most noticeably in the 1990s when the treatment for diabetes mellitus was intensified and the screening programs in DR were strengthened (Diabetes Control and Complications Trial Research Group, 1993; Purola et al., 2022). In addition to the better and novel therapies of these diseases, the decline in VI could be explained by the improved awareness of the risks of vision-threatening diseases, improved eye care, and new aids. For example, the use of more up to date spectacles and other aids may have become more common, particularly after the economic depression that occurred in Finland during the 1990s.

6.2 Social impact of glaucoma and glaucoma care

6.2.1 Impact of glaucoma on health-related quality of life and mental health

Although glaucoma and other vision-threatening have been associated with poor HRQoL in many previous studies, these earlier evaluations have limited to vision-related HRQoL instruments, clinical settings, and/or specific subpopulations (Floriani et al., 2016; Machado et al., 2019; Rulli et al., 2018; Wu et al., 2019). Based on generic HRQoL instruments and population-based samples utilized in **Studies I** and **II**, we observed significantly deteriorated HRQoL amongst persons with a verified glaucoma diagnosis as well as persons who only suspected to have glaucoma in comparison with those without glaucoma. Similar difference was apparent between persons with unoperated cataract and/or RD and those without eye diseases.

A closer look on the individual HRQoL dimensions revealed that glaucoma is most strongly associated with increased difficulties in usual activities, self-care, mobility, and vision. Freeman and co-workers (Freeman et al., 2008) reported similar results based on a vision-related HRQoL instrument: they observed that glaucoma affects mobility and increases difficulties in various visual tasks.

Alongside HRQoL, both verified and self-suspecting glaucoma patients reported significantly poorer mental health based on the BDI and GHQ-12. On the other hand, the association between BDI and glaucoma became non-significant after adjusting for age, sex, and the most common co-morbidities, and only a small association remained regarding GHQ-12 in 2000. Comparable to our results, Popescu and co-workers (Popescu et al., 2012) reported patients with eye diseases (including glaucoma) having a higher probability of being depressed compared with healthy individuals, although their study was based a clinical sample and the difference remained even after adjusting for age, sex, ethnicity, education, cognitive score, limitations in activities of daily living, social support, and lens opacity. In similar to the self-suspecting glaucoma patients in our study, Jung and co-workers (Jung and Park, 2016) reported in a population-based study that undiagnosed glaucoma positives might be more depressed compared with non-glaucoma controls, even though the degree of depression may not be sufficient for a depression diagnosis. However, they did not include validated instruments such as the BDI for measuring depression. There is also a possibility that persons who suspect to have glaucoma are in general more suspicious and worried about their state of health with detrimental effects on their QoL and mental health. All in all, considering that mental disorders such as depression contribute as a major public health concern worldwide, the declining association between vision-threatening eye diseases and mental health as observed in our study is an encouraging trend that warrants future investigation.

Interestingly, neither medical nor surgical treatment of glaucoma showed direct association with generic HRQoL or mental health amongst glaucoma patients. We observed little association even between the individual dimensions of HRQoL and glaucoma treatments, indicating that glaucoma therapies have a minimal impact on one's well-being. Our findings parallel with those from Guedes and co-workers (Guedes et al., 2013), who observed no significant difference between glaucoma patients treated with either surgery or medicine in relation to vision-related QoL. They also showed that glaucoma surgery is associated with worse vision-related QoL only in patients with early glaucoma possibly due to psychological burden. Furthermore, Hyman and co-workers (Hyman et al., 2005) reported no difference in vision-related HRQoL between treated and untreated glaucoma patients in an Early Manifest Glaucoma Trial Group study. We have now shown this phenomenon at the population level using generic HRQoL and mental health instruments.

The average HRQoL and mental health improved significantly between 2000–2011 among glaucoma patients and glaucoma negatives in the cross-sectional setting. As far as we know, this is the first time this type of positive development in glaucoma has been reported using generic HRQoL instruments. The fact that these improvements occurred particularly among glaucoma patients may indicate a potentially diminished impact of glaucoma on generic HRQoL and mental health. This positive trend may also indicate an increase in the overall well-being and generic HRQoL since the overall health has been reported to have increased in Finland between 2000 and 2011 (Koskinen et al., 2012). The causes for the improved overall health include better availability of health services, aids, and treatment.

In contrast to the improved well-being observed in the cross-sectional settings, in the longitudinal setting patients who had glaucoma already at the beginning of the follow-up did not show such improvement in HRQoL during the 11-year follow-up. In fact, a small decline in HRQoL was observed in both glaucoma patients and glaucoma negatives who belonged to the same glaucoma group at both the time points. The decline in HRQoL is most likely related to the ageing of the participants as observed in **Study I**. However, newly diagnosed glaucoma during the 11-year follow-up had only a minor effect on generic HRQoL and mental health. This phenomenon could be understood that the decrease in the detrimental impact of glaucoma on generic HRQoL and mental health as observed in the cross-sectional setting is related to the new glaucoma cases rather than the changes amongst patients who have had glaucoma for a longer time. The improved glaucoma therapies and accessibility to glaucoma care as well as the improved awareness of glaucoma and its nature may have attenuated the fear of blindness due to the disease among new generations of glaucoma patients.

6.2.2 Role of reduced visual acuity in the social impact of glaucoma

The association between reduced VA and poor well-being is well known (Brown and Barrett, 2011; Finger et al., 2011; Kempen et al., 2012; McKean-Cowdin et al., 2010; Purola et al., 2023b; Taipale et al., 2019). The detrimental impact of declining VA on generic HRQoL and mental health was also clearly evident in **Studies I** and **II**. Considering the detrimental impact glaucoma has on vision, the role of reduced VA among glaucoma patients regarding HRQoL and mental health requires closer inspection.

Previous publications have suggested that the awareness of the disease itself may affect the sense of well-being in glaucoma patients due to the fear of declining vision (Jampel et al., 2007; Su et al., 2015; Wang et al., 2012). Although this factor cannot be ignored, based on **Studies I** and **II** the effect of VI had a significantly stronger detrimental effect on generic HRQoL and mental health than glaucoma, cataract, or RD alone, suggesting that reduced VA is the major determinant of the worsened HRQoL and mental health in the vision-threatening eye diseases. This implication is supported by the fact that the three individual HRQoL dimensions associated with glaucoma, self-care, mobility, and vision, were also affected by VI. In concordance with our results, Knudtson and co-workers (Knudtson et al., 2005) reported reduced VA having a significant detrimental effect on generic HRQoL irrespective of pathologic reasons such as glaucoma, unoperated cataract, and AMD. However, their data were based on a regional setting and lacked a longitudinal point of view. Furthermore, poor generic HRQoL has been associated with glaucoma patients with reduced VA in particular (Jung and Park, 2016). Besides eye diseases, we observed VI having an equal or stronger impact on generic HRQoL compared with other major medical conditions such as hypertension, diabetes, and heart diseases. This position of VI in the light of other medical conditions regarding generic HRQoL has also been reported in previous studies (Chia et al., 2004; Esteban et al., 2008; Nutheti et al., 2006).

Considering the pivotal role of vision loss in the well-being of glaucoma patients, the declined prevalence, mildened severity, and delayed onset of glaucoma-related VI in the past 40 years as discussed in Section 6.1 are likely essential factors in the decreasing influence of glaucoma on generic HRQoL and mental health observed between 2000 and 2011. This positive trend has important clinical implications. Because the number of people affected by glaucoma and other vision-threatening eye diseases is increasing due to the increasing life expectancy and growth of elderly population, it is important to prevent the increase of VI and blindness caused by these diseases. Our results suggest that the spreading of awareness of the potential hazards of vision-threatening eye diseases possesses very little effect on one's well-being compared with the benefits of early diagnosis of these diseases, and therefore the spreading of this awareness should be strengthened to prevent the detrimental social impact of declining vision.

6.3 Economic impact of glaucoma and glaucoma care

6.3.1 Impact of glaucoma on health care and productivity

To our knowledge, sub-study **III** is the first cost-of-illness study on glaucoma to report both direct and indirect costs associated with the disease based on multilinked, nationally representative data. The comprehensive data allowed us to include both eye- and non-eye-related treatments, whereas prior economic studies have mostly focused on the treatment modalities of glaucoma.

In 2019, the expenditures of health care in Finland were EUR 23.4 billion in total (Official Statistics of Finland, 2019). Based on our economic estimations, the age- and sex-adjusted direct additional expenditures associated with glaucoma corresponded to 0.86% (EUR 201 931 493) of that cost. While the estimated indirect costs associated with glaucoma in our study were smaller than the direct costs, they are also considerable: additional productivity losses caused by glaucoma in Finland were EUR 67 032 633 at the 2019 cost level. In that year the Finnish gross domestic product was EUR 239.9 billion in total, of which glaucoma alone corresponded to

0.03%. Furthermore, the costs of glaucoma can be considered underestimated due to the high percentage of undiagnosed glaucoma. Both direct and indirect costs associated with glaucoma showed strong dependency on VA and other co-morbidities. This trend is likely explained by the fact that these factors are associated either directly with glaucoma or indirectly through ageing (Dielemans et al., 1996; Briggs et al., 2016; Lim et al., 2016). All in all, the direct and indirect costs of glaucoma can be considered substantial, and the economic burden of glaucoma is likely to increase in the future alongside the increasing life expectancy and shifting in age distribution in Finland and around the world.

The deficit of comprehensive, nationwide estimations of glaucoma-related direct and indirect costs makes the comparison of our results with other studies difficult. Further difficulties are imposed by the differences in the organization of glaucoma care around the world. In 1990 in the UK, the direct medical costs associated with glaucoma were estimated to be GBP 61 million and the indirect costs due to lost production GBP 41 million (Coyle and Drummond, 1995). In 2004, the annual direct medical costs of glaucoma were estimated to be USD 2.9 billion in the US (Rein et al., 2006) and the annual direct eye-related costs of glaucoma AUD 144.2 million in Australia (Taylor et al., 2006). Importantly, all these studies only included costs related to glaucoma treatment.

We observed noticeable differences in the costs between glaucoma therapies. Even after adjusting for age and sex, the annual total direct costs were EUR 2 207 (31.1%) higher for an operated patient than a medicated patient. Similarly, annual indirect costs for an operated patient were EUR 9 087 (49.5%) higher than for a medicated patient. Considering the association between co-morbidities and reduced VA with additional direct and indirect costs among glaucoma patients as discussed previously, these higher costs among operated glaucoma patients may be explained by the fact that the patients needing glaucoma surgery are often unable to take care of their medication due to their co-morbidities and that glaucoma surgery is in many cases the last option to prevent the progression of glaucoma and consequent loss of vision. However, the indirect additional costs of operated glaucoma were significant even after adjusting for co-morbidities, which likely suggests the severity and specific surgical indications of the operated glaucoma patients.

6.3.2 Role of reduced visual acuity in the economic burden of glaucoma

Although the role of treatment in the economic burden of glaucoma has been studied extensively, based on our observations, the major proportion of the direct additional costs associated with glaucoma are not directly caused by its treatment but rather the increased use of non-eye-related health services, particularly hospitalization. The average time spent hospitalized among glaucoma patients is also significantly higher in comparison with non-glaucomatous population. Furthermore, we observed a strong relationship between decreasing distance VA and increasing direct costs regardless of whether a person had glaucoma or not. As mentioned in Section 2.1.2, vision loss is associated with falls and injuries, both of which are a major cause of hospitalizations and consequently a likely cause of the economic burden associated with reduced VA (Mikhailova et al., 2018). In similar, glaucoma patients have been reported increased risk of falls and other accidents, which contribute to significant amount of bed days with an economic and operational impact on the hospitals (Ramulu et al., 2012; McGinley et al., 2020; Lin et al., 2021).

We also observed a strong relationship between decreasing distance VA and increasing indirect costs regardless of glaucoma. Loss of productivity among glaucoma patients is likely contributable to the reduced VA associated with the disease because VI is associated with nursing home admission, falls, injuries, accidents, and femur fracturs that can all lead to work invalidity (Bramley et al., 2008; Mikhailova et al., 2018). In fact, VI and blindness are regarded as major causes of productivity losses worldwide (Marques et al., 2021).

Based on these associations, we can conclude that most of the additional costs of glaucoma are related to the irreversible vision loss associated with glaucoma and its progression. Therefore, the role of early intervention in glaucoma care to prevent the progression of VI is vital in alleviating the economic burden of the disease on the society.

6.4 Public health implications

The mutual conclusion of the sub-studies of this thesis is that the major determinant of the social and economic burden of glaucoma is the deteriorating VA caused by the disease; hence, the prevention of vision loss caused by glaucoma is a key factor in reducing the burden of the disease on both the patient and the society. Although the effects of reduced VA are similar in other vision-threatening eye diseases, glaucoma has a major role in the prevention of the detrimental impact of VI in the society because the irreversible vision loss caused by it is preventable if the challenges and obstacles in its awareness, diagnostics, and treatment would be resolved.

Because glaucoma remains asymptomatic until the advanced stages, health education that influences individuals to be aware of the disease and its risks and to seek regular and periodic eye care is needed to strengthen the early detection and proper management of the disease. Furthermore, therapeutic approaches should also more emphasize the subjective perception of the condition. Still, the need for national screening programs for glaucoma has remained controversial due to the lack of clear evidence in the cost-effectiveness and practicality of such programs (Burr et al., 2007; Vaahtoranta-Lehtonen et al., 2007). Although the results of our studies back the need and usefulness for prompt and effective screening for glaucoma, especially for those at risk, more information is needed for the full determination of screening campaigns in Finland and other countries. Nonetheless, the results of this thesis may serve as a base to develop intervention measures and appropriate strategies to increase the awareness of glaucoma among patients and physicians. This can only happen if increased resources are properly put into detection, management, and eye health promotion. Finally, it is good to remember that the unawareness and underdiagnosis is also common in other diseases such as type II diabetes mellitus (Zhang et al., 2017). Therefore, it is relevant to improve the overall awareness of diseases as well.

The decline in glaucoma-related VI highlights the significance of effective glaucoma care and underlines the importance that the level of ophthalmological services will correspond to the continuing ageing of the population. The treatment of glaucoma in its early stages improves outcomes in the preservation of visual outcome (Heijl et al., 2002), which highlights the significance of early detection and timely management of the disease. In the case of irreversible VI, low vision aids and rehabilitation have proven effective regardless of the cause of the VI; hence, providing access to cost-effective health-care technologies with the potential to reduce the detrimental effects of vision loss should be given priority. In addition to the preservation of visual outcome in clinical practice, it is important to identify the unique key factors that contribute to a patient's individual health status to aid the patient effectively. All in all, since the Finnish health care has been under many changes in recent years, the level and accessibility to glaucoma care should hopefully remain adequate considering the low-price tag of glaucoma treatment compared with the total costs of glaucoma.

6.5 Strengths and limitations

6.5.1 Survey data

The main strength of the **Studies I**, **II**, and **III** was the use of data from two nationwide surveys with high participation rates. The survey samples represent the Finnish adult population at the two time points, and the surveys addressed public health issues more comprehensively than national health surveys do on average. The use of pre-calculated weights in the surveys allowed the generalization of the data to represent the target population at both the time points. Due to the survey design, we were able to include a relatively long follow-up period of 11 years, which provided the opportunity to evaluate temporal aspects. The study design allowed for highly comparable measures across points in time. The decline in participation rates from 2000 to 2011 was relatively small and was further corrected by applying the weights. In contrast to many earlier surveys, the study populations in Health 2000 and 2011 did not consist of specific patient groups collected from health care units, which allows for better generalization of the results. All analyses were conducted on the highest possible number of participants. The estimated outcomes in this study are generalizable to the Finnish adult population or to a similar setting in terms of population age structure as well as financial support system from government regarding the economic evaluations, for example, all Nordic countries and several European countries.

The surveys also had limitations. Participation in the health examination may have been selective seen as there were differences in participation rates between the health examinations and the total surveys, leading to limitations on the external validity of the results. Even so, participants with mobility and other restrictions, which may have been a major limitation in participating in the health examination, were offset by conducting home visits that included the measurement of vision. Although the non-participation in 2011 was accounted for by using updated weights, the non-participation was particularly common among males, in younger age groups, and in lower education groups, which may have potentially caused bias in relation to these groups regardless of the used weights (Härkänen et al., 2016). Other clinical parameters besides VA such as VF, contrast sensitivity, stereopsis, and dark adaptation were not measured in the health examination; therefore, they were not used in the determination of impaired vision among survey participants. The lack of VF data on glaucoma patients may have particularly caused underestimation of the impact of glaucoma and related vision loss on the studied factors. Still, the impact of defective VF on EQ-5D and 15D has remained uncertain both in clinical settings and at the population level (Browne et al., 2012; Datta et al., 2008; van Gestel et al., 2010). Furthermore, based on the NVREK data, the cause for glaucoma-related VI was in most cases decreased VA. The lack of VF data in defining glaucoma may have had increased the underestimation of its prevalence (Kapetanakis et al., 2016), although the use of multiple sources for defining the glaucoma groups should have reduced this bias. The variation in the age between the studied subgroups was large, but we accounted this for by using age-stratification and age-adjustment. Both the surveys included predominantly Finnish participants; hence, the results may not be directly applicable to other countries.

Self-reported data on the diseases allowed the investigation of the impact of a diagnosis or the awareness of the disease on the patient. Although the number of co-morbidities acquired from the interview data was rather large, it is still possible that all potential confounding factors may not have been revealed and some residual confounding remains. In addition, we had to combine the co-morbidities into rather large groups because new diagnoses during the 11-year follow-up were scarce for many specific diseases. We could not differentiate AMD from self-reported RD reliably, and therefore, the outcomes related to RD should be generalized to AMD with caution.

We applied widely used and validated instruments of both generic HRQoL and mental health included in the surveys. Because a valid assessment of HRQoL requires reports directly from patients rather than physicians or other parties, generic, self-reported questionnaires were utilized. Instead of vision-related HRQoL instruments as often applied in this type of studies, we used generic HRQoL instruments for better comparability and generalization of the results. Both EQ-5D and 15D are known to be sensitive for different levels of VA (Purola et al., 2023c; Taipale et al., 2019). Nevertheless, persons who do not complete HRQoL questionnaires are often older and may have poorer functioning (Kopp et al., 2003). This aspect can introduce selection bias and reduction in statistical power and can lead to misleading results regarding HRQoL, with a particular impact on longitudinal HRQoL due to poor compliance in questionnaire completion as the study or disease progresses and patients drop out. In addition, self-reported instruments can be influenced by the subjective nature of QoL (Macedo et al., 2017). The EQ-5D instrument is known to have a low sensitivity in the upper scores, commonly referred as a ceiling-effect, which leads subjects having mild health problems to potentially score maximum in addition to those with excellent health. It also evaluates a rather limited number of dimensions, although the more comprehensive 15D was used alongside.

Our prevalence-based bottom-up approach reduces the misallocation of costs, which is more likely to occur in top-down approach (Jo, 2014). Even though the prevalence-based approach may not accurately quantify the long-term consequences of glaucoma, leading to underestimation of costs (Jo, 2014), our long, 13-year follow-up time based on the register data should alleviate potential biases associated with this approach. For the economic evaluations, we were not able to include laboratory costs in private health care, although laboratory costs were included in public health care unit costs, which should alleviate this deficiency in total cost analyses. We were also unable to include the costs of care outside the health system as well as non-health care costs such as those caused by social services, childcare, and housekeeping. Drugs and prescriptions were also not included in the cost analyses, although we discussed their share based on the medication cost estimations by Parkkari and co-workers (Parkkari et al., 2020; see **Study III**). While the costs of disability pensions and early retirement were included, productivity losses might be underestimated because we were not able to get data on sick leaves and unemployment subsidies. We could not differentiate eye- and non-eye-related self-reported outpatient health care service visits, and we could not complement the self-reported outpatient health care service data from Health 2011 due to low response rates in the corresponding questions. Although the share of ophthalmologist visits in health centers should be small, the share among private practitioners can be higher, increasing risk for bias.

6.5.2 Register data

Various national registers were used in the sub-studies, particularly the NVREK in **Study IV**, which carries both strengths and limitations. The main strength of the NVREK was the large dataset based on routinely collected health registers, ensuring good coverage of the population and the comparability of the results with those from studies in the other Western countries. NVREK included data from four decades, allowing a relatively large timescale of 40 years. The classification of VI was based on the Finnish national definitions and recommendations modified from the WHO 1973 definitions, which covered both decreased VA and VF defects (WHO Study Group on the Prevention of Blindness, 1973), and therefore, the register data covered glaucoma cases in the four decades relatively well. We analyzed the incidence of VI rather than the prevalence to control the survival.

NVREK data also had limitations. The register was established in 1983, and therefore, the reports from the early 1980s also include persons who became visually impaired before 1983. As a result, the registered data from the early 1980s can manifest as inflated incidence and underestimated prevalence. It is also difficult to evaluate the exact time point at which a person becomes visually impaired, and it is even more difficult to estimate when the vision-threatening disease itself emerges. In the elderly population, many of the patients are likely to suffer from more than one vision-threatening disease. Therefore, to minimize this bias, we analyzed only those patients who had glaucoma as the main diagnosis for causing VI. As in the survey data, the NVREK data included predominantly people with Finnish backgrounds, and therefore, the results may not be directly applicable to other countries.

It is important to point out that the prevalence of treated glaucoma collected from the KELA data does not reflect the prevalence of glaucoma, which carries several possible biases. As discussed in Section 2.2.2, glaucoma remains largely undiagnosed even in well-developed countries. There is also a possibility that glaucoma diagnoses made for the special reimbursement of glaucoma medication can cause misclassification biases. In addition, the KELA data were available since 1986, which can even further bias the results of the first decade of the NVREK data.

In **Studies II** and **III**, the classification of glaucoma included register data on observations made by an ophthalmologist, which can cause biases. For example, high IOP may have been diagnosed as glaucoma, even though it may not have been the case. On the other hand, this limitation is a common problem in this field because glaucoma diagnoses are sometimes difficult to set due to the lack of well-standardized global glaucoma guidelines.

6.6 Future perspectives

In the future, the number of patients with glaucoma and other vision-threatening eye diseases is expected to increase with the ageing of the populations. When persons live longer with good or adequate vision, they retain their functional capacity, work ability, and well-being longer. Therefore, all attempts need to be made to prevent the deterioration of vision by further improving the efficiency and accessibility of eye care and the awareness of glaucoma and other vision-threatening eye diseases.

To achieve these objectives, we need more population-based studies on glaucoma with generic HRQoL instruments, comprehensive economic evaluations and cost-efficiency studies, sufficient longitudinal settings, and standardized methodology. Further research in other countries and populations is necessary to address the social and economic implications of glaucoma in the big picture and to corroborate the results of this thesis. Future studies will also hopefully shed more light on the practicality and cost-effectiveness of different glaucoma therapies as well as screening and other public health programs for glaucoma.

Our next aim is to provide more contemporary estimates on the prevalence of glaucoma and the distribution of glaucoma diagnoses using the recently completed FinHealth 2017 health examination survey (Koponen et al., 2018) and the ongoing Healthy Finland Survey 2023 ("Terve Suomi -tutkimus - THL," 2023), which continue the tradition of the well-established, population-based Health Surveys in Finland. Comparing different types of glaucoma and glaucoma treatment in more detail could uncover the details in the variations, interactions, and influencing mechanisms in the social and economic effects of glaucoma. Since the quality of register data has improved in recent years, more detailed assessment in these areas becomes available.

7 CONCLUSIONS

This dissertation addressed the social and economic impact of glaucoma and glaucoma care at the population level. Taken together, vision loss associated with glaucoma and other vision-threatening eye diseases is a major determinant of the detrimental social and economic impact of these diseases. The results provide new insight into the need of preventive eye care and the status of eye diseases and vision in public health. The following list details the conclusions drawn from the results of the studies.

1. The number of patients with glaucoma and other vision-threatening eye diseases is slowly increasing in Finland due to the ageing of the population; yet the prevalence of overall and glaucoma-related visual impairment is decreasing. Glaucoma-related visual impairment is also mildening, and its onset is occurring at a later age. These positive trends are likely explained by the improved diagnostics, therapies, and awareness of glaucoma and other vision-threatening eye diseases.

2. Glaucoma and other vision-threatening eye diseases are associated with worsened generic health-related quality of life and mental health; however, this detrimental influence of these eye diseases is more related to impaired vision than the awareness of the disease itself. Furthermore, the detrimental effect of eye diseases and visual impairment on these factors diminished between 2000 and 2011. This positive trend was likely steered by the newly diagnosed cases. Neither glaucoma medication nor glaucoma surgery affected generic health-related quality of life or mental health. Therefore, the information directed to the public on the risks and prevention of blindness can and should be strengthened to prevent the deleterious effects of visual impairment. These observations should also encourage the promotion of early detection of glaucoma and the importance of glaucoma therapies and the adherence to them.

3. Glaucoma is associated with an increased health care resource consumption mostly due to other than eye-related care, which is likely linked to the vision loss and the increased number of co-morbidities among glaucoma patients. Consequently, impaired vision due to glaucoma constitutes as a major economic burden for the health care system and society, highlighting the importance of early glaucoma interventions.

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9 ORIGINAL COMMUNICATIONS

PUBLICATION
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Prevalence and 11-year incidence of common eye diseases and their relation to health-related quality of life, mental health, and visual impairment

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Quality of Life Research 2021;30(8):2311–2327
doi: 10.1007/s11136-021-02817-1

Quality of Life Research (2021) 30:2311–2327
https://doi.org/10.1007/s11136-021-02817-1

Prevalence and 11-year incidence of common eye diseases and their relation to health-related quality of life, mental health, and visual impairment

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Accepted: 4 March 2021 / Published online: 23 March 2021

Abstract

Purpose To study the prevalence and incidence of the most common eye diseases and their relation to health-related quality of life (HRQoL), depression, psychological distress, and visual impairment in the aging population of Finland.

Methods Our study was based on two nationwide health surveys conducted in 2000 and 2011. Eye disease status data were obtained from 7379 and 5710 individuals aged 30 + years, of whom 4620 partook in both time points. Both surveys included identical indicators of HRQoL (EuroQol-5 Dimension [EQ-5D], 15D), depression (Beck Depression Inventory [BDI]), psychological distress (General Health Questionnaire-12 [GHQ-12]), visual acuity, and self-reported eye diseases. We assessed the impact of known eye diseases on these factors, adjusted for age, gender, and co-morbidities.

Results Prevalence of self-reported eye diseases was 3.1/2.7% for glaucoma, 8.1/11.4% for cataract, and 3.4/3.8% for retinal degeneration in 2000 and 2011, and the average incidence between 2000 and 2011 was 22, 109, and 35 /year/10,000 individuals, respectively. These eye diseases were associated with a significant decrease in EQ-5D and 15D index scores in both time points. BDI and GHQ-12 scores were also worsened, with some variation between different eye diseases. Impaired vision was, however, the strongest determinant of declined HRQoL. During the 11-year follow-up the effect of eye diseases on HRQoL and mental health diminished.

Conclusion Declined HRQoL associated with eye diseases is more related to impaired vision than the awareness of the disease itself, and this declining effect diminished during the follow-up. Therefore, information directed to the public on the risks and prevention of blindness can and should be strengthened to prevent the deleterious effects of visual impairment.

Keywords Eye disease · Health-related quality of life · Incidence · Mental health · Prevalence · Visual impairment

Plain English summary

The prevalence of vision-threatening diseases, such as glaucoma, cataract, and age-related macular degeneration, is likely to increase in developed countries due to aging population and rising life expectancy. Decreased vision is known to worsen the quality of life in eye disease patients. However, a majority of the research on the connection of quality of life with vision and eye diseases has been based on relatively small study populations and vision-specific questionnaires. In this respect, generic instruments could improve the comparability and generalization of the results. In this study, we have evaluated the prevalence and incidence of the most common eye diseases and their impact on generic quality of life in the Finnish adult population during 11 years. This study indicates that even though the prevalence of vision-threatening diseases

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is increasing, their impact on quality of life is diminishing. The impact of eye diseases on quality of life is related to the impaired vision rather than the awareness of the disease itself. Thus, the information directed to the public about eye diseases and their risks should be strengthened to promote early diagnosis and prevent the declining effect of visual impairment on quality of life and increasing health care costs.

Introduction

The aging population, rising life expectancy, and unfavorable changes in lifestyle, such as unhealthy eating habits and decreased exercise, in developed countries are likely to increase the prevalence of vision-threatening diseases in the future [1–3]. The most common causes of visual impairment include glaucoma, cataract, and age-related macular degeneration that mainly affect older adults, and inherited retinal diseases affecting young population [4–6], although the permanent deterioration of visual acuity (VA) caused by cataract can usually be prevented with modern surgery [4, 7].

Decreased VA can significantly affect the quality of life (QoL) of an individual even before the individual has become visually impaired ($VA \leq 0.25$, Snellen decimal equivalent) [8] and, in fact, the awareness of an eye disease, such as glaucoma, is thought to reduce QoL through the fear of declining vision before the loss of VA affects the patient's life [7, 9–11]. However, a majority of the previously conducted research on the connection of QoL with VA and eye diseases has been based on relatively small study samples that may not be representative on larger populations [9, 12–14]. Furthermore, many studies have measured QoL using vision-related assessments [15, 16], but more generic instruments could allow better comparison to other diseases and defects. Therefore, we aimed to study the prevalence and incidence of glaucoma, cataract, retinal degenerations (RDs), and their relation to decreased VA and visual impairment using data from two cross-sectional surveys and an 11-year longitudinal follow-up study that are representative of the Finnish adult population. Furthermore, we aimed to study their impact on QoL and mental health using generic instruments included in the surveys that assess health-related quality of life (HRQoL), depression, and psychological distress.

Materials and methods

Study population and design

We utilized two nationwide health examination surveys performed in Finland. They were carried out by the Finnish Institute for Health and Welfare, the first one in 2000–2001 and a follow-up in 2011 [17, 18]. In both surveys, the information on eye diseases and co-morbidities was collected in face-to-face interviews, whereas the assessment of HRQoL and mental health was based on self-administered questionnaires. The Health 2000 Survey analyzed a sample of 9922 adults aged 18 years or over living in mainland Finland. The sample was selected by a stratified two-stage cluster sampling design. The Health 2011 Survey analyzed a sample of all living members of the Health 2000 sample who had not refused to be contacted, aged 29 years or over, and a new sample of 1994 young adults aged 18 to 28 years. For this study, we only included participants aged 30 years or over in both cross-sectional and longitudinal samples. Both surveys provided a probability-clustered sampling and weighting scheme that estimates health statistics that are representative of Finnish adult population aged 30 years or over at the time of sampling [19, 20]. In addition, the scheme accounts for the oversampling of people aged 80 years or over in 2000 by doubling the sample fraction. The unweighted participation rate was 93% in the Health 2000 Survey while in the follow-up it was 73%. Separate weights were applied for the surveys to produce results representing the Finnish population at each time points [21].

Self-reported eye disease status

Both surveys included an interview with the following questions on eye diseases: “Has a doctor diagnosed one of the following diseases: cataract, glaucoma, retinal degeneration, or other visual defect or eye trauma?” Only the individuals who had replied “yes” or “no” to at least one of these questions were chosen for the further analyses, classified as “eye disease status known”. Individuals who had only answered “no” to this set of questions were considered to not have eye diseases. There was also self-reported information on previously performed cataract operations. Only unoperated cataract patients were included in the evaluation of HRQoL, mental health, and VA, as cataract surgeries improve VA and have been demonstrated to improve QoL as well [22].

Assessment of health-related quality of life

HRQoL scores were evaluated using generic preference-based 3-level version of EuroQol-5 Dimension (EQ-5D-3L, later referred as EQ-5D) and 15D questionnaires that assess physical, psychological, and social functioning and well-being [23, 24]. 15D is a self-administrated measure of HRQoL comprising one question for each of the 15 dimensions—mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. Each question contains five answer options on a scale of 1 (no difficulties) to 5 (extreme difficulties).

A single index score is obtained by weighting the obtained scores with population-based preference weights based on an application of the multi-attribute utility theory [25]. In this study, the 15D was weighted using Finnish preference weights with a scale of 0 (representing HRQoL equal to being dead) to 1 (representing the best possible HRQoL). Mean change/difference of ≥ 0.015 was considered to be clinically meaningful [26].

EQ-5D contains one question for each of the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each question contains three answer options on a scale of 1 (no difficulties) to 3 (extreme difficulties), and they can be converted into EQ-5D index scores on a scale identical to the 15D index score. In this study, EQ-5D was weighted using UK time trade-off weights on a scale between − 0.59 (representing HRQoL equal to being dead) and 1 (representing the best possible HRQoL) to improve comparability with other populations [27]. Mean change/difference of ≥ 0.07 was considered to be clinically meaningful [28].

Assessment of mental health

The state of mental health was assessed using two self-report questionnaires, Beck Depression Inventory (BDI) and General Health Questionnaire-12 (GHQ-12). In the first survey, BDI-21 comprising 21 questions was used to evaluate depression, whereas in the follow-up survey a shorter version, BDI-13, containing 13 questions, was used [29, 30]. A total score was calculated for both questionnaires with a scale of 0–63 for BDI-21 and 0–39 for BDI-13, where higher points indicate major depression. Total scores of ≥ 10 for BDI-21 and ≥ 5 for BDI-13 were used as cut-off points to categorize an individual as having depression [31].

GHQ-12 is a questionnaire comprising 12 questions that evaluate different dimensions of psychological distress, including depression, anxiety, social interaction, and confidence [32, 33]. The answers were dichotomized according to whether difficulties were presented or not (0 = no, 1 = yes). A total score with a scale of 0–12 was calculated using the dichotomized points, with 12 representing the highest psychological distress. A total score of > 3 was considered as indicative of psychological distress [17, 18].

Visual acuity tests

In both surveys, the distance VA was measured by a study nurse binocularly at 4 m with current visual correction. Illumination was set to ≥ 350 lx on the modified logMAR letter chart published by Precision Vision [19, 20, 34]. All VA values are presented as Snellen decimal equivalents. Low VA values outside the modified logMAR letter chart that could not be determined were reported as 0.01. The classified VA values were following: VA ≥ 1.0 (good vision), VA 0.63–0.8 (adequate vision), VA 0.32–0.5 (weak vision), VA 0.125–0.25 (impaired vision), and VA < 0.1 (severe vision loss or blindness) [8]. Habitual binocular distance VA ≤ 0.25 was considered as impaired vision. We found the binocular evaluation of VA important because the relation of vision and HRQoL was studied.

Co-morbidities

Common diseases assessed in the interview (data available from 7371 to 7385 and 5714 to 5720 participants in 2000 and 2011) were accounted for their potential impact on the HRQoL and mental health. The diseases were classified into major co-morbidity groups according to Taipale and colleagues [8]: heart diseases (myocardial infarction, angina pectoris, heart failure, arrhythmias, and “other heart disorders”); respiratory diseases (asthma, chronic obstructive pulmonary disease, chronic bronchitis, and “other pulmonary disease”); vascular diseases (stroke and varicose veins in lower limbs); musculoskeletal conditions (rheumatoid arthritis, osteoarthrosis, fractures, and osteoporosis); psychiatric conditions (psychotic disorders, depression, anxiety, psychoactive substance abuse, and “other psychiatric disease”). Furthermore, hypertension, diabetes, Parkinson’s disease, and unspecified cancer were included as separate groups.

Co-morbidity status was determined according to Taipale and colleagues [8] so that individuals were considered to have co-morbidity if they reported any of the conditions included in the co-morbidity group. When analyzing new incident diagnoses during the follow-up period, each condition was scrutinized in 2000 baseline and in 2011 follow-up. If the subject reported at least one new condition included in the co-morbidity group in 2011, they were classified as having incident co-morbidity, regardless of the presence of other conditions of that specific co-morbidity group at baseline.

Statistical analyses

The data were analyzed using R software version 3.5.1 [35], and it included both cross-sectional survey samples for all cross-sectional and longitudinal analyses. The sampling design, the oversampling of individuals aged 80 years or over, and the loss to follow-up were accounted for by using Survey package 3.37 for R [36] and weighting scheme calculated by the Finnish Institute for Health and Welfare.

For the prevalence and incidence analyses, population totals and ratios were estimated using functions *svytotal* and *svyratio* included in the Survey package. Individuals with missing data in analyzed variables were excluded. As the distribution of the continuous variable data was skewed, Mann–Whitney *U* test was used for the between-group comparisons. The impact of age, gender, eye diseases, impaired distance VA, and co-morbidities on HRQoL and mental health were estimated through linear regression, and standardized regression coefficients were calculated using lm.beta package 1.5-1 for R [37]. Multicollinearity in regression analyses was measured through variance inflation factors using car package 2.1-5 for R [38, 39]. Odds ratios (ORs) with 95% confidence intervals were calculated using logistic regression analysis, adjusted for age, gender, and co-morbidities. For all analyses, a two-tailed p value of <0.05 was considered to be statistically significant.

Results

Eye disease status of the participants

Figure 1 presents the number of the individuals with self-reported eye disease in the two surveys that were included in the analyses. In total, 8028 individuals aged 30 years or over had been invited in the 2000 survey and 8006 in the 2011 survey. Eye disease status data was obtained from 7379 and 5710 individuals, of whom 4620 took part in both time points and were included in the 11-year follow up. Table 1 shows the number, mean age, and the gender distribution of the survey samples, individuals with/without eye diseases, and individuals with impaired/good distance VA in both surveys and in the 2011 follow-up. It also includes the number of individuals with eye disease status known who had available data on HRQoL, mental health, and distance VA. The data in all analyses were compared between individuals with eye diseases and those with no eye diseases, and individuals with impaired distance VA and those with good distance VA.

Prevalence and incidence of eye diseases

The estimated prevalence and incidence of glaucoma, cataract, RD, and visual impairment in the Finnish adult population is shown in Table 2. The prevalence of cataract and RD increased between the time points, whereas glaucoma and visual impairment decreased. The prevalence and incidence of all eye diseases and visual impairment increased with age, and they appeared to be more common in women, particularly in age group 75 + years (Fig. 2).

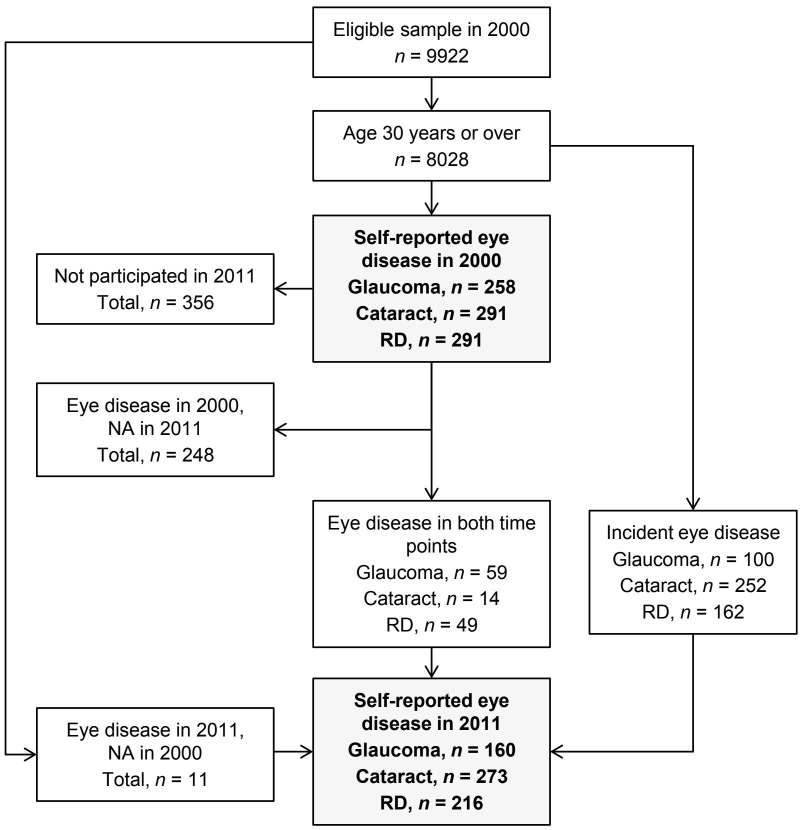


Fig. 1 Flow chart of glaucoma, unoperated cataract, and retinal degeneration (RD) status. *NA* not applicable

Table 1 Summary of the participants aged 30 years or over in Health 2000 and 2011 studies

	2000			2011			11-year follow-up group in 2011		
	n	Mean age (SD)	% women	*n*	Mean age (SD)	% women	*n*	Mean age (SD)	% women
Eligible sample	8028	54.2 (16.2)	54.7	8006	55.3 (15.6)	53.0	6360	60.6 (12.9)	55.5
Eye disease status known	7379	54.2 (16.1)	55.2	5710	55.6 (14.6)	55.4	4620	60.0 (12.1)	55.6
No eye diseases	4793	52.1 (15.6)	51.8	4067	53.3 (14.2)	53.2	3122	58.3 (11.7)	53.2
Glaucoma	258	71.1 (13.6)	75.2	160	72.0 (11.2)	66.9	159	72.2 (10.8)	66.7
Cataract, all	740	76.7 (10.4)	73.6	663	73.8 (10.1)	63.7	654	74.1 (9.6)	63.6
Cataract, unoperated	291	74.3 (10.1)	74.9	273	71.1 (9.0)	64.8	268	71.4 (8.5)	64.9
Cataract, operated	449	78.2 (10.3)	72.8	390	75.7 (10.5)	62.3	386	76.0 (9.9)	62.5
RD	291	73.5 (12.4)	67.7	216	73.1 (12.0)	62.0	211	73.7 (11.0)	62.0
Distance VA measured	6644	53.6 (15.5)	55.3	4554	56.5 (14.1)	55.7	3804	60.1 (11.9)	55.5
Good distance VA (≥ 1.0)	4943	48.6 (12.2)	53.6	3678	53.5 (12.7)	55.7	3002	57.4 (10.3)	54.9
Impaired distance VA (≤ 0.25)	147	80.0 (11.7)	74.1	52	76.8 (13.7)	61.5	45	77.9 (13.1)	62.2
EQ-5D index score available	6131	53.5 (15.7)	55.9	4024	55.8 (13.9)	56.3	3082	59.4 (11.7)	56.8
15D index score available	6149	53.2 (15.2)	55.7	4212	56.3 (13.8)	56.2	3460	59.8 (11.6)	56.1
BDI total score available	6297	52.7 (14.9)	55.0	4300	56.1 (13.8)	56.0	3562	59.6 (11.5)	55.7
GHQ-12 total score available	6530	53.2 (15.3)	55.1	4445	56.2 (14.0)	55.8	3685	59.8 (11.7)	55.7

The 11-year follow-up group includes the individuals who participated in both years (aged 30 years or over) and the eye disease status of these individuals in 2011

RD retinal degeneration, *SD* standard deviation, *VA* visual acuity

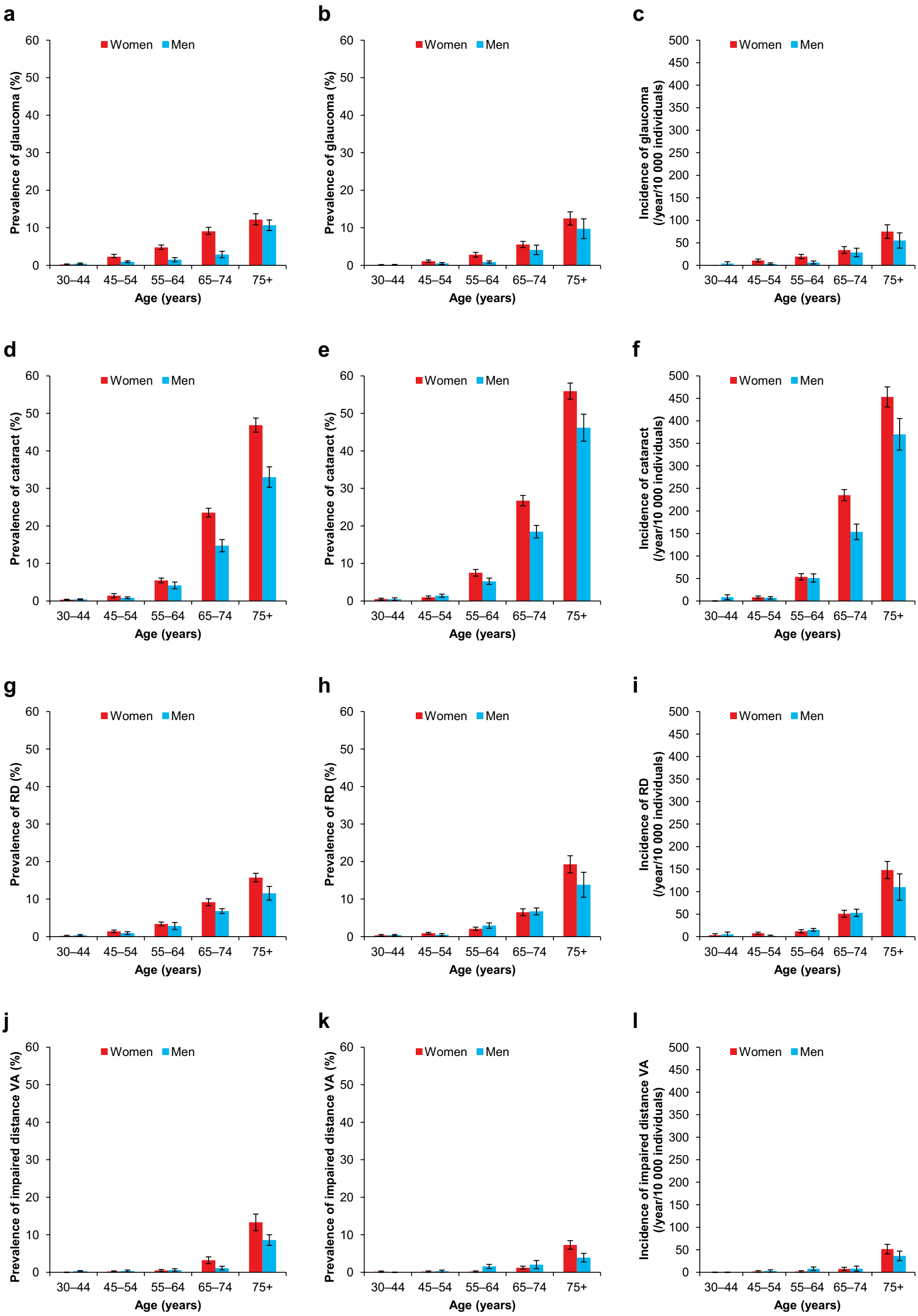
Cross-sectional impact of eye diseases on health-related quality of life, mental health, and visual acuity

EQ-5D and 15D index scores were lower ($p < 0.0001$) in individuals with eye disease or visual impairment compared to those with no eye disease or with good distance VA in both time points, indicating lower HRQoL in eye disease patients and visually impaired (Fig. 3). This difference was also clinically meaningful in both time points. However, the mean values of these scores were higher in 2011 than in 2000 in all eye disease groups ($p < 0.01$) and individuals with visual impairment ($p < 0.05$). Individuals with no eye diseases and those with good distance VA had better HRQoL in 2011 only according to 15D score ($p = 0.0001$ and $p = 0.036$, respectively). Moreover, the improvement of mean HRQoL seen in all eye disease groups and those with visual impairment was clinically meaningful between the time points, except for glaucoma with EQ-5D.

Table 2 Estimated prevalence and incidence with 95% confidence intervals (CIs) of eye diseases and visual impairment in the Finnish population aged 30 years or over in 2000 and 2011

	2000		2011		Incidence 2000–2011	
	N (95% CI)	Prevalence % (95% CI)	*N* (95% CI)	Prevalence % (95% CI)	*N* (95% CI)	*N*/year/10,000 individuals (95% CI)
Glaucoma	100,517 (76,226–124,808)	3.10 (2.95–3.26)	83,453 (64,288–102,618)	2.70 (2.47–2.93)	52,026 (40,359–63,693)	22 (20–23)
Cataract, all	262,927 (200,002–325,852)	8.11 (7.76–8.48)	353,082 (270,532–435,632)	11.41 (10.88–11.94)	257,658 (196,158–319,158)	109 (104–114)
Cataract, unoperated	107,955 (79,476–136,434)	3.50 (3.23–3.77)	140,120 (108,073–172,167)	4.86 (4.60–5.12)	122,239 (93,419–151,059)	55 (52–59)
RD	111,652 (87,115–136,189)	3.45 (3.29–3.61)	118,285 (88,207–148,363)	3.83 (3.46–4.20)	83,843 (61,808–105,878)	35 (31–38)
Impaired distance VA (≤ 0.25)	48,405 (34,479–62,331)	1.58 (1.40–1.76)	31,275 (23,799–38,751)	1.27 (1.13–1.41)	21,134 (15,506–26,762)	10 (8–12)

RD retinal degeneration, *VA* visual acuity


a
b
c
d
e
f
g
h
i
j
k
l
Women
Men
Prevalence of glaucoma (%)
Incidence of glaucoma (/year/10 000 individuals)
Prevalence of cataract (%)
Incidence of cataract (/year/10 000 individuals)
Prevalence of RD (%)
Incidence of RD (/year/10 000 individuals)
Prevalence of impaired distance VA (%)
Incidence of impaired distance VA (/year/10 000 individuals)
30–44
45–54
55–64
65–74
75+
Age (years)

◂**Fig. 2** Prevalence of glaucoma, cataract, retinal degeneration (RD), and impaired distance visual acuity (VA; ≤ 0.25) in 2000 and 2011, and their incidence 2000–2011 (with 95% confidence intervals) in the Finnish population aged 30 years or over by gender and age. Prevalence of glaucoma in 2000 (**a**) and 2011 (**b**), and incidence 2000–2011 (**c**); prevalence of cataract in 2000 (**d**) and 2011 (**e**), and incidence 2000–2011 (**f**); prevalence of RD in 2000 (**g**) and 2011 (**h**), and incidence 2000–2011 (**i**); prevalence of visual impairment in 2000 (**j**) and 2011 (**k**), and incidence 2000–2011 (**l**)

All eye disease groups and visually impaired had worse ($p < 0.0001$) BDI-21 total scores compared to individuals with no eye diseases or those with good distance VA (Fig. 3). Similar difference was found for BDI-13 total scores in all eye disease groups ($p < 0.0001$) and visually impaired ($p = 0.002$). Because the scales of the BDI questionnaires between the time points were not comparable, the mean change between time points was not evaluated.

The effect of various eye diseases on GHQ-12 varied: it was most severe in RD ($p < 0.0001$ in both time points) and least severe in glaucoma ($p = 0.037$, only in 2011). Only individuals with RD ($p = 0.004$) and those with no eye disease or with good distance VA ($p < 0.0001$) showed better GHQ-12 scores in 2011 than in 2000. All eye disease groups had worse ($p < 0.0001$) distance VA compared to those with no eye diseases in both time points. All groups showed better mean distance VA in 2011 than in 2000. Overall, RD was associated with lowest scores in all these parameters compared to other eye diseases in 2000, but in 2011 this difference was significant only in EQ-5D ($p = 0.010$) and distance VA ($p < 0.0001$). However, visual impairment showed the highest impact on these parameters compared to all eye diseases in both time points, excluding BDI-21 and BDI-13, in which no significant difference was found between eye diseases and visual impairment.

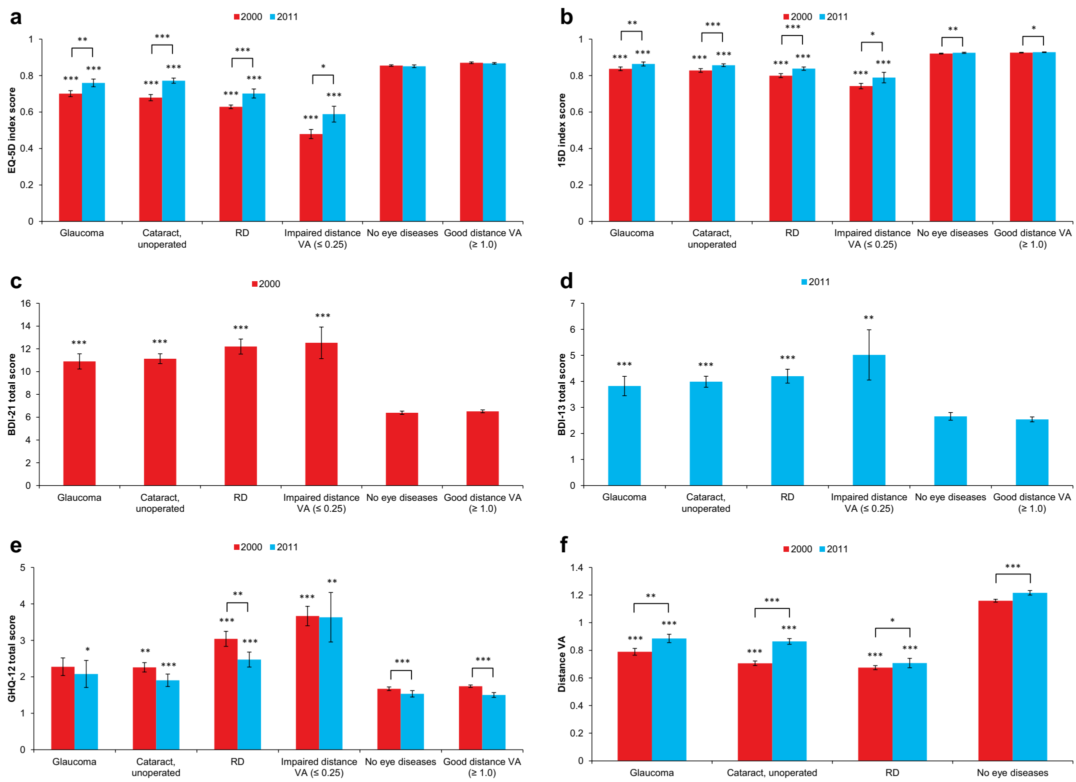


Fig. 3 Mean values (with standard error bars) of health-related quality of life index scores (**a**, **b**), mental health total scores (**c**–**e**), and distance visual acuity (VA; **f**) in both time points. When calculating statistical significance (Mann–Whitney U test), eye disease groups were tested against individuals with no eye diseases, and individuals with impaired distance VA were tested against those with good distance VA within the same year. In addition, mean values were compared between time points in each group. *RD* retinal degeneration. *Denotes statistical significance with $p < 0.05$. **Denotes statistical significance with $p < 0.01$. ***Denotes statistical significance with $p < 0.0001$

Table 3 Adjusted odds ratios (ORs) of EQ-5D dimensions, five most affected 15D dimensions, and BDI and GHQ-12 total scores indicative of depression or psychological distress compared to those with no eye diseases or with good distance visual acuity (VA)

	EQ-5D dimensions (95% CI)					Five most affected 15D dimensions (95% CI)					Mental health (95% CI)	
	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression	Vision	Usual activities	Mobility	Vitality	Depression	BDI-21 ≥10 in 2000, BDI-13 ≥ 5 in 2011	GHQ− 12 > 3
2000												
Glaucoma	1.44 (0.92–2.28)	0.99 (0.71–1.40)	**1.61*** **(1.16–2.24)**	1.17 (0.95–1.45)	1.19 (0.71–2.02)	**2.25**** **(1.64–3.09)**	**1.71*** **(1.16–2.51)**	1.61 (1.00–2.58)	1.20 (0.80–1.78)	1.37 (1.01–1.86)	1.40 (1.03–1.91)	1.08 (0.78–1.50)
Cataract, unoperated	1.11 (0.78–1.59)	0.76 (0.59–0.96)	1.11 (0.84–1.48)	1.36 (0.94–1.96)	1.06 (0.70–1.61)	**2.38**** **(1.57–3.60)**	1.19 (0.81–1.76)	1.25 (0.89–1.75)	**1.46*** **(1.14–1.88)**	0.98 (0.69–1.41)	**1.60*** **(1.15–2.24)**	0.88 (0.73–1.07)
RD	**2.23**** **(1.60–3.09)**	1.13 (0.87–1.45)	**1.81**** **(1.38–2.39)**	**2.51**** **(1.65–3.83)**	**1.62*** **(1.12–2.34)**	**4.45***** **(3.35–5.91)**	**2.45**** **(1.67–3.57)**	**1.83**** **(1.30–2.56)**	**2.23**** **(1.55–3.20)**	**1.70*** **(1.25–2.30)**	**2.00**** **(1.56–2.57)**	**1.63**** **(1.26–2.11)**
Impaired distance VA (≤ 0.25)	**2.70**** **(1.60–4.55)**	**6.54**** **(4.05–10.6)**	**8.44**** **(4.90–14.5)**	1.11 (0.66–1.90)	**3.72**** **(1.85–7.48)**	**22.21***** **(14.6–33.8)**	**2.65*** **(1.37–5.14)**	**2.77**** **(1.99–3.86)**	**2.51**** **(1.51–4.17)**	1.84 (1.06–3.20)	1.49 (0.83–2.71)	**2.90**** **(2.18–3.86)**
2011												
Glaucoma	**1.53*** **(1.12–2.07)**	1.19 (0.74–1.89)	1.11 (0.60–2.05)	1.07 (0.68–1.68)	0.77 (0.41–1.42)	1.86 (0.94–3.68)	**1.84*** **(1.17–2.89)**	1.30 (1.00–1.69)	**1.62*** **(1.09–2.42)**	1.14 (0.88–1.45)	1.35 (0.86–2.11)	1.24 (0.69–2.23)
Cataract, unoperated	1.25 (0.91–1.71)	0.56 (0.34–0.94)	0.75 (0.52–1.10)	0.92 (0.61–1.39)	0.58 (0.31–1.09)	**2.30**** **(1.54–3.43)**	**1.53*** **(1.12–2.10)**	**1.51*** **(1.07–2.12)**	0.95 (0.67–1.37)	1.47 (0.98–2.19)	1.23 (0.90–1.69)	0.90 (0.57–1.43)
RD	1.19 (0.89–1.60)	1.22 (0.73–2.04)	1.39 (0.96–2.01)	1.33 (0.89–1.98)	0.96 (0.57–1.61)	**3.55***** **(2.71–4.66)**	**1.89*** **(1.31–2.71)**	1.11 (0.69–1.77)	**1.48*** **(1.13–1.94)**	1.09 (0.79–1.49)	1.29 (0.77–2.16)	1.49 (1.04–2.12)
Impaired distance VA (≤ 0.25)	**2.24*** **(1.15–4.37)**	**6.13**** **(3.23–11.6)**	**4.64**** **(2.18–9.88)**	0.90 (0.44–1.81)	**2.91*** **(1.44–5.88)**	**44.51**** **(16.9–117.1)**	**3.28*** **(1.53–7.04)**	2.04 (0.86–4.84)	2.31 (0.97–5.52)	1.38 (0.78–2.43)	1.65 (0.87–2.51)	**3.23**** **(1.88–5.54)**

The ORs and 95% confidence intervals (CIs) were estimated through logistic regression analysis adjusted for age, gender, and co-morbidities. Bolded values denote statistically significant ($p < 0.05$) ORs compared to reference group. Reference group (OR = 1.0) for individuals with eye diseases included those with no eye diseases, and reference group for individuals with impaired distance VA included those with good distance vision (VA ≥ 1.0). *RD* retinal degeneration

*Denotes statistical significance with $p < 0.05$

**Denotes statistical significance with $p < 0.01$

***Denotes statistical significance with $p < 0.0001$

Table 4 Multivariable linear regression analysis examining the impact of eye diseases, visual impairment, age, gender, and co-morbidities on EQ-5D and 15D index values, and GHQ-12 and BDI-21 total scores in 2000

	Change in EQ-5D ($n=5643$)		Change in 15D ($n=5777$)		Change in GHQ-12 ($n=6064$)		Change in BDI-21 ($n=5886$)	
	B coefficients	Beta coefficients	B coefficients	Beta coefficients	B coefficients	Beta coefficients	B coefficients	Beta coefficients
Constant	1.062***		1.035***		1.605*		2.437**	
Age	− 0.003***	− 0.213***	− 0.002***	− 0.259***	− 0.008	− 0.039	0.058**	0.115**
Male gender	0.012**	0.031**	− 0.0004	− 0.002	− 0.148	− 0.025	− 1.23***	− 0.087***
Glaucoma	− 0.007	− 0.005	− 0.008	− 0.013	− 0.021	− 0.001	0.428	0.009
Cataract, unoperated	− 0.013	− 0.012	**− 0.017**	− 0.034	− 0.135	− 0.009	0.844	0.022
RD	− 0.047*	− 0.038*	**− 0.033***	− 0.057*	0.654*	0.036*	1.713*	0.038*
Impaired distance VA (≤ 0.25)	**− 0.210*****	− 0.125***	**− 0.083****	− 0.099**	1.464*	0.055*	1.091	0.016
Heart disease	− 0.041**	− 0.069**	**− 0.032*****	− 0.112***	0.256*	0.029*	0.804*	0.037*
Pulmonary disease	− 0.022*	− 0.044*	**− 0.024****	− 0.103**	0.305*	0.042*	1.081**	0.062**
Vascular disease	− 0.025*	− 0.047*	− 0.007	− 0.028	0.269*	0.035*	0.476	0.025
Musculoskeletal condition	− 0.059***	− 0.148***	**− 0.017****	− 0.093**	0.361*	0.062*	1.167**	0.083**
Hypertension	− 0.011*	− 0.024*	− 0.007*	− 0.036*	0.145	0.023	0.488	0.032
Diabetes	**− 0.073****	− 0.081**	**− 0.033****	− 0.077**	0.327	0.025	1.577*	0.049*
Psychiatric disorder	**− 0.129*****	− 0.219***	**− 0.068*****	− 0.247***	2.118***	0.246***	6.635***	0.319***
Parkinson's disease	**− 0.195***	− 0.059*	**− 0.072****	− 0.041**	2.153*	0.044*	3.194	0.026
Cancer	− 0.013	− 0.013	**− 0.018**	− 0.042	0.352	0.025	1.240	0.037
R^2	0.283***	0.283***	0.359***	0.359***	0.088***	0.088***	0.200***	0.200***
Adjusted R^2	0.281***	0.281***	0.358***	0.358***	0.086***	0.086***	0.198***	0.198***

The unstandardized B coefficients show the magnitude of the impact on health-related quality of life and mental health, while the standardized Beta coefficients allow the comparison of the explanatory variables with each other. Clinically meaningful B coefficients are bolded (≥ 0.07 for EQ-5D and ≥ 0.015 for 15D). *RD* retinal degeneration, *VA* visual acuity

*Denotes statistical significance with $p < 0.05$

**Denotes statistical significance with $p < 0.01$

***Denotes statistical significance with $p < 0.0001$

Cross-sectional impact of eye diseases on the individual dimensions of health-related quality of life

The individual HRQoL dimensions were evaluated using ORs by comparing those with difficulties to those without difficulties. In addition, mental health was assessed by using the cut-off points for GHQ-12 and BDI total scores. For HRQoL, the most affected dimensions in individuals with eye disease and those with visual impairment were usual activities and mobility in EQ-5D, and vision, usual activities, and vitality in 15D (Table 3). There was variation in how the dimensions were affected between the eye diseases: among those with RD the majority of the individual dimensions were affected in both EQ-5D and 15D, whereas among those with unoperated cataract none of the EQ-5D dimensions differed from those with no eye diseases, even though the index score was significantly lower. Pain/discomfort and anxiety/depression in EQ-5D was only affected in those with RD in 2000, and anxiety/depression in EQ-5D was affected in visually impaired in both time points. The vision dimension in 15D was most affected in all eye diseases and visually impaired. Individuals with visual impairment showed high odds for having difficulties, including eight-fold increase in usual activities (EQ-5D) and sixfold increase in self-care (EQ-5D) in 2000 compared to individuals with good distance VA. Self-care (EQ-5D) was affected in individuals with visual impairment but not in those with eye disease.

Table 5 Multivariable linear regression analysis examining the impact of eye diseases, visual impairment, age, gender, and co-morbidities on EQ-5D and 15D index values, and GHQ-12 and BDI-13 total scores in 2011

	Change in EQ-5D ($n=3763$)		Change in 15D ($n=3936$)		Change in GHQ-12 ($n=4148$)		Change in BDI-13 ($n=4018$)	
	B coefficients	Beta coefficients	B coefficients	Beta coefficients	B coefficients	Beta coefficients	B coefficients	Beta coefficients
Constant	1.009***		1.002***		1.932***		1.356*	
Age	−0.001**	−0.112**	−0.0008**	−0.134**	−0.020**	−0.098**	0.007	0.022
Male gender	0.009	0.025	0.0007	0.004	−0.155	−0.029	−0.303*	−0.039*
Glaucoma	−0.024	−0.019	−0.005	−0.010	0.377	0.020	0.648	0.024
Cataract, unoperated	0.002	0.003	**−0.023****	−0.065**	0.043	0.004	0.410	0.024
RD	−0.004	−0.004	−0.009	−0.017	0.081	0.005	−0.426	−0.017
Impaired distance VA (≤0.25)	**−0.126***	−0.058*	**−0.091***	−0.080*	1.066	0.032	2.307	0.044
Heart disease	−0.042**	−0.082**	**−0.027*****	−0.115***	0.676**	0.087**	1.056**	0.094**
Pulmonary disease	−0.040**	−0.078**	**−0.026****	−0.112**	0.267	0.035	0.310	0.028
Vascular disease	−0.012	−0.022	−0.004	−0.017	0.129	0.017	−0.083	−0.007
Musculoskeletal condition	−0.068***	−0.194***	**−0.018****	−0.112**	0.373*	0.070*	0.449*	0.058*
Hypertension	−0.039**	−0.100**	**−0.016****	−0.090**	0.321*	0.055*	0.362*	0.043*
Diabetes	−0.040	−0.060	**−0.026***	−0.086*	0.481	0.048	0.344	0.023
Psychiatric disorder	**−0.127*****	−0.226***	**−0.074*****	−0.286***	2.425***	0.285***	4.992***	0.406***
Parkinson's disease	**−0.216**	−0.069	**−0.106***	−0.066*	1.473	0.034	3.209	0.045
Cancer	0.006	0.008	−0.005	−0.015	0.097	0.009	−0.050	−0.003
R^2	0.187***	0.187***	0.250***	0.250***	0.114***	0.114***	0.188***	0.188***
Adjusted R^2	0.183***	0.183***	0.247***	0.247***	0.111***	0.111***	0.185***	0.185***

The unstandardized B coefficients show the magnitude of the impact on health-related quality of life and mental health, while the standardized Beta coefficients allow the comparison of the explanatory variables with each other. Clinically meaningful B coefficients are bolded (≥0.07 for EQ-5D and ≥0.015 for 15D). *RD* retinal degeneration, *VA* visual acuity

*Denotes statistical significance with $p<0.05$

**Denotes statistical significance with $p<0.01$

***Denotes statistical significance with $p<0.0001$

For mental health, depression in 2000 (BDI-21 ≥ 10) was more prevalent among individuals with RD and unoperated cataract compared to those with no eye diseases. In 2011, BDI-13 was not significantly affected in any of the groups. Psychological distress (GHQ-12 > 3) was found more prevalent among individuals with RD in 2000 and visual impairment in both time points.

Cross-sectional analyses corrected with age, gender, and co-morbidities

The effect of the awareness of the eye diseases on the HRQoL and mental health was evaluated using linear regression analyses, including age, gender, and co-morbidities (Tables 4 and 5). After these corrections, the impact of impaired distance VA on HRQoL was more significant than any of the eye diseases. Only RD showed significant impact on 15D, GHQ-12, and BDI-21 of all eye diseases in 2000, whereas in 2011 only unoperated cataract showed significant impact on 15D of all eye diseases. In addition to visual impairment, psychiatric disorder and Parkinson's disease had high impact on HRQoL. However, the overall effect and/or association of all these diseases and visual impairment on HRQoL and mental health were lower in 2011 than in 2000. No significant change was observed in the outcome when only statistically significant ($p<0.05$) factors were included as explanatory variables in stepwise-insertion analysis.

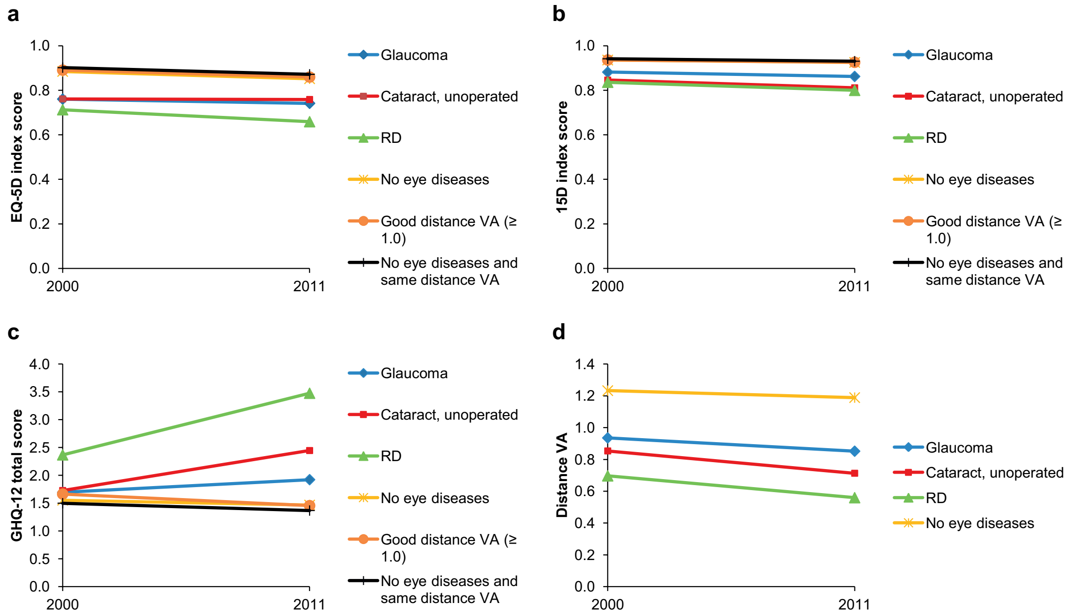


Fig. 4 Change in health-related quality of life (**a**, **b**), psychological distress (**c**), and distance visual acuity (VA; d) in individuals with same eye status in both time points. Low scores for EQ-5D and 15D indicate worse quality of life and high score for GHQ-12 worse mental health. For reference, a group of individuals with no eye diseases and same distance VA in both time points was included. *RD* retinal degeneration

Multicollinearity ranged from 1.007 to 1.520 denoting no or very little multicollinearity.

Longitudinal impact of eye diseases on health-related quality of life and mental health

The longitudinal effect of newly-diagnosed eye diseases on the changes in EQ-5D, 15D, and GHQ-12 during the follow-up was evaluated using linear regression, which also included age, gender, incident co-morbidities, and baseline scores (see table in Online Resource 1). BDI was not included as the different scales of the questionnaires were not fully comparable between the surveys. Incident visual impairment and Parkinson's disease were not included as their number was low ($n < 50$).

Newly-diagnosed eye diseases had no direct independent association in the change of the dependent variables, except for unoperated cataract which was associated with a small decrease in 15D index score. The highest impact on EQ-5D, 15D, and GHQ-12 change both clinically and statistically was observed in newly diagnosed psychiatric disorder and baseline index/total score. No significant change was observed in the outcome when only statistically significant ($p < 0.05$) factors were included as explanatory variables in stepwise-insertion analysis. Multicollinearity ranged from 1.007 to 1.208, denoting no or very little multicollinearity.

Furthermore, the longitudinal setting was utilized when observing the change in the HRQoL, GHQ-12 scores, and distance VA in individuals who had same eye status in both time points (Fig. 4). Individuals with visual impairment in both time points were not included as their number was low ($n = 8$). All groups, including those with no eye diseases and with good distance VA, showed a small decline in the HRQoL values, with clinically meaningful decline in 15D values in all eye disease groups. All eye disease groups showed worsening in the GHQ-12 total score and all groups showed decrease in the distance VA. The impact of aging was visualized (Fig. 5), which shows that the decline in HRQoL and distance VA, and worsening in GHQ-12 is associated with aging.

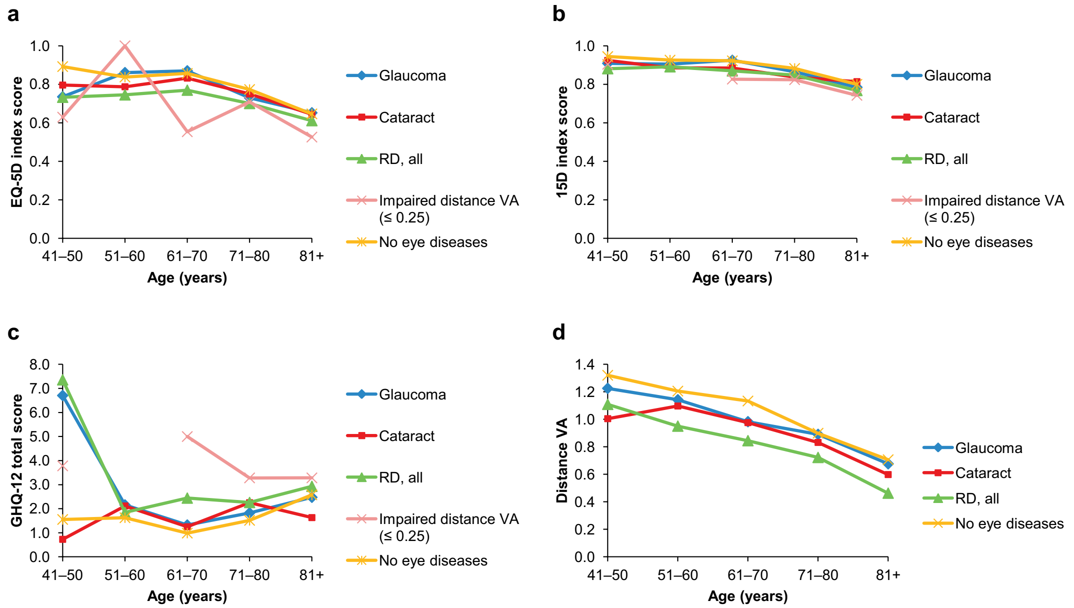


Fig. 5 Relation of age to health-related quality of life (**a**, **b**), psychological distress (**c**), and distance visual acuity (VA; **d**) in individuals who had participated in both time points by age and 2011 eye status. Low scores for EQ-5D and 15D indicate worse quality of life and high score for GHQ-12 worse mental health. Few data points for young individuals with impaired VA are missing as the number of these individuals was low. *RD* retinal degeneration

Association between health-related quality of life, mental health, and visual acuity

Figures 6 and 7 show the overall shape of association between HRQoL, mental health, and distance VA in both time points. The decrease in the HRQoL and the worsening in mental health are associated with decreasing distance VA in all groups, including those with no known eye diseases.

Discussion

Individuals with eye diseases and visual impairment have lower HRQoL, VA, and worsened mental health compared to individuals without eye diseases and those with good vision. Of all the individual dimensions of the used generic HRQoL instruments, vision, usual activities, vitality, and mobility were most affected. Previous publications have shown that visually impaired people express declined generic HRQoL and vision-related QoL and have more difficulties in the activities of daily living [40–43]. Because vision was significantly affected in all eye diseases and the difficulties in usual activities, vitality, and mobility were prevalent in individuals with visual impairment, the difficulties in these dimensions may be associated with the decreased VA. The worsened mental health in eye diseases may also be associated with the declined VA, as Taipale and colleagues previously showed with identical data set that BDI and VA seem to have a linear connection [8]. Furthermore, increased depression and anxiety have been previously associated with visual impairment, particularly among older adults [42–44]. Li and colleagues reported an association between age-related eye diseases, visual impairment, and declined generic HRQoL similar to our results, although they did not find association with psychological distress [45]. However, they only included individuals aged 65 years or over, and therefore, the results may not be comparable.

The average HRQoL improved between the cross-sectional studies in all eye disease groups and visually impaired individuals, including a clinically meaningful increase between the time points. Individuals without known eye diseases or with good vision showed minor, although clinically non-meaningful, improvement in HRQoL only according to 15D. When evaluating mental health, only those with RD, as well as individuals without eye diseases or with good vision showed improvement between time points according

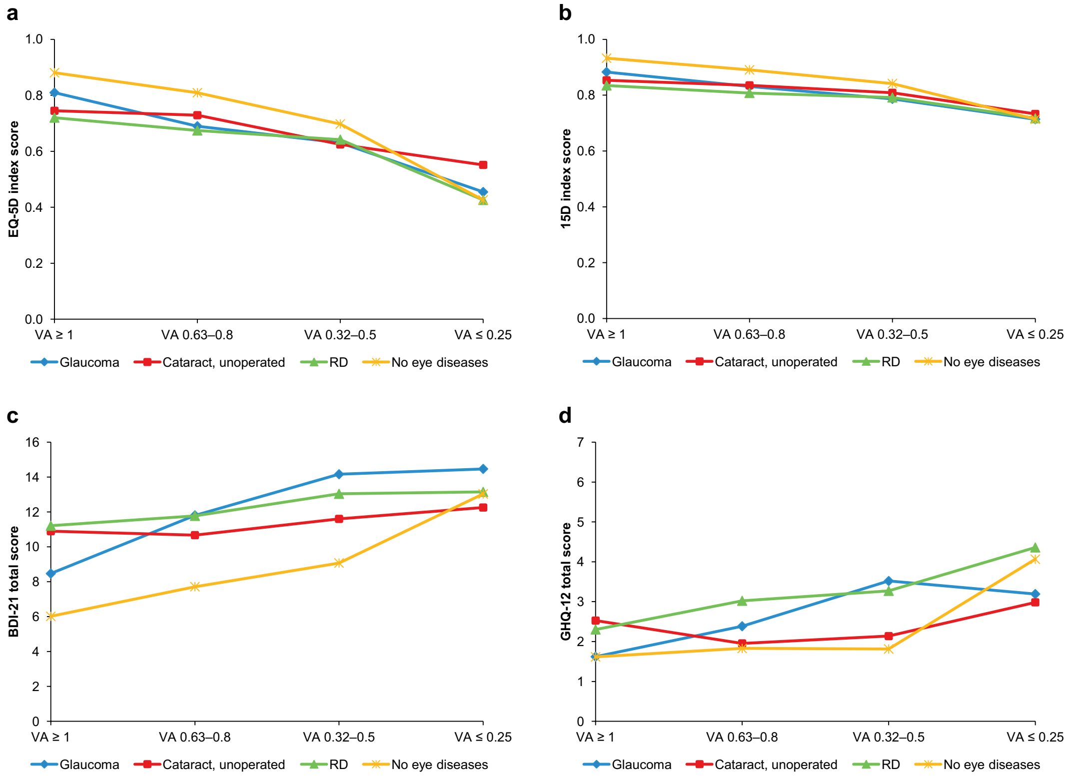


Fig. 6 Mean values of health-related quality of life (**a**, **b**) and mental health (**c**, **d**) compared to distance visual acuity (VA) in 2000. *RD* retinal degeneration

to GHQ-12. These results suggest that the effect of the eye diseases and visual impairment on these factors had decreased between the time points and that the well-being of eye disease patients and visually impaired individuals has increased in 11 years. Similar improvement in the overall well-being in Finland between 2000 and 2011 has been reported previously [18]. This better well-being of patients suffering from eye disease or visual impairment may be due to better availability of health services, aids, and treatment.

When the cross-sectional analyses were corrected with age, gender, and co-morbidities, RD was associated with a small decline in HRQoL and mental health in 2000, and unoperated cataract with HRQoL in 2011 only according to 15D. However, visual impairment showed more significantly declining effect on HRQoL in both time points, indicating that the impaired vision may have a stronger impact on HRQoL than the awareness of the eye disease itself. Similar results were reported by Knudtson et al. [46], who found that decreased visual function appeared to have a significant effect on the decline in QoL irrespective of pathologic reasons, such as age-related eye diseases. In our study, this association of the eye diseases and visual impairment on HRQoL and mental health was lower in 2011 than in 2000. In longitudinal setting, newly diagnosed eye diseases did not appear to have a direct effect on HRQoL or mental health. Similar to present study, Nutheti et al. reported that the effect of cataract and retinal diseases on generic HRQoL was associated with VA, whereas the effect of glaucoma and corneal diseases were independent of VA [9]. This difference in glaucoma could be explained by the many differences in these two populations regarding age, health, and social care systems.

In the longitudinal setting, individuals with or without eye diseases in both time points showed small decline in their HRQoL in contrast to the improvement found in the cross-sectional setting. This decline was most probably related to the fact that the subjects were 11 years older at the end of follow up. Furthermore, all eye disease groups, visually impaired, and individuals with no eye diseases

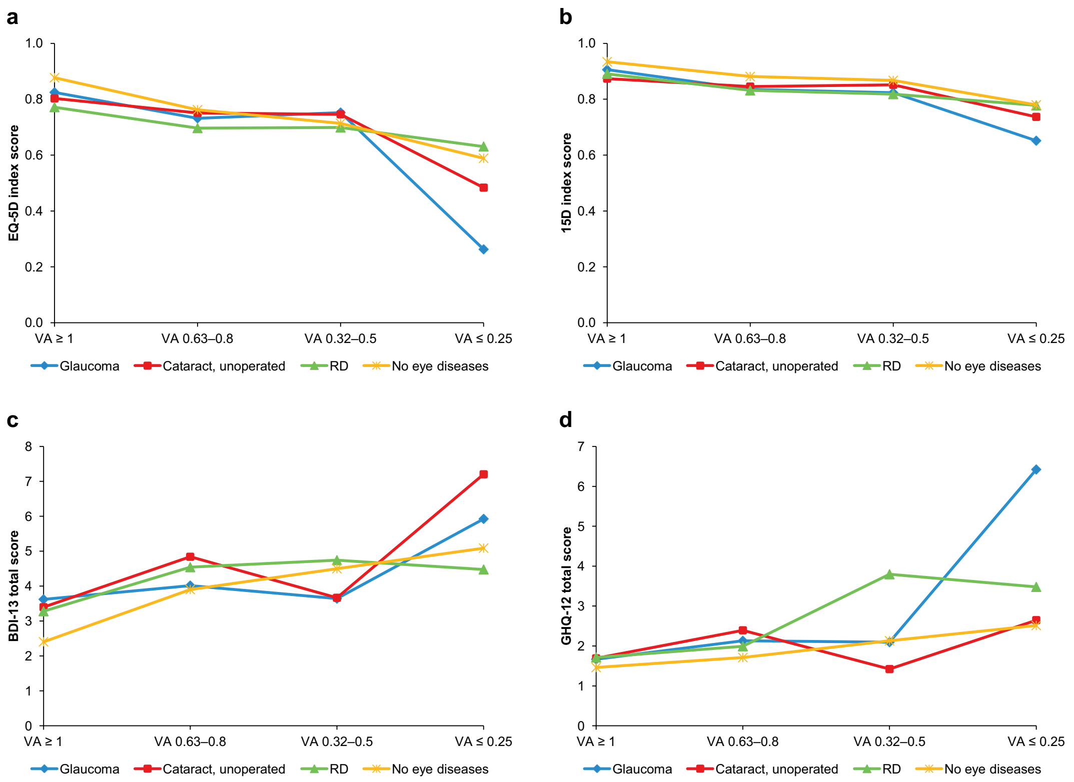


Fig. 7 Mean values of health-related quality of life (**a**, **b**) and mental health (**c**, **d**) compared to distance visual acuity (VA) in 2011. *RD* retinal degeneration

showed negative association between HRQoL, impaired distance VA, and age. Visual impairment has been previously associated with aging [47], and in our study, the prevalence and incidence of impaired vision as well as vision-affecting eye diseases increased with age.

The strengths of this study include a large study sample representing Finnish adult population aged 30 years or over in two cross-sectional surveys and a longitudinal study with a relatively long follow-up of 11 years. As the study population and design were widely collected and comprehensive, the impact of confounding factors was low. Furthermore, our data did not consist of specific patient groups collected from health-care units, which allows better generalization of the results. High proportion of the individuals participated in both surveys, and the overall adherence to present study can be considered to be good, as mentioned previously by Taipale et al. who used identical data set [8]. In addition, loss to follow-up was compensated by applying calibrated weighting scheme [18]. As a valid assessment of HRQoL requires reports directly from patients rather than physicians or other parties, we used generic HRQoL questionnaires in both time points. We did not use vision-related QoL instruments for better comparability and generalization of the results.

There are also potential limitations in our study. First, self-reported instruments, EQ-5D in particular, assess a limited number of dimensions and can be influenced by the subjective nature of QoL [14]. Furthermore, all eye diseases were self-reported, physician-made diagnoses, but the diagnoses were not confirmed by physicians in the study. We were also unable to include visual impairment caused by diminishing visual field, as well as the examination of contrast sensitivity. The number of visually impaired in the longitudinal analyses were rather low. The variation in the age of the participants was large, but we corrected this by adjusting the age in the analyses. The questionnaire did not include data whether cataract patients had uni- or bilateral cataract. However, in most cases, cataract is bilateral although often an asymmetric disease [48]. In those cases, bilateral VA is determined by the VA of the better eye. We also had to combine comorbidities into rather large groups, as new diagnoses during the 11-year follow-up are scarce for many specific diseases. In the longitudinal setting, the right-censoring may have an effect on the results, although this has been tried to minimize by the weighting scheme. Finally, as the study population was predominantly Finnish, the results may not be applicable to other countries and ethnicities, although our use of UK time-trade-off weights for EQ-5D may improve the comparability.

In the future analyses, more large, population-based studies are required to validate the generalization of our results into other settings. Furthermore, additional longitudinal studies with over 10 years of follow-up are needed to ascertain the longitudinal effect of the eye diseases and declining VA on QoL.

In conclusion, our results show that common eye diseases have a declining effect on HRQoL, mental health, and distance VA. However, the decline in HRQoL is not directly affected by the awareness of the eye disease but more likely by the declined VA associated with these diseases. The overall association of these diseases with HRQoL and mental health has decreased between years 2000 and 2011. Furthermore, during the 11-year follow-up newly diagnosed eye diseases showed minor effect on these parameters. This has important clinical implications. As the number of people affected by vision-threatening eye diseases is increasing due to the aging and growth of older population, it is important to prevent the increase of visual impairment caused by these diseases. Our results suggest that the spreading of awareness of the potential hazards of vision-threatening diseases possess very little effect on these parameters compared to the benefits of early diagnosis of these diseases, and therefore should be strengthened to prevent the declining effect of visual impairment on quality of life and increasing healthcare costs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11136-021-02817-1.

Author contributions Research design was by SVPK, PRJS, HAR, HMTU, and MUIO. HMTU and MUIO managed the project. Data acquisition was by SVPK, PRJS, and HAR. Data was analyzed by PKMP, JEN, and HAR. All authors contributed to the interpretation of data. PKMP and HMTU prepared the first draft and finalized the manuscript based on comments from all other authors.

Funding This work was supported by Tampereen seudun Näkövammaisten tukisäätiö s.r, Tampere; Sokeain Ystävät r.y, Helsinki; and Elsemay Björn Fund, Helsinki. Funding sources did not influence the study design, data collection, analysis, interpretation, or writing the publication. The corresponding author had full access to all the data in the study and had responsibility for the decision to submit the paper for publication.

Data availability Full study protocol, contact details, publications, and the process for collaborating and data requests can be found on the website (thl.fi/health2000).

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the Health 2000 and 2011 studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethical approval process details are discussed in previous publications [19, 20].

Informed consent Participants received an information letter regarding the study beforehand. Two informed consents were obtained in the beginning of the study for each individual: one for the health interview and the other for the health examinations [19]. Participants were provided appropriate information concerning the study and asked to sign informed consents again before the follow-up examination in 2011 [20].

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PUBLICATION
II

Improving health-related quality of life and mental health in glaucoma during 11 years and their association with vision loss and treatment of the disease

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Acta Ophthalmologica 2022;100(1):e221–e232
doi: 10.1111/aos.14883

Acta Ophthalmologica

Acta Ophthalmologica 2022

Improving health-related quality of life in glaucoma during 11 years and its association with vision loss and treatment of the disease

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ABSTRACT.
Purpose: **To evaluate the impact of glaucoma on health-related quality of life (HRQoL) and mental health in the ageing population of Finland.**
Methods: **Altogether 7380 and 5774 Finnish individuals aged 30 years and older with known eye disease status were studied in 2000 and 2011, respectively, in two population-based surveys, including an 11-year follow-up of 4683 participants. Data on HRQoL (EQ-5D-3L, 15D), depression (BDI), psychological distress (GHQ-12) and eye disease diagnoses were obtained from self-reported assessments. Information on glaucoma was complemented with the medication, diagnosis and eye surgery data obtained from the Finnish Health Registries. Distance visual acuity was assessed using the Snellen eye chart test. In logistic regression analyses, data were corrected for age, gender and the most common comorbidities.**
Results: **Glaucoma patients with verified diagnosis (n = 192 in 2000, n = 202 in 2011) and individuals with self-suspected glaucoma (n = 100 in 2000, n = 41 in 2011) showed a significant decrease in their HRQoL. Glaucoma was also associated with worsened overall mental health based on BDI and GHQ-12 results. Visual impairment associated with glaucoma is the major determinant of the reduced HRQoL and mental health. Neither glaucoma medication nor glaucoma surgery affected these parameters. The impact of glaucoma on HRQoL and mental health diminished between 2000 and 2011 in a cross-sectional setting. The newly diagnosed glaucoma during the 11-year follow-up had a minimal effect on them.**
Conclusion: **Glaucoma patients show reduced HRQoL and mental health, which is associated with vision loss regardless of the awareness or treatment of the disease. However, this effect seems to be diminishing over time, and the newly diagnosed glaucoma did not show a significant effect on either HRQoL or mental health.**

Key words: epidemiology – glaucoma – health-related quality of life – impaired vision – mental health – population survey

Acta Ophthalmol. 2022: 100: e221–e232

doi: 10.1111/aos.14883

Introduction

Glaucoma is a chronic disease characterized by the progressive degeneration of retinal ganglion cells (Weinreb et al. 2014). It is the second leading cause of irreversible loss of vision worldwide, affecting more than 60 million individuals in the world, with approximately 16% being bilaterally blind (Forsman et al. 2007; Peters et al. 2013). However, the number may be higher as the disease can remain asymptomatic until a relatively late stage (Weinreb et al. 2014). The pathogenesis of glaucoma is not fully understood. However, the level of intraocular pressure is related to retinal ganglion cell degeneration (Weinreb et al. 2014). At the moment, the only proven method to treat the disease is the reduction of intraocular pressure, usually via ocular hypotensive drugs, laser treatment and surgery (Weinreb et al. 2014). In addition to elevated intraocular pressure, other risk factors for glaucoma include old age, myopia, exfoliation and African ethnicity (Quigley & Broman 2006; Weinreb et al. 2014).

The impact of glaucoma on the quality of life (QoL), mental health and visual acuity (VA) has been previously assessed in many countries through cross-sectional studies. However, most of these studies have utilized vision-related QoL instruments, and therefore, the results may not be generalizable (Freeman et al. 2008;

Medeiros et al. 2015; Jones et al. 2017; Machado et al. 2019). Furthermore, studies that have utilized more generic health-related quality of life (HRQoL) instruments that evaluate physical, psychological and functional well-being, lack longitudinal setting or have a small study population (Wolfram et al. 2013; Jung & Park 2016).

To answer these unmet needs, our aim in this study was to evaluate the impact of glaucoma on generic HRQoL and mental health, and the cross-sectional and longitudinal differences in these parameters in the Finnish adult population during an 11-year follow-up. We utilized two commonly used generic HRQoL-based instruments, EuroQol-5 Dimension (EQ-5D-3L) (Brooks 1996; Dolan 1997) and 15D (Sintonen 1995; Sintonen 2001). Because these instruments have a limited spectrum on mental health, we included Beck Depression Inventory (BDI) (Beck & Beck 1972) and General Health Questionnaire-12 (GHQ-12) (Goldberg 1972; Pevalin 2000) that evaluate depression and psychological distress.

Materials and methods

Study design

We used two nationwide health examination surveys carried out by the Finnish Institute for Health and Welfare. They represent the Finnish adult population at two different time points: the first one was carried out in 2000–2001 and a follow-up in 2011. Both the surveys included home interviews and comprehensive health examinations conducted at a nearby screening centre. If the invited participants did not attend the health examination, an abridged examination was conducted at home or in an institution. The Health 2000 Survey analysed a sample of 9922 adults aged 18 years or over living in mainland Finland. The sample was selected by a stratified two-stage cluster sampling design. The Health 2011 Survey included all living participants of the Health 2000 Survey, who agreed to be contacted and were aged 29 years or over. In addition, a new sample of 1994 young adults aged 18–28 years was also included. More detailed information has been published previously (Aromaa & Koskinen 2004; Koskinen et al. 2012). For the current study, we have only included participants aged 30 years and older. Both the surveys provided a probability-clustered sampling and weighting scheme, which estimates the health statistics that are representative of Finnish adult population aged 30 years and older at the time of sampling (Heistaro 2008; Lundqvist & Mäki-Opas 2016). The sampling scheme also accounts for designed oversampling of people aged 80 years and older in the 2000 survey baseline to correct the low participation rate of elder adults. The unweighted participation rate was 93% in the Health 2000 Survey while in the follow-up it was 73%. Different weights were applied to both the surveys to account for the loss between the two time points (Härkänen et al. 2016).

Both the survey samples were linked to the Social Insurance Institution of Finland (Kela) registers to obtain data on the reimbursement for glaucoma medication (data available from 1965 to 2011) and the number of glaucoma medication prescriptions (data available from 1999 to 2011). We also included data of different glaucoma diagnoses and eye operations obtained from the Care Registers for Social Welfare and Health Care (HILMO). This data included inpatient care (HILMO data, available from 1968 to 2011) and outpatient visits (AvoHILMO data, available from 1997 to 2011).

Assessment of glaucoma status

Both the surveys included an interview with the following questions on eye diseases: 'Has a doctor diagnosed you with one of the following diseases: cataract, glaucoma, retinal degeneration or other visual defect or injury'? The participants who had answered to eye disease questionnaire and/or had register data on glaucoma were included in the 'eye disease status known' group.

Individuals suffering from glaucoma were evaluated using three categories. The first category, 'self-reported glaucoma', included participants who reported having glaucoma in the survey questionnaire. The second category, 'verified glaucoma', included participants that fall into one of these following conditions: (1) were granted special reimbursement for glaucoma medication by Kela; (2) with a high number (>10) of glaucoma medication prescriptions between 1999–2000 (2000 survey) or 1999–2011 (2011 survey); (3) had glaucoma medication prescriptions since 2011 (2011 survey); (4) had a verified glaucoma diagnosis according to the HILMO/AvoHILMO data (International Classification of Diseases diagnosis codes 37500–37520, 37598–37599 for version 8, 3651–3659 for version 9, and H40, H40.1–H40.9 for version 10); or (5) had undergone at least one of the following eye operations according to the HILMO/AvoHILMO data: trabeculectomy and iridectomy, glaucoma shunt operation, non-penetrating glaucoma surgery, other filtering operation and transscleral laser coagulation of ciliary body. These conditions were used as some individuals had glaucoma medication prescriptions only for a short duration, indicating they were suffering from another disease than chronic glaucoma. The third category, 'self-suspected glaucoma', consisted of participants who had self-reported glaucoma but did not belong to the verified glaucoma category. This classification is shown in Table 1. 'Glaucoma negatives' group included individuals with a known eye disease status but did not belong to any of the above mentioned three glaucoma categories. For the analyses, we also separated 'glaucoma medication' group that included all glaucoma patients with glaucoma medication prescriptions, and 'glaucoma operated' group with verified glaucoma patients that had undergone at least one of the listed eye operations or had self-reported glaucoma operation in the survey questionnaire.

Assessment of health-related quality of life

Health-related quality of life (HRQoL) was evaluated using two generic preference-based instruments, a three-level version of EuroQol-5 Dimension (EQ-5D-3L, later referred to as EQ-5D) and 15D. EQ-5D is a self-administrated questionnaire comprising of one question for each of the five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question contains three answers on a scale of 1 (no difficulties) to 3 (extreme difficulties). These scores can then be converted into EQ-5D index scores on a scale between 0 (representing HRQoL equal to being dead) and 1 (representing the best possible HRQoL). We used EQ-5D weighted with UK time trade-off

Table 1. Classification of glaucoma in Health 2000 and 2011 surveys.

	Classification conditions for 2000 survey	Classification conditions for 2011 survey
Glaucoma, self-reported	Reported glaucoma in the questionnaire	Reported glaucoma in the questionnaire
Glaucoma, verified	Granted special reimbursement for glaucoma medication by Kela in 2000 or before OR High number (>10) of glaucoma medication prescriptions between 1999 and 2000 (Kela) OR Verified glaucoma diagnosis between 1968 and 2000 (HILMO/AvoHILMO) OR Undergone eye operation due to glaucoma between 1997 and 2000 (HILMO/AvoHILMO)	Granted special reimbursement for glaucoma medication by Kela in 2011 or before OR High number (>10) of glaucoma medication prescriptions between 1999 and 2011 (Kela) OR Verified glaucoma diagnosis between 1968 and 2011 (HILMO/AvoHILMO) OR Undergone eye operation due to glaucoma between 1997 and 2011 (HILMO/AvoHILMO) OR Glaucoma medication prescriptions since 2011
Glaucoma, self-suspected	Self-reported glaucoma, but not included in the verified glaucoma group	Self-reported glaucoma, but not included in the verified glaucoma group

HILMO/AvoHILMO, Care Registers for Social Welfare and Health Care; Kela, Social Insurance Institution of Finland.

weights on a scale between −0.59 (representing HRQoL equal to being dead) and 1 (representing the best possible HRQoL) to improve comparability with other populations (Dolan 1997). A difference of ≥0.07 is considered to be clinically meaningful (Walters & Brazier 2005). 15D is a Finnish preference-based measure of HRQoL consisting of 15 dimensions/questions – mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. Each question contains five answer options on a scale of 1 (no difficulties) to 5 (extreme difficulties). A single index score is obtained by weighting the scores with population-based preference weights (Sintonen 2001). We used Finnish preference weights with a scale between 0 (representing HRQoL equal to being dead) and 1 (representing the best possible HRQoL). A difference of ≥0.015 is considered to be clinically meaningful (Alanne et al. 2015).

Assessment of mental health

Both the surveys included two self-reported instruments that evaluate mental health, Beck Depression Inventory (BDI) and General Health Questionnaire-12 (GHQ-12). Beck Depression Inventory (BDI) is used to assess depression (Beck & Beck 1972) and GHQ-12 evaluates 12 dimensions of psychological distress, including depression, anxiety, social interaction and confidence (Goldberg 1972; Pevalin 2000). In the 2000 survey, a 21-item BDI-21 was used, whereas in the 2011 survey a shorter version, a 13-item BDI-13 was used (Aalto et al. 2012). The answers for GHQ-12 were dichotomized according to whether difficulties were presented or not (0 = no, 1 = yes). A total score was calculated for all the three instruments on a scale of 0 to 63 for BDI-21, 0 to 39 for BDI-13 and 0 to 12 for GHQ-12. Higher score points indicate major depression or psychological distress. Total scores of ≥10 for BDI-21, ≥5 for BDI-13 and >3 for GHQ-12 are used as cut-off points indicative of depression or psychological distress (Beck et al. 1988; Aromaa & Koskinen 2004; Koskinen et al. 2012).

Visual acuity tests

Both the surveys included a habitual distance VA measurement by a study nurse binocularly at 4 m, with current vision correction. Illumination was set to ≥350 lux on the modified logMAR letter chart published by Precision Vision (Ferris et al. 1982; Heistaro 2008; Lundqvist & Mäki-Opas 2016). All VA values were presented as decimal (Snellen) equivalents. Low VA values that could not have been determined were reported as 0.01. We used the following classifications: VA ≥ 1.0 (good vision), VA 0.63–0.8 (adequate vision), VA 0.32–0.5 (weak vision), VA 0.125–0.25 (impaired vision), and VA < 0.1 (severe vision loss or blindness) (World Health Organization 2018). Habitual distance VA ≤ 0.25 was considered as impaired vision.

Comorbidities

To eradicate the potential effect of common diseases on HRQoL, self-reported diseases in both the surveys were categorized into major comorbidity groups according to Taipale and co-workers (Taipale et al. 2019) and our previous study (Purola et al. 2021). These include heart diseases (myocardial infarction, angina pectoris, heart failure, arrhythmias and 'other heart disorders'), respiratory diseases (asthma, chronic obstructive pulmonary disease, chronic bronchitis and 'other pulmonary disease'), vascular diseases (stroke and varicose veins in lower limbs), musculoskeletal conditions (rheumatoid arthritis, osteoarthrosis, fractures and osteoporosis), and psychiatric conditions (psychotic disorders, depression, anxiety, psychoactive substance abuse and 'other psychiatric disease'). Moreover, hypertension, diabetes, Parkinson's disease and unspecified cancer were each categorized as a separate group. An individual was considered to have comorbidity if they reported having any of the conditions included in the comorbidity groups.

Statistical analyses

All analyses were performed using R software version 3.5.1 (R Core Team, R Foundation for Statistical Computing, Austria). Our data included both the survey samples, which were used for cross-sectional and longitudinal analyses. We used Survey package 3.37 for R (Lumley 2004) and weighting scheme calculated by the Finnish

Institute for Health and Welfare to account for the sampling design, the oversampling of individuals aged 80 years and older, and the loss to follow-up. For the prevalence and incidence analyses, we estimated population totals and ratios using functions *svytotal* and *svyratio* included in the Survey package. Individuals with missing data in analysed variables were excluded. Because the data of the continuous variables were non-normally distributed, we used Mann–Whitney *U* test for between-group comparisons, Wilcoxon's signed-rank test to compare the matched pairs, and the Kruskal–Wallis test to compare multiple groups. Odds ratios (ORs) with 95% confidence intervals were calculated using logistic regression analysis, corrected for age, gender and comorbidities. For all analyses, a two-tailed p-value of <0.05 was considered as the cut-off for statistical significance.

Informed consent

All procedures in the Health 2000 and 2011 studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethical approval process details are discussed in previous publications (Heistaro 2008; Lundqvist & Mäki-Opas 2016). All the participants received an information letter regarding the study beforehand. Two informed consents were obtained at the beginning of the study from everyone: one for the health interview and the other for the health examinations (Heistaro 2008). The participants were provided with appropriate information concerning the study and asked to sign an informed consent again before the follow-up examination in 2011 (Lundqvist & Mäki-Opas 2016).

Results

Study population

In total, 8028 individuals aged 30 years and older participated in the 2000 survey, 8006 in the 2011 survey, and 6360 in both the surveys. Of these individuals, 7380 and 5774 had known eye disease status in 2000 and 2011, respectively, and 4683 individuals took part in both the time points and were included in the 11-year follow-up study. The number of self-reported glaucoma patients was 258 in 2000 and 160 in 2011, verified glaucoma patients 192 in 2000 and 202 in 2011, and self-suspected glaucoma patients 100 in 2000 and 41 in 2011 (Fig. S1). The flow chart of the glaucoma patient selection in both the time points is shown in Fig. 1. The number, mean age and gender distribution of the study population are shown in Table 2, as well as the available data on HRQoL, mental health and distance VA of the individuals with known eye disease status.

Prevalence and incidence of glaucoma

The estimated total prevalence and incidence of the three glaucoma groups in the Finnish adult population in 2000 and 2011 are shown in Table 3, and by age and gender in Fig. 2. The prevalence and incidence of glaucoma increased with age in verified and self-reported glaucoma patients in both the time points, but the association with age was less evident in self-suspected glaucoma patients. The prevalence and incidence of self-reported glaucoma and self-suspected glaucoma were higher in women in both the time points, but this difference in gender distribution was less prevalent in verified glaucoma patients. The percentage of different glaucoma diagnoses in the Finnish adult population in both the time points was estimated using HILMO data, which is shown in Table S1.

Cross-sectional impact of glaucoma on health-related quality of life and mental health

EQ-5D and 15D mean scores were significantly reduced in the three glaucoma groups compared to glaucoma negatives in both the time points, as shown in Figs 3A and B. Glaucoma treatment groups also showed statistically significant worsening in both the time points. All glaucoma groups showed clinically meaningful worsening in these factors when compared to glaucoma negatives in both the time points.

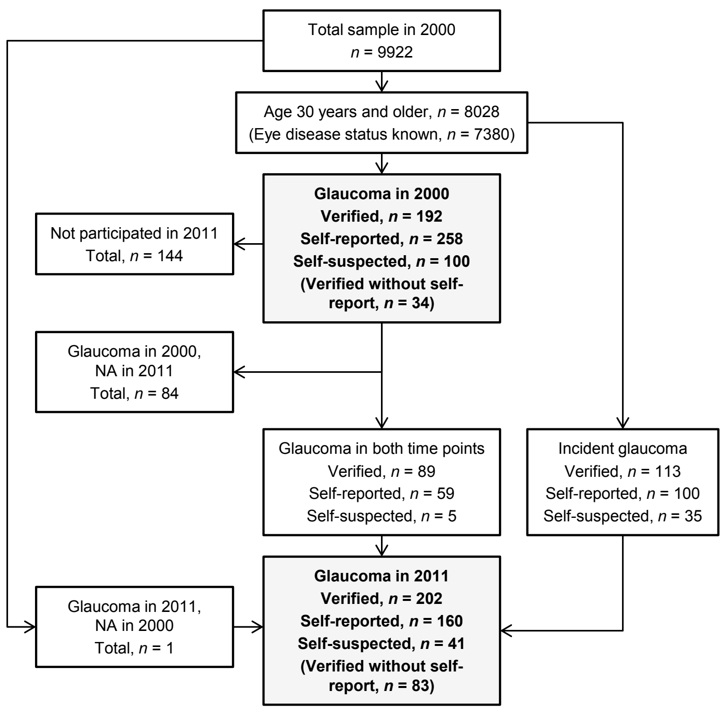

Fig. 1. Selection of the three glaucoma groups in 2000 and 2011. NA = not applicable.

Table 2. Summary of the study population aged 30 years and older.

	2000			2011			11-year follow-up group in 2011[a]		
	n	Mean age (SD)	% women	*n*	Mean age (SD)	% women	*n*	Mean age (SD)	% women
Eligible sample	8028	54.2 (16.2)	54.7	8006	55.3 (15.6)	53.0	6360	60.6 (12.9)	55.5
Eye disease status known	7380	54.2 (16.1)	55.2	5774	55.8 (14.7)	55.7	4683	60.3 (12.2)	56.0
Glaucoma, self-reported	258	71.1 (13.6)	75.2	160	72.0 (11.2)	66.9	159	72.2 (10.8)	66.7
Glaucoma, verified	192	74.4 (11.4)	71.4	202	75.1 (10.7)	67.8	201	75.1 (10.7)	67.7
Glaucoma, self-suspected	100	67.2 (15.5)	81.0	41	65.2 (13.9)	80.5	40	66.0 (13.1)	80.0
Glaucoma, medication	143	73.7 (13.4)	72.7	186	75.5 (11.9)	67.2	185	75.5 (11.6)	67.0
Glaucoma, operated	59	74.5 (11.7)	67.8	38	74.8 (11.2)	55.3	38	74.8 (11.2)	55.3
Special reimbursement for glaucoma medication	177	74.6 (11.4)	71.2	175	76.1 (10.2)	67.4	174	76.0 (10.2)	67.2
Glaucoma negatives	7088	53.5 (15.8)	54.4	5531	55.1 (14.3)	55.1	4442	59.5 (11.9)	55.2
Distance VA measured	6644	53.6 (15.5)	55.3	4560	56.5 (14.1)	55.7	3810	60.1 (11.9)	55.5
Impaired distance VA (≤0.25)	147	80.0 (11.7)	74.1	53	76.6 (13.7)	60.4	46	77.6 (13.1)	60.9
EQ-5D index score available	6131	53.5 (15.7)	55.9	4029	55.8 (13.9)	56.3	3086	59.4 (11.7)	56.8
15D index score available	6149	53.2 (15.2)	55.7	4214	56.3 (13.8)	56.2	3462	59.8 (11.6)	56.1
BDI total score available	6297	52.7 (14.9)	55.0	4303	56.1 (13.8)	56.0	3565	59.6 (11.5)	55.7
GHQ-12 total score available	6530	53.2 (15.3)	55.1	4449	56.2 (14.0)	55.8	3689	59.8 (11.7)	55.7

SD = standard deviation, VA = visual acuity.
[a] The follow-up group includes the 2011 eye status of the individuals who had participated in both time points.

Table 3. Estimated prevalence and incidence with 95% confidence intervals (CIs) of the three glaucoma groups in the Finnish population aged 30 years and older in 2000 and 2011

	2000		2011		Incidence 2000–2011	
	N (95% CI)	Prevalence % (95% CI)	*N* (95% CI)	Prevalence % (95% CI)	*N* (95% CI)	*N*/year/ 10 000 individuals (95% CI)
Glaucoma, verified	75 683 (57 534–93 832)	2.33 (2.19–2.48)	79 758 (60 199–99 317)	2.57 (2.30–2.85)	45 325 (34 490–56 160)	19 (17–20)
Glaucoma, self-reported	100 517 (76 226–124 808)	3.10 (2.95–3.26)	83 453 (64 288–102 618)	2.70 (2.47–2.93)	52 026 (40 359–63 693)	22 (20–23)
Glaucoma, self-suspected	37 349 (27 648–47 050)	1.15 (1.06–1.25)	21 455 (16 245–26 665)	0.69 (0.61–0.77)	18 233 (13 851–22 615)	7 (6–8)

BDI mean scores, visualized in Figs 3C and D were significantly worse in all glaucoma groups compared to glaucoma negatives. For GHQ-12 (Fig. 3E), only the verified glaucoma group in 2000 showed significant worsening ($p = 0.037$, Mann–Whitney *U* test) compared to glaucoma negatives. All glaucoma groups showed a decrease ($p < 0.0001$) in the distance VA compared to glaucoma negatives, as shown in Fig. 3F. There was no statistically significant change in the effect of glaucoma on VA when self-reported cataract and retinal degeneration were included as covariates (Table S2).

No significant difference was found between the three glaucoma groups, except in the distance VA in 2000 ($p = 0.0002$, Kruskal–Wallis test), in which the verified group had the worst value and the self-suspected group the highest. No significant difference was found between treated and untreated glaucoma patients. Impaired distance vision (VA ≤ 0.25) showed a stronger deteriorating impact on both HRQoL and mental health compared to all glaucoma groups. When comparing these parameters between 2000 and 2011, verified and self-reported groups showed an increase ($p < 0.01$) in EQ-5D, 15D, and distance VA scores, and the verified group showed improvement in GHQ-12 ($p = 0.0042$). The verified group showed a clinically meaningful increase in both EQ-5D and 15D, and the self-reported group in 15D. Both treatment groups showed statistically significant improvement in GHQ-12 and distance VA, as well as statistically significant and clinically meaningful improvement in EQ-5D and 15D. Glaucoma negatives had a statistically significant ($p < 0.01$) but not clinically meaningful increase in these parameters.

Individual EQ-5D and 15D dimensions (difficulties versus no difficulties), as well as BDI and GHQ-12 cut-off points indicative of depression and psychological distress, were assessed using ORs, as shown in Table 4. In 2000, only the self-reported glaucoma group showed an increase in difficulties concerning usual activities according to EQ-5D. In 2011, both verified and self-reported groups showed an increase in difficulties amongst mobility, and the

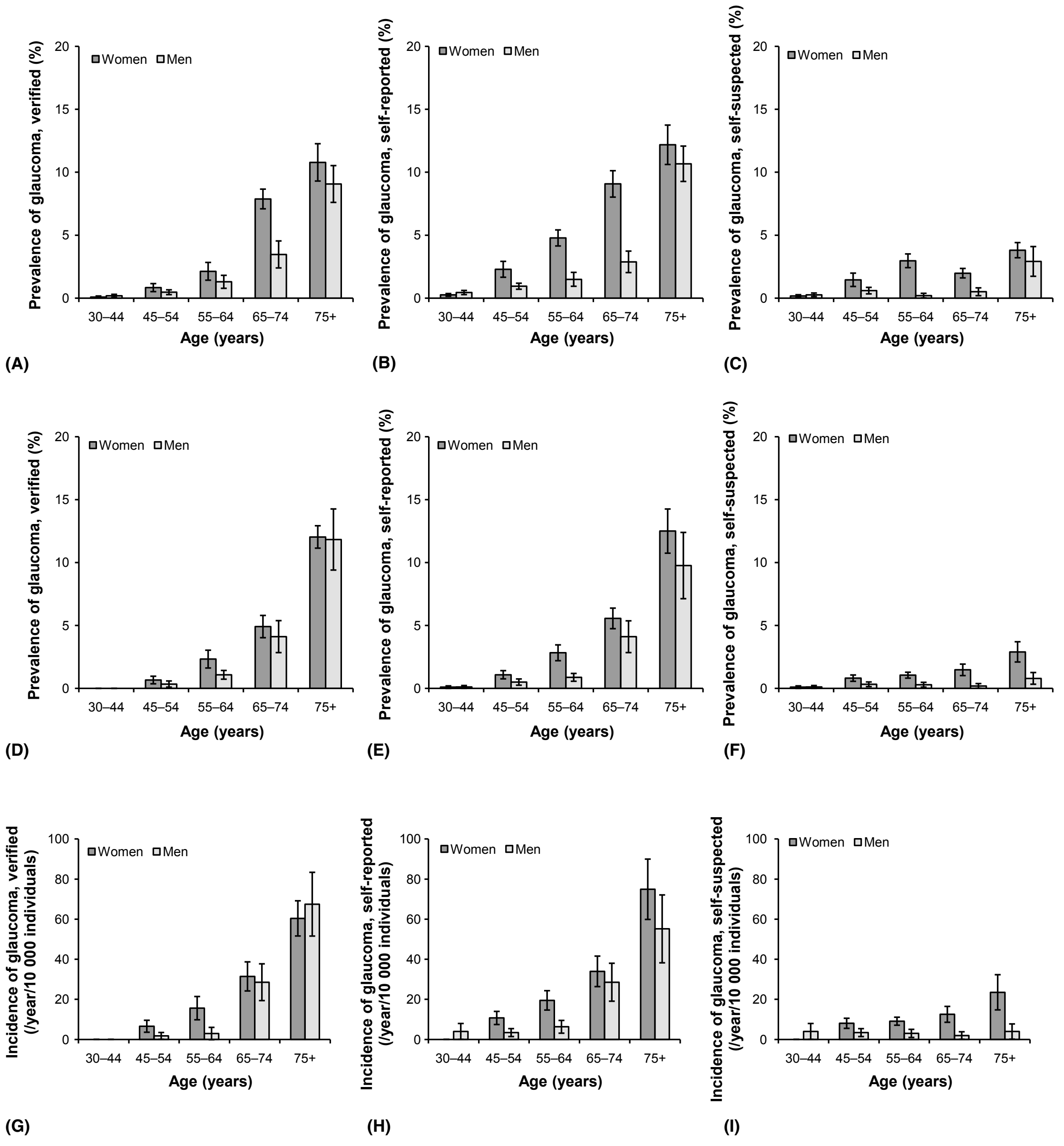

Fig. 2. Estimated prevalence (with 95% confidence intervals) of the three glaucoma groups in the Finnish adult population (age 30 years and older) by age and gender in 2000 (A–C) and 2011 (D–F), and the incidence between 2000 and 2011 (G–I).

self-suspected group in self-care, in the EQ-5D results. When assessing the five most affected 15D dimensions, both verified and self-reported groups showed an increase in difficulties amongst vision and usual activities, and self-suspected group an increase in mobility in 2000 and vision in 2011. In 2011, both verified and self-reported groups showed an increase in difficulties amongst usual activities and mental function. Verified glaucoma patients who had undergone eye surgery due to the disease showed increased odds for pain and discomfort and difficulties in usual activities compared to untreated glaucoma patients in 2000, but no significant difference was found in 2011 between treated and untreated. When evaluating the odds for mental health, only the verified glaucoma group showed increased odds for psychological distress in 2000.

The association between glaucoma, HRQoL, mental health and distance VA were observed in both the time points, as shown in Figs S2 and S3. Verified and self-reported glaucoma patients, glaucoma negatives and glaucoma patients with known glaucoma

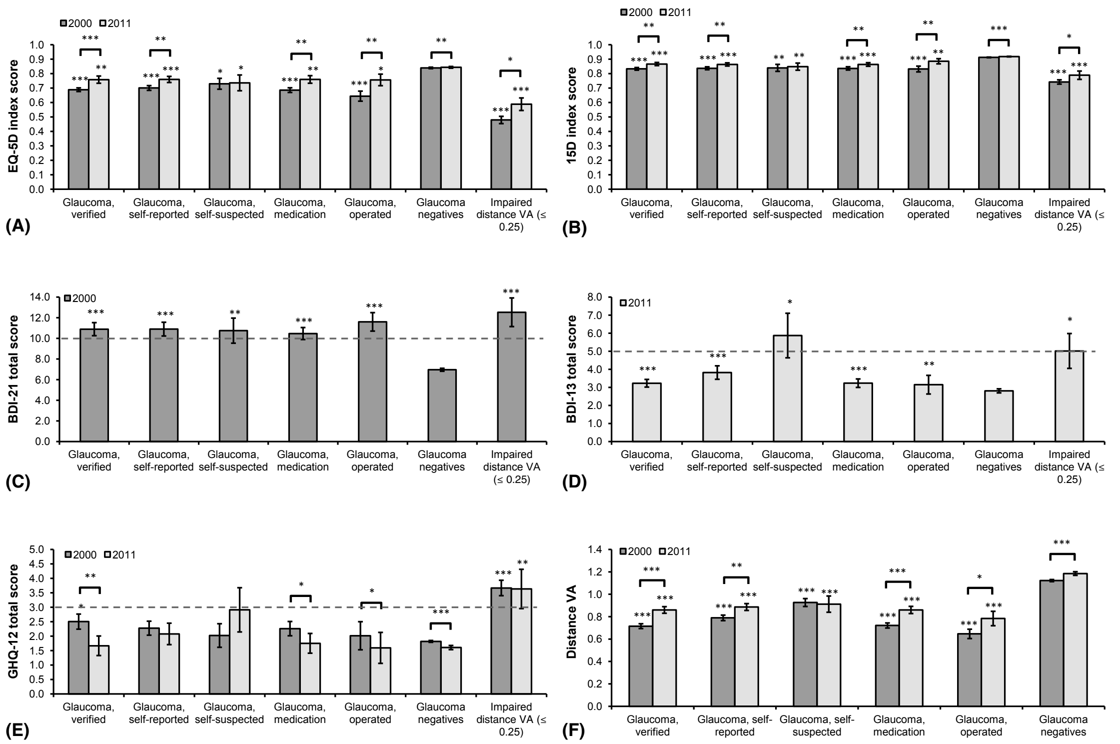

Fig. 3. The index/total score means of EQ-5D (A), 15D (B), BDI (C, D), GHQ-12 (E), and distance visual acuity (VA; F) in glaucoma patients, glaucoma negatives and visually impaired in cross-sectional studies conducted in 2000 and 2011. When calculating statistical significance (Mann–Whitney *U* test), glaucoma and visual impairment groups were tested against glaucoma negatives within the same year. In addition, mean values were compared between time points in each group. Dashed lines represent clinically meaningful cut-off values for BDI-21 (≥10), BDI-13 (≥5), and GHQ-12 (>3). *Denotes statistical significance with $p < 0.05$. **Denotes statistical significance with $p < 0.01$. ***Denotes statistical significance with $p < 0.0001$.

medication showed a decrease in HRQoL scores and worsening of mental health when their VA diminished. Individual HRQoL dimensions were observed in the 2000 study, as shown in Figs S4 and S5. Usual activities, self-care and mobility showed a similar association with VA in both EQ-5D and 15D, as well as vision in 15D. Self-suspected glaucoma patients and operated glaucoma patients were not included, as the number of individuals with impaired VA was low.

Longitudinal impact of glaucoma on health-related quality of life and mental health

The longitudinal effect of glaucoma on HRQoL during the 11-year follow-up was investigated amongst individuals who had participated in both the surveys. Because the number of self-suspecting glaucoma patients was low, they were excluded from the longitudinal analyses. Individuals with the same glaucoma status in both the time points are shown in Fig. 4. When investigating HRQoL, verified and self-reported glaucoma groups showed statistically significant ($p = 0.024$ and $p = 0.036$, respectively, Wilcoxon signed-rank test) and clinically meaningful decrease between the time points with 15D. Glaucoma negatives showed a decline ($p < 0.0001$) in EQ-5D and 15D, although there was no clinically meaningful difference. For GHQ-12, only glaucoma negatives showed a significant improvement ($p < 0.0001$). For distance VA, verified ($p = 0.0006$) and self-reported ($p = 0.035$) glaucoma groups and glaucoma negatives ($p < 0.0001$) showed significant decline.

Newly diagnosed glaucoma patients who were glaucoma negative in 2000 but had been diagnosed with glaucoma during the 11-year follow-up are shown in Fig. 5. Only the verified group showed statistically significant decline in EQ-5D ($p = 0.002$) and 15D ($p = 0.006$), although only 15D had a clinically meaningful decrease. Distance VA had declined in verified ($p = 0.011$) and self-reported ($p = 0.047$) glaucoma patients.

Discussion

Participants with a verified glaucoma diagnosis, as well as participants who only suspected to have glaucoma, showed a significant decrease in their generic HRQoL compared to individuals without glaucoma. The decrease was, however, more notable amongst individuals suffering from visual impairment. A similar association between glaucoma patients with visual symptoms and declined QoL has been reported in previous publications,

Table 4. Corrected odds ratios (ORs) for EQ-5D dimensions, most affected 15D dimensions, and mental health scores indicative of depression or psychological distress compared to individuals without glaucoma or glaucoma treatment in 2000 and 2011.

	EQ-5D dimensions					Five most affected 15D dimensions					Mental health	
2000	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression	Vision	Usual activities	Mobility	Vitality	Mental function	BDI-21 sum ≥10	GHQ-12 sum >3
Glaucoma, verified	1.37 (0.97–1.92)	0.94 (0.60–1.47)	1.33 (0.92–1.92)	1.04 (0.82–1.34)	1.21 (0.71–2.07)	**2.26 (1.68–3.06)**	**1.80 (1.18–2.75)**	1.27 (0.85–1.92)	1.07 (0.78–1.47)	0.89 (0.60–1.32)	1.15 (0.83–1.60)	**1.37 (1.06–1.76)**
Glaucoma, self-reported	1.42 (0.90–2.23)	1.02 (0.71–1.46)	**1.60 (1.10–2.33)**	1.09 (0.86–1.36)	1.05 (0.65–1.69)	**1.83 (1.34–2.50)**	**1.64 (1.13–2.37)**	1.62 (1.05–2.52)	1.18 (0.82–1.70)	0.97 (0.67–1.40)	1.27 (0.91–1.76)	1.07 (0.80–1.45)
Glaucoma, self-suspected	1.72 (0.81–3.65)	1.34 (0.60–2.96)	1.82 (0.88–3.74)	1.36 (0.82–2.24)	0.79 (0.34–1.79)	1.34 (0.78–2.28)	1.41 (0.61–3.23)	**2.71 (1.40–5.25)**	1.28 (0.65–2.55)	1.06 (0.56–2.00)	1.23 (0.73–2.09)	0.72 (0.39–1.34)
Glaucoma, medication	0.71 (0.36–1.39)	1.08 (0.49–2.39)	0.71 (0.30–1.69)	0.82 (0.49–1.36)	0.82 (0.38–1.77)	1.18 (0.80–1.74)	1.11 (0.50–2.45)	0.66 (0.28–1.56)	0.76 (0.30–1.94)	0.87 (0.44–1.72)	0.76 (0.38–1.50)	0.63 (0.36–1.12)
Glaucoma, operated	1.28 (0.43–3.79)	1.22 (0.61–2.43)	**3.14 (1.46–6.75)**	**2.91 (1.53–5.53)**	1.34 (0.53–3.42)	1.37 (0.68–2.71)	1.23 (0.37–4.13)	0.83 (0.31–2.19)	0.92 (0.31–2.72)	0.58 (0.23–1.46)	1.50 (0.85–2.66)	0.74 (0.38–1.45)
2011	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression	Vision	Usual activities	Mobility	Vitality	Mental function	BDI-13 sum ≥ 5	GHQ-12 sum > 3
Glaucoma, verified	**1.73 (1.18–2.54)**	1.00 (0.57–1.75)	1.21 (0.71–2.07)	1.02 (0.64–1.62)	0.66 (0.31–1.42)	1.25 (0.65–2.43)	**1.85 (1.30–2.63)**	1.39 (0.96–2.02)	1.42 (0.97–2.08)	**1.45 (1.05–1.99)**	1.25 (0.79–1.96)	1.21 (0.61–2.41)
Glaucoma, self-reported	**1.50 (1.11–2.03)**	1.30 (0.89–1.89)	1.16 (0.65–2.10)	1.06 (0.68–1.64)	0.83 (0.48–1.47)	1.47 (0.83–2.62)	**1.64 (1.12–2.40)**	1.21 (0.95–1.54)	1.56 (1.05–2.31)	**1.49 (1.07–2.08)**	1.26 (0.75–2.10)	1.23 (0.69–2.17)
Glaucoma, self-suspected	1.14 (0.47–2.78)	**2.86 (1.52–5.39)**	1.66 (0.60–4.64)	1.22 (0.64–2.34)	1.51 (0.75–3.04)	**2.78 (1.20–6.43)**	1.47 (0.77–2.82)	1.05 (0.50–2.17)	2.84 (1.17–6.91)	1.43 (0.77–2.65)	1.85 (0.75–4.57)	1.09 (0.55–2.18)
Glaucoma, medication	1.26 (0.36–4.49)	0.50 (0.17–1.49)	0.84 (0.25–2.81)	0.47 (0.20–1.16)	0.44 (0.11–1.81)	0.62 (0.17–2.28)	0.98 (0.42–2.29)	0.85 (0.30–2.40)	0.46 (0.16–1.35)	0.90 (0.31–2.58)	0.53 (0.20–1.38)	1.52 (0.50–4.59)
Glaucoma, operated	0.42 (0.16–1.12)	0.15 (0.02–1.09)	0.53 (0.19–1.48)	2.06 (0.44–9.59)	0.10 (0.01–1.65)	0.83 (0.29–2.36)	0.48 (0.23–1.04)	0.40 (0.10–1.55)	0.64 (0.17–2.38)	0.61 (0.22–1.67)	0.68 (0.19–2.42)	0.82 (0.18–3.73)

The ORs and 95% confidence intervals were estimated through logistic regression analysis corrected for age, gender and the most common comorbidities. Bolded values denote statistically significant ($p < 0.05$) ORs. Verified, self-reported and self-suspected glaucoma patients were compared to glaucoma negatives (OR = 1.0), glaucoma patients with glaucoma medication to all glaucoma patients without glaucoma medication, and verified glaucoma patients who had undergone eye surgery due to the disease to all verified glaucoma patients who had not been operated.

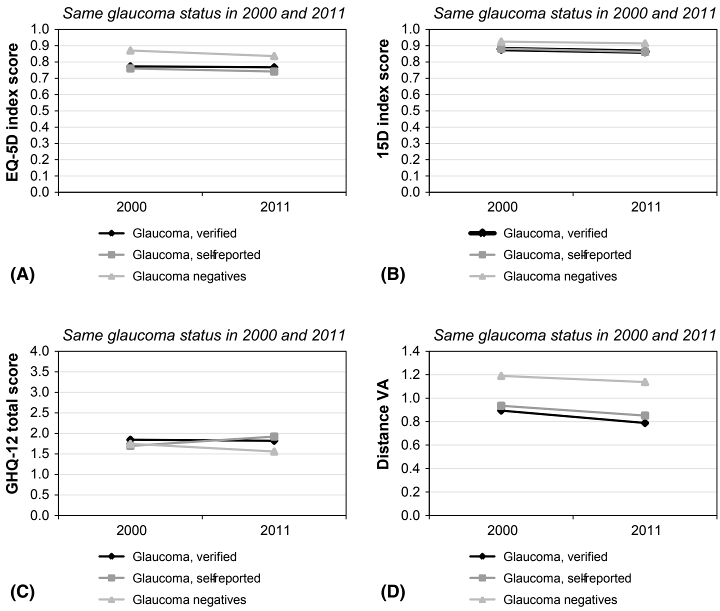

Fig. 4. Change in health-related quality of life (A, B), psychological distress (C) and distance visual acuity (VA; D) in glaucoma negatives and glaucoma patients with *the same glaucoma status* in both time points during the 11-year follow-up.

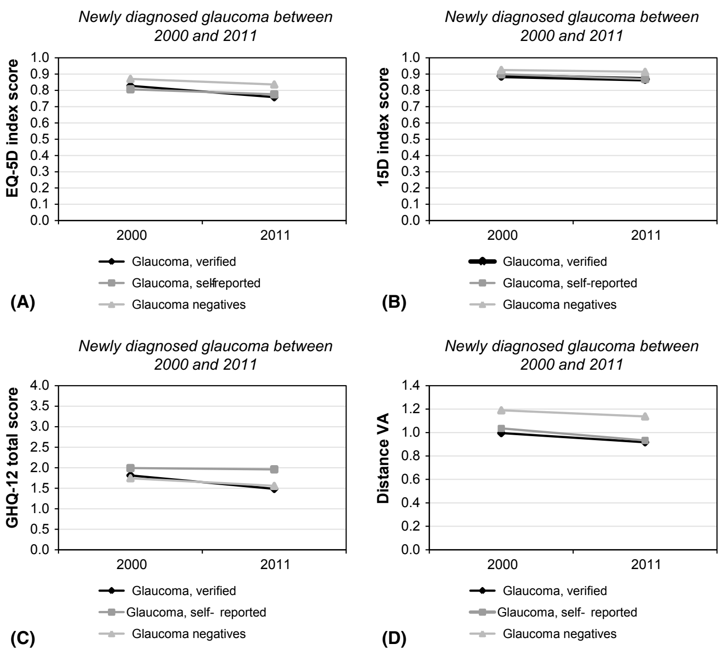

Fig. 5. Change in health-related quality of life (A, B), psychological distress (C) and distance visual acuity (VA; D) in individuals with *newly diagnosed glaucoma* (verified or self-reported) during the 11-year follow-up (2000–2011). Individuals with glaucoma negative status in both time points are shown as reference.

which have utilized vision-related HRQoL instruments (Floriani et al. 2016; Rulli et al. 2018; Machado et al. 2019; Wu et al. 2019). In our study, the mean score in these values was increasing between 2000–2011 in the cross-sectional setting, indicating an increase in the overall well-being and the potentially diminished role of glaucoma on generic HRQoL. As far as we know, this is the first time this type of effect of glaucoma has been reported using generic HRQoL instruments.

Worsening of mental health was more common amongst glaucoma patients and those who only suspected to have glaucoma based on significant worsening of the BDI scores compared to the non-glaucomatous population. Similar results were reported by Jung and co-workers (Jung & Park 2016), who found that undiagnosed glaucoma positives might be more depressed compared to non-glaucoma controls, even though the degree of depression may not be sufficient for a depression diagnosis. Patients with visual impairment and eye diseases, including glaucoma, have shown to have a higher probability of being depressed and having problems with anxiety/depression than healthy individuals (Popescu et al. 2012; Jung & Park 2016). In our study, the effect of visual impairment had a significantly stronger effect on BDI than glaucoma alone. Previous publications have suggested that the awareness of the eye disease itself may affect the sense of well-being in glaucoma patients because of the fear of declining vision (Jampel et al. 2007; Wang et al. 2012; Su et al. 2015). In our study, verified glaucoma patients also showed an increased prevalence of psychological distress as well as overall worsening of the GHQ-12 total score in 2000.

When investigating the individual dimensions of the used generic HRQoL instruments, all three glaucoma groups showed the most difficulties concerning usual activities, self-care, mobility and vision. These dimensions also showed an association with decreasing VA. Similar results were reported by Freeman and co-workers (Freeman et al. 2008), who implemented a vision-related HRQoL instrument and discovered that glaucoma affects mobility and increases difficulties in various visual tasks. In our study, worsening in the overall HRQoL and mental health also showed association with decreasing VA in both glaucoma patients and glaucoma negatives, which supports the known association between decreased QoL and impaired vision (McKean-Cowdin et al. 2010; Quaranta et al. 2016). Jung and co-workers demonstrated that glaucoma may affect EQ-5D, especially in patients with reduced VA (Jung & Park 2016). The strong impact of visual impairment on HRQoL in this study supports our previous study, in which we used identical data set to identify declined VA as the major determinant in the decreased HRQoL in the most common eye diseases (Purola et al. 2021). However, as all glaucoma groups showed worsened scores in these parameters compared to glaucoma negatives, glaucoma and fear of it nonetheless can affect the common activities of life, and therefore HRQoL.

Medical treatment as such showed no significant difference in generic HRQoL or mental health amongst glaucoma patients. This is most probably because glaucoma treatment is potentially having both positive and negative effects on QoL (Quaranta et al. 2016). Glaucoma patients who had undergone eye surgery due to their disease showed increased odds for pain/discomfort and difficulties in the usual activities according to EQ-5D in 2000. No difference in HRQoL or mental health was found between operated and unoperated glaucoma patients in 2011. This parallels with results from Guedes et al. (2013), who found no significant difference between glaucoma patients treated with either surgery or medicine, and that glaucoma surgery is associated with a lower vision-related QoL only in patients with early glaucoma, possibly due to psychological burden. Moreover, Hyman and co-workers reported no difference in vision-related HRQoL between treated and untreated glaucoma patients in an EMGT-study (Hyman et al. 2005).

In the longitudinal setting, patients having glaucoma already at the beginning of follow-up did not show similar improvement in HRQoL during the 11-year follow-up that was found as in the cross-sectional comparison. In fact, a small decline in HRQoL was found in both glaucoma patients and glaucoma negatives who had the same eye status in both the time points, most probably related to ageing. Improvement in HRQoL in the cross-sectional setting could be explained by the fact that newly diagnosed glaucoma during the 11 years had only a minor effect on generic HRQoL. Furthermore, no effect was observed in mental health with newly diagnosed glaucoma. This indicates that the decrease in the deteriorating effects of glaucoma on generic HRQoL and mental health is related to new glaucoma cases rather than the changes amongst those patients that have had glaucoma already in 2000. Riva and co-workers (Riva et al. 2019) reported improved vision-related QoL and reduction in glaucoma-related symptoms during their one-year follow-up study consisting of newly diagnosed primary open-angle glaucoma patients, and they suggested that it could be due to the patients' psychological processes and adaptation to the diagnosis.

The greatest strengths of our study were that our data were based on two nationwide surveys with high participation rates, and the loss between time points was relatively small and was further corrected by applying the weights. As most of the individuals participated in both the surveys, we were able to include a relatively long, 11-year longitudinal follow-up study. Furthermore, we used generic HRQoL instruments rather than vision-related instruments for better comparability and generalization of our results. Lastly, we were able to use comprehensive Finnish nationwide health registries when obtaining data from verified diagnoses, medical therapies and glaucoma surgeries.

However, our study also has potential limitations. As the number of different glaucoma diagnoses was relatively low, we could not account for differences between the various glaucoma types, and instead, we combined all glaucoma diagnoses into a single verified glaucoma group. For the same reasons, we did not account for the effects of various types of eye drops or surgeries on HRQoL. Both the surveys included predominantly Finnish participants, and therefore, the results may not be applicable to other countries and ethnicities. However, we used UK time-trade-off weights for EQ-5D, which may improve the comparability with other ethnicities.

In the future studies, more nationwide-based studies on glaucoma with generic HRQoL instruments and longitudinal settings of 10+ years could improve the comparability and generalization of our results. Furthermore, full data on the different types of glaucoma and medication could make it possible to assess a more detailed effect of glaucoma treatment on HRQoL.

In conclusion, our results show that glaucoma as well as self-suspicion of it have a deteriorating impact on generic HRQoL and mental health. However, the impaired VA associated with glaucoma is stronger determinant of these parameters than the awareness or suspicion of the disease. Moreover, this deteriorating impact appears to be diminishing since the effects were less significant in 2011 than in 2000. This reflects merely the fact that newly diagnosed glaucoma during the 11-year follow-up seemed to have only a minor effect on the HRQoL and mental health rather than improvement in these parameters amongst old glaucoma patients. Treatment of glaucoma, neither the medication nor surgery, does not have significant effect on generic HRQoL or mental health.

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Received on November 3rd, 2020.
Accepted on April 4th, 2021.

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This study was supported by Tampereen seudun Näkövammaisten tukisäätiö s.r, Tampere; Sokeain Ystävät r.y, Helsinki; and Elsemay Björn Fund, Helsinki. Funding sources did not influence the study design, data collection, analysis, interpretation or writing of the publication. The decision of publishing the results was completely made by the authors. PKMP, JEN, MMP, MUIO, SVPK, HAR, PRJS and HMTU declare no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Glaucoma groups in 2000 (A) and 2011 (B).

Figure S2. Association between health-related quality of life (A, B) and mental health (C, D) with distance visual acuity (VA) in verified and self-reported glaucoma patients, glaucoma negatives and glaucoma patients with known glaucoma medication in 2000.

Figure S3. Association between health-related quality of life (A, B) and mental health (C, D) with distance visual acuity (VA) in verified and self-reported glaucoma patients, glaucoma negatives and glaucoma patients with known glaucoma medication in 2011.

Figure S4. Individual EQ-5D dimensions and their association with distance visual acuity (VA) in verified and self-reported glaucoma patients, glaucoma negatives and glaucoma patients with known glaucoma medication in 2000

Figure S5. Individual 15D dimensions and their association with distance visual acuity (VA) in verified and self-reported glaucoma patients, glaucoma negatives and glaucoma patients with known glaucoma medication in 2000

Table S1. Estimated percentages of different glaucoma diagnoses in the Finnish population aged 30 years and older in 2000 and 2011.

Table S2. Linear regression analysis examining the impact of glaucoma on distance visual acuity with cataract and retinal degeneration (RD) as covariates in 2000 and 2011.

PUBLICATION
III

Price tag of glaucoma care is minor compared with the total direct and indirect costs of glaucoma: Results from nationwide survey and register data

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PLOS ONE 2023;18(12):e0295523
doi: 10.1371/journal.pone.0295523

PLOS ONE

RESEARCH ARTICLE

Price tag of glaucoma care is minor compared with the total direct and indirect costs of glaucoma: Results from nationwide survey and register data

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OPEN ACCESS

Citation: Purola PKM, Taipale J, Väätäinen S, Harju M, Koskinen SVP, Uusitalo HMT (2023) Price tag of glaucoma care is minor compared with the total direct and indirect costs of glaucoma: Results from nationwide survey and register data. PLoS ONE 18(12): e0295523. https://doi.org/10.1371/journal.pone.0295523

Editor: Ryo Asaoka, Seirei Hamamatsu General Hospital, JAPAN

Received: July 14, 2023

Accepted: November 21, 2023

Published: December 20, 2023

Data Availability Statement: The Ethics committee has stated that under applicable law, the study data cannot be made publicly available or stored in public repositories because individual level data contains sensitive health information. Anonymized data can be requested for a study that has been approved by a local ethics committee and meet the criteria for access to confidential data. The permission to access the data can be applied through the Finnish Institute for Health and Welfare (thl.fi/en/web/thl-biobank/for-researchers) or

Abstract

Background

The estimations of the economic burden of glaucoma have focused on comparing different treatment modalities; hence, the total direct and indirect costs of glaucoma at population level are not well known.

Objective

To estimate the direct and indirect costs of glaucoma and its treatment in Finland.

Methods

Economic and glaucoma data were collected from the cross-sectional nationwide Health 2000 health examination survey linked to multiple national registers, which allowed a 13-year follow-up between 1999–2011 among survey participants. Direct costs covered eye- and non-eye-related hospitalizations and outpatient visits, outpatient health care services, and travel costs among participants aged 30 years or older, adjusted for age and sex. Indirect costs covered premature retirement and productivity losses among participants aged 30–64 years. Glaucoma patients ($n = 192$) were compared with non-glaucomatous population ($n = 6,952$).

Results

The annual additional total direct costs were EUR 2,660/glaucoma patient, EUR 1,769/glaucoma patient with medication, and EUR 3,979/operated glaucoma patient compared with persons without glaucoma. The respective additional total indirect costs were EUR 4,288, EUR 3,246, and EUR 12,902 per year. In total, the additional annual direct and indirect

through the Findata permit procedure (https://www.findata.fi/en/).

Funding: PKMP received funds from Tampereen seudun Näkövammaisten tukisäätiö s.r, Tampere, Finland; Glaukooma Tukisäätiö Lux s.r, Helsinki, Finland; Elsemay Björn Rahasto, Helsinki, Finland; Finnish Federation of the Visually Impaired, Helsinki, Finland; Päivikki ja Sakari Sohlbergin Säätiö, Helsinki, Finland; and Juho Vainion Säätiö, Helsinki, Finland. JT received funds from Tampereen kaupungin tiederahasto, Tampere, Finland; Sokeain Ystävät - De Blindas Vänner sr., Helsinki, Finland; Silmä- ja kudospankkisäätiö, Helsinki, Finland; and Silmäsäätiö s.r., Helsinki, Finland. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

expenditures associated with glaucoma in Finland were EUR 202 million (0.86% of total expenditures of health care) and EUR 71 million (0.03% of the Finnish gross domestic product) arising mainly from non-eye-related hospitalizations and productivity losses, respectively.

Conclusion

Glaucoma is associated with an increased health care consumption mainly due to non-eye-related health care, which can be explained by the vision loss as well as increased number of co-morbidities among glaucoma patients. Therefore, glaucoma constitutes a major economic burden for the health care system and society, highlighting the importance of early glaucoma interventions. The difference in direct and indirect costs between glaucoma treatment groups is explained by the uneven distribution of co-morbidities.

Introduction

Glaucoma is an optic neuropathy characterized by progressive degeneration of retinal ganglion cells. Globally, over 70 million individuals suffer from glaucoma [1]. In Finland, there are over 80,000 glaucoma patients, of which approximately 8% are visually impaired with visual acuity (VA) lower than 0.3 (Snellen decimals) [2, 3]. The prevalence of glaucoma is increasing globally due to the rapidly growing number of older people [1, 2, 4]. Other risk factors for glaucoma besides age include elevated intraocular pressure, family history, presence of exfoliative material, myopia, and African ethnicity [5]. Currently, there are three types of glaucoma treatments: drugs, surgical procedures, and laser treatments [6]. Even though timely and effective treatment could prevent the deterioration of vision, glaucoma remains as one of the leading causes of blindness worldwide. Furthermore, the low public awareness, the asymptomatic early stages of glaucoma, and the non-adherence to prescribed therapy can lead to inadequate control of glaucoma, with severe consequences for both the individual and the society [7].

Given the social consequences of glaucoma and the limited resources available to health care providers, it is crucial to provide appropriate information to facilitate the decision making and the allocation of health care resources. However, the impact of glaucoma on total direct and indirect costs at population level is not well known. Majority of the previous glaucoma-related publications have focused on comparing different treatment modalities at clinical settings [8–11]. Few studies have estimated either direct or indirect costs of glaucoma and its treatment [12–15].

Hence, there is a need for a comprehensive picture of the economic burden of glaucoma including all eye- and non-eye-related direct and indirect costs associated with the disease—for example, hospitalizations due to falls and injuries. More population-wide studies are also required to corroborate the previous findings and to provide accurate estimates of the costs in different nationwide settings. Furthermore, the use of multiple data sources, such as national surveys and registers, is uncommon, even though it could provide more accurate estimates on the use of health care services and both direct and indirect costs. Therefore, our aim was to evaluate the economic impact of glaucoma and its treatment on the Finnish society by combining the data of a nationwide health examination survey and national health registers, estimating both direct and indirect costs associated with the disease.

Materials and methods

Study design, data, and population

The Finnish Institute for Health and Welfare (THL) conducted the nationwide Health 2000 survey which collected comprehensive information on health and well-being in Finland during 2000–2001 [16]. The representative sample of the Finnish adult population was selected by utilizing a probability-clustered sampling and weighting scheme. The survey included a face-to-face interview, self-administered questionnaires, and a thorough health examination. The sample included 8,028 subjects aged 30 years and older, and the unweighted participation rate was 93%. The sample weights were calibrated by post-stratification, defined by age, sex, region, and native language to account for non-response and missing data. The details of the survey methods have been published elsewhere [16].

Information on the use of outpatient health care services was collected in the interview, including the number of private, occupational, health center, and other doctor visits, and the number of occupational, home care, and outpatient nurse visits during the preceding 12 months.

The habitual distance VA was measured in the health examination by an educated study nurse binocularly at 4 m. Illumination was set to $\geq$ 350 lx on the modified logMAR letter chart. All VA values are presented as Snellen decimals. Low VA values outside the modified logMAR letter chart that could not be determined were reported as 0.01. Based on previous studies [17, 18], distance VA was classified into following groups: VA $\geq$ 1.0 (good vision), VA 0.63–0.8 (adequate vision), VA 0.32–0.5 (weak vision), and VA $\leq$ 0.25 (visual impairment).

The survey sample was linked to national registers. Data on entitlements to reimbursement for glaucoma medication (during 1965–2011) and the number of glaucoma medication prescriptions (ATC S01E; 1999–2011) of the survey participants were obtained from the registers maintained by the Social Insurance Institution of Finland (Kela). Data on the diagnoses and operations of the survey participants were obtained from the Care Registers for Social Welfare and Health Care maintained by the Finnish Institute for Health and Welfare. The care register data covered inpatient care visits (Hilmo, 1968–2011), which included the number and length of hospitalizations, and specialized health care outpatient visits (AvoHilmo, 1997–2011). A follow-up time was calculated for each participant separately to account for the survival of the participants. The period of scrutinization was extended to 13 years (1.1.1999–31.12.2011) to represent the mean annual usage more accurately. The follow-up durations were corrected for participants who had died during the follow-up period (n = 1,279) with a range of 1.2–13.0 years. We included all eye- and non-eye-related hospitalizations and outpatient visits. Eye-related hospitalizations and visits were considered those with main diagnosis H00–H59 International Classification of Diseases (ICD) version 10.

Information on the status and time of retirement were collected in the interview of the Health 2000 survey. To improve the quality of the retirement data and to account the follow-up, additional retirement information were acquired from the Health 2011 health examination survey [19], a follow-up to the Health 2000 survey conducted in Finland in 2011–2012, for participants who partook at both time points.

Based on the Hilmo/AvoHilmo and Kela register data, survey participants were classified into three glaucoma groups following the same procedure as in our previous study [2]: glaucoma, all; glaucoma treated with medication; and operated glaucoma. Laser treatments were not included as a separate group. Survey participants who did not belong to these groups were considered to not have glaucoma and were classified as glaucoma negatives. The details of the classification are shown in Table 1. We analyzed participants who had either survey visits available or both survey and Hilmo/AvoHilmo visits available.

Table 1. Classification of glaucoma.

Glaucoma, all	Entitlement to special reimbursement for glaucoma medication between 1965–2000 (Kela data) OR High number (> 10) of glaucoma medication prescriptions between 1999–2000 (Kela data) OR Glaucoma diagnosis[a] between 1968–2000 (Hilmo/AvoHilmo data) OR Eye operation[b] due to glaucoma between 1997–2000 (Hilmo/AvoHilmo data)
Glaucoma, medication	Glaucoma and glaucoma medication prescriptions between 1999–2000 (Kela data)
Glaucoma, operated	Glaucoma and eye operation[b] due to glaucoma between 1997–2000 (Hilmo/AvoHilmo data) OR Glaucoma and self-reported glaucoma operation in the Health 2000 survey interview
Glaucoma negatives	No glaucoma based on the register data before 31.12.2011 or death AND No self-reported glaucoma based on the Health 2000 Survey interview

Hilmo/AvoHilmo = inpatient/outpatient visits in the Care Registers for Social Welfare and Health Care, Kela = Social Insurance Institution of Finland

[a]International Classification of Diseases diagnosis codes 37500–37520, 37598–37599 for version 8, 3651–3659 for version 9, and H40, H40.1–H40.9 for version 10

[b]At least one of the following: trabeculectomy and iridectomy, glaucoma shunt operation, nonpenetrating glaucoma surgery, other filtering operation, and transscleral laser coagulation of ciliary body

https://doi.org/10.1371/journal.pone.0295523.t001

Cost analysis

This economic evaluation was performed in accordance with the CHEERS 2022 guidelines (S1 Appendix) [20]. We utilized a prevalence-based bottom-up approach to assess both the direct and indirect costs associated with glaucoma. The direct costs were based on registered hospitalizations and outpatient visits, self-reported outpatient health care services, and travel costs for outpatient visits during the follow-up. Unit costs were converted to 2019 level in the analyses based on the most recent estimates on health expenditure and financing in Finland [21–23], and they are listed in S1 Table. Public health care costs included laboratory, administrative, and other collateral costs. For private practitioners, we examined mean administrative costs of three major private health care service providers and in the analyses, we applied weighted average according to the market shares. The proportions of emergency and non-emergency visits have been applied to the unit costs for outpatient visits based on Sotkanet-database and the outpatient visit data from Pirkanmaa Hospital District: in 2019, the proportions of emergency visits were 37.2% in primary health care, 9.8% in specialized health care, and 8.4% specifically for ophthalmologists. Based on the features of Finnish health care system, current proportions are the most precise estimates we can provide. The unit costs do not include the customer fees as our focus was on societal costs. Drug costs and direct non-health care costs excluding transportation were not included in the study as appropriate data were not available. The calculation of travel costs for outpatient visits has been described previously [22].

The indirect costs comprised premature retirement and related productivity losses. The number of premature retirement years was calculated for each person with known time of retirement, starting from age of 30 years up to 64 years. If the person was known to have retired, but the time of retirement was not known, the average retirement age in the population was used instead, separately for glaucoma groups (59.5 years, n = 11) and glaucoma negatives

(57.4 years, *n* = 268). If the person was older at the time of the survey than the average age, the age at the time of the survey was used (Health 2000 or 2011, 42 glaucoma negatives). If the person had died before age of 65 years during the follow-up, the years were calculated up to age at death. If the person was younger than 65 years during the follow-up, the years were calculated up to age in 2011. Productivity losses were calculated using the premature retirement years. The annual indirect costs were estimated by dividing the total costs by the mean duration of working career in Finland (32.6 years in 2011) [24]. The indirect costs were also converted to 2019 euros in the analyses (S1 Table). Because this is a retrospective population-based study, intangible costs such as pain and suffering and care provided by nonpaid caregivers were not included in the analyses.

Statistical methods

All data were analyzed with R software (v. 4.2.1, R Core Team, R Foundation for Statistical Computing, Austria). The sampling design of the survey was accounted for using Survey package 3.37 for R [25] and weighting scheme calculated by the Finnish Institute for Health and Welfare. One glaucoma negative and one verified glaucoma patient were excluded from further analyses as high outliers. Age- and sex-adjusted costs as well as non-adjusted costs were calculated. We estimated the total costs at population level by applying the weights. As the data were continuous and quantitative, we calculated means, standard deviations, and standard errors. Because the distribution of the data was right-skewed, we used the Kruskal–Wallis test for multiple comparisons, adjusted with the Dunn–Bonferroni correction from package DescTools 0.99.44 [26]. Pearson correlation coefficients were calculated using jtools package 2.1.4 [27], which is an increment to the Survey package that accounts for the sampling design. For all analyses, a two-tailed p value of < 0.05 was considered as statistically significant.

To account for different co-morbidities and other confounders, we applied generalized linear models to evaluate the total direct and indirect costs. The self-reported co-morbidities were collected from the Health 2000 survey interview data, and they included unoperated cataract, retinal degeneration, heart diseases, pulmonary diseases, vascular diseases, musculoskeletal conditions, hypertension, diabetes, psychiatric disorders, Parkinson's disease, and unspecified cancer. The co-morbidities were selected and grouped according to our previous publications [17, 18]. Other confounders were age, sex, and visual impairment (distance VA ≤ 0.25). Because the cost data were right-skewed and the proportion of participants with zero costs was under 20% [28], we applied Tweedie distribution using gamma with log link scale response which showed the best fit using package statmod 1.4.36 [29]. We used both forward and backward stepwise methods to evaluate the fitness of the generalized linear model, and for the final analysis we chose a model with non-eye-related co-morbidities. We estimated the marginal means and contrasts using package emmeans 1.7.3 [30].

Ethics approval and informed consent

The Health 2000 Survey was approved by the Coordinating Ethics Committee at the Hospital District of Helsinki and Uusimaa in Finland [16]. The survey was conducted in accordance with the ethical standards of the institutional and national research committees, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants [16].

Results

Of the 8,028 members of the Health 2000 survey sample, 7,367 (91.8%) had information available on glaucoma status and both direct and indirect costs. Of the 192 study participants who had economic data available and had glaucoma, 141 were treated with medication, 59 were treated with surgery (of which 39 were also treated with medication), and 31 had no known treatment. Details of the study population are summarized in Table 2.

All glaucoma groups showed significantly higher number of both eye-related and non-eye-related hospitalizations and outpatient visits than persons without glaucoma even after adjusting for age and sex ($p < 0.001$; Fig 1). Outpatient care was more frequent than inpatient care among both glaucomatous and non-glaucomatous subjects. Five percent and four percent of glaucoma patients had no non-eye-related hospitalizations or outpatient visits compared with 28% and 16% among the glaucoma negatives, respectively. The annual average time spent hospitalized due to eye- or non-eye-related diagnosis was significantly higher in all glaucoma groups than among persons without glaucoma even after adjusting for age and sex ($p < 0.001$; Table 3). Travel costs of eye- and non-eye-related outpatient visits were significantly higher in all glaucoma groups than persons without glaucoma even after adjusting for age and sex ($p < 0.001$). Glaucoma patients had a higher self-reported outpatient health care service use than persons without glaucoma even after adjusting for age and sex ($p < 0.001$; Fig 2); however, glaucoma patients treated with medication or surgery had lower use of occupational health care than persons without glaucoma ($p < 0.001$) due to their higher retirement number. Visits to "other doctor" were omitted from the figure due to their low number (average 9 visits / 100 persons / year in the study population). No statistically significant differences were observed within the three glaucoma groups in any of the above-mentioned parameters.

Direct mean costs are shown in Table 4 and 95% confidence intervals in S2 Table. All glaucoma groups showed significantly higher direct costs than persons without glaucoma even after adjusting for age and sex ($p < 0.001$), yet no statistically significant differences were observed within the three glaucoma groups. After adjusting for age and sex, the observed health care expenditure in the total Finnish glaucomatous population was EUR 202 million (non-adjusted EUR 886 million) higher compared with the expected level based on average costs per person in the non-glaucomatous population at the 2019 cost level. The share of eye-related expenses was 12.9% of the age- and sex-adjusted additional expenditure and 2.7% of the non-adjusted additional expenditure among the glaucomatous population. The additional adjusted expenditures were EUR 100 million (non-adjusted EUR 521 million) among glaucoma patients treated with medication and EUR 92 million (non-adjusted EUR 346 million) among operated glaucoma patients. The share of adjusted additional eye-related expenses was 20.9% (non-adjusted 4.1%) for medicated and 7.8% (non-adjusted 2.9%) for operated glaucoma patients. Glaucoma patients who had been operated but did not use glaucoma

Table 2. Summary of the health 2000 study population aged 30 year and older.

	n	% women	Mean age (years; SD)
Eligible sample	8,028	55	54 (16)
Direct and indirect costs known	7,368[a]	55	54 (16)
Glaucoma status known	7,367	55	54 (16)
Glaucoma, all	192	71	74 (11)
Glaucoma, medication	141	73	74 (11)
Glaucoma, operated	59	68	75 (12)
Glaucoma negatives	6,952	54	53 (16)

SD = standard deviation

[a]Four persons had missing data on retirement status

https://doi.org/10.1371/journal.pone.0295523.t002

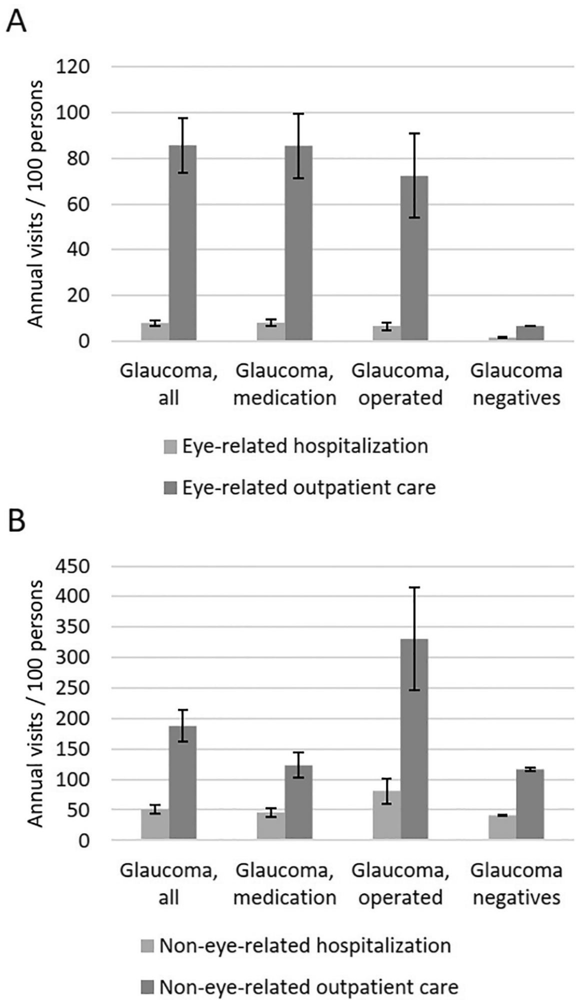

Fig 1. Average eye-related (A) and non-eye-related (B) hospitalizations and outpatient visits per year adjusted for age and sex with 95% confidence intervals. Differences between glaucoma groups and glaucoma negatives were statistically significant ($p < 0.001$). There were no significant differences within glaucoma groups. Data on hospitalizations and outpatient visits were collected during 1999–2011.

https://doi.org/10.1371/journal.pone.0295523.g001

medication showed two times higher non-eye-related costs in comparison to glaucoma patients with only medical treatment (S3 Table). Most of the direct expenditures came from hospitalizations: 83.4% of adjusted costs (non-adjusted 82.3%) among glaucoma negatives, 78.8% (non-adjusted 91.2%) among glaucoma patients, 81.5% (non-adjusted 89.4%) among glaucoma patients treated with medication, and 73.8% (non-adjusted 90.9%) among operated glaucoma patients. Overall, most of the additional costs among glaucomatous population came from non-eye-related hospitalizations.

Table 3. Mean time spent hospitalized annually per 100 persons adjusted for age and sex.

	Eye-related hospitalization (days; 95% CI)	Non-eye-related hospitalization (days; 95% CI)
Glaucoma, all	14 (12–16)	679 (583–774)
Glaucoma, medication	17 (14–19)	619 (517–721)
Glaucoma, operated	14 (11–18)	742 (552–931)
Glaucoma negatives	2 (2–2)	488 (476–499)

Differences between glaucoma groups and glaucoma negatives were statistically significant ($p < 0.001$). There were no significant differences within glaucoma groups.
Data on hospitalization length were collected during 1999–2011.
CI = confidence interval

https://doi.org/10.1371/journal.pone.0295523.t003

Indirect mean costs due to premature retirement are shown in Table 5 and 95% confidence intervals in S4 Table. A total of 3,801 participants with glaucoma status known reported to have retired by 2011. Among study participants aged 30–64 years, premature retirement was granted to 29 (85.3%) glaucoma patients, 21 (80.8%) glaucoma patients with medication, 7 (70.0%) operated glaucoma patients, and 1572 (29.8%) glaucoma negatives by 2011. There were no statistical differences in personal indirect costs between the three glaucoma groups and glaucoma negatives and within the three glaucoma groups. However, at the population level, glaucoma was associated with a total additional expenditure of EUR 71 million per year in comparison to glaucoma negatives at the 2019 cost level. The additional expenditures were EUR 41 million among glaucoma patients treated with medication and EUR 63 million among

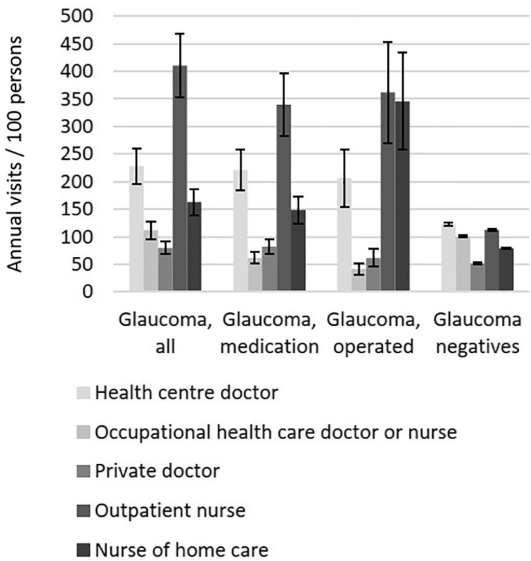

Fig 2. Average self-reported use of outpatient health care services in the year 2000 adjusted for age and sex with 95% confidence intervals. Differences between glaucoma groups and glaucoma negatives were statistically significant ($p < 0.001$). There were no significant differences within glaucoma groups.

https://doi.org/10.1371/journal.pone.0295523.g002

Table 4. Mean annual direct health care costs in the Finnish population aged 30 years and older at the 2019 cost level.

	Annual costs per person (EUR)												Annual costs in Finland (EUR)
	Hospitalizations		Outpatient visits		Outpatient health care services	Outpatient travels		Total costs[a]		Additional costs (vs. glaucoma negatives)		Population[b]	Total additional costs
	Eye	Non-eye	Eye	Non-eye	All	Eye	Non-eye	Eye	Non-eye	Eye	Non-eye		All
Non-adjusted costs													
Glaucoma negatives	22	4,001	16	376	434	2	36	40	4,847			3,067,899	
Glaucoma, all	175	14,915	162	511	722	20	46	357	16,193	318	11,347	75,979	886,240,017
Glaucoma, medication	207	12,436	186	508	729	24	47	417	13,721	378	8,874	56,344	521,259,595
Glaucoma, operated	226	17,866	215	672	846	29	57	471	19,441	431	14,594	22,996	345,523,136
Adjusted for age and sex													
Glaucoma negatives	24	4,415	16	379	451	2	36	42	5,281			3,067,899	
Glaucoma, all	152	6,141	209	610	798	24	50	385	7,598	343	2,317	75,979	202,094,791
Glaucoma, medication	178	5,601	209	400	644	25	35	412	6,680	370	1,399	56,344	99,674,677
Glaucoma, operated	154	6,712	177	1,074	1,085	22	79	352	8,950	310	3,669	22,996	91,500,191

All eye- and non-eye-related adjusted and non-adjusted direct annual costs per person were significantly higher in the three glaucoma groups compared with glaucoma negatives ($p < 0.001$), but there were no significant differences within the three glaucoma groups. 95% confidence intervals are provided in S2 Table.

[a]Total eye costs consist of eye-related hospitalizations, outpatient visits, and outpatient travels during 1999–2011; total non-eye-related costs consist of non-eye-related hospitalizations, outpatient visits, and outpatient travels during 1999–2011 and all outpatient health care services in 2000

[b]Calculated using population weights in the Health 2000 survey

https://doi.org/10.1371/journal.pone.0295523.t004

operated glaucoma patients. Productivity losses comprised majority (70.9%) of the total indirect expenditures in all groups.

After adjusting for age, sex, and non-eye-related co-morbidities (S5 Table), glaucoma or its treatment did not show statistically significant association with total direct costs compared with glaucoma negatives. When sex and non-eye-related co-morbidities were set constant and age at the average of the glaucomatous population in Finland (71.9 years), the mean annual total direct costs were EUR 46,746 (95% confidence interval [CI] 27,470–66,022) for a glaucoma patient, EUR 43,591 (95% CI 23,985–63,196) for a glaucoma patient with medical treatment, and EUR 54,721 (95% CI 28,570–80,872) for an operated glaucoma patient at the 2019 cost level. In a model that also included eye-related co-morbidities (unoperated cataract,

Table 5. Mean indirect costs in the Finnish population aged 30–64 years at the 2019 cost level.

	Costs per person retired prematurely (EUR)				Annual costs per person retired prematurely (EUR)[a]			Annual costs in Finland (EUR)[a]
	Premature retirement	Productivity loss	Total costs	Additional costs (vs. glaucoma negatives)	Total costs	Additional costs (vs. glaucoma negatives)	Population[b]	Total additional costs
Glaucoma negatives	154,185	376,151	530,336		16,268		2,415,553	
Glaucoma, all	194,823	475,294	670,118	139,782	20,556	4,288	16,613	71,233,046
Glaucoma, medication	184,947	451,198	636,145	105,809	19,514	3,246	12,687	41,177,951
Glaucoma, operated	276,467	674,473	950,941	420,605	29,170	12,902	4,902	63,245,527

No statistical differences were observed in personal indirect costs between the three glaucoma groups and glaucoma negatives and within the three glaucoma groups. Data were collected during 1999–2011. 95% confidence intervals are provided in S4 Table.

[a]Annual costs calculated by dividing costs per person by the average years expected to work in a lifetime in Finland (32.6 years in 2011) [24]

[b]Calculated using population weights in the Health 2000 survey

https://doi.org/10.1371/journal.pone.0295523.t005

retinal degeneration, visual impairment), visual impairment showed third strongest impact on total direct costs after Parkinson's disease and psychiatric disorders.

Total indirect costs adjusted for age, sex, and non-eye-related are shown in Table 6. Only operated glaucoma showed statistically significant association with total indirect costs compared with glaucoma negatives after adjusting for these predictors (additional indirect costs EUR 23,015; p = 0.019). When sex and non-eye-related co-morbidities were set constant and age at the average of the glaucomatous population below age of 65 years in Finland (55.3 years), the mean annual total indirect costs were EUR 33,718 (95% CI 20,857–46,578) for a glaucoma patient, EUR 33,974 (95% CI 19,168–47,780) for a glaucoma patient with medical treatment, and EUR 49,204 (95% CI 21,159–77,249) for an operated glaucoma patient at the 2019 cost level. In a model that also included eye-related co-morbidities, visual impairment showed strongest impact on total indirect costs of all included predictors.

The association between distance vision and both direct and indirect costs is illustrated in Fig 3. The two lowest vision groups were combined due to low number of glaucoma patients under 65 years of age in these groups. A strong negative association between vision and costs was observed regardless of whether a person has glaucoma or not: correlation coefficients in the studied groups ranged from -0.24 to -0.36 regarding direct costs and from -0.16 to -0.58 regarding indirect costs. Although both direct and indirect cost appeared to be higher among glaucoma patients than negatives, no statistically significant differences were observed.

Discussion

To our knowledge, this is the first cost-of-illness study of glaucoma to report both direct and indirect costs associated with the disease based on nationally representative data. The comprehensive data allowed us to include eye- and non-eye-related treatments, as well as to compare glaucoma with other co-morbidities. Here we show that glaucoma is associated with a high economic burden on the society. The major proportion of the costs is not directly caused by treatment of glaucoma, but rather the increased use of non-eye-related health services, as well as loss of productivity. In addition, different treatment options for glaucoma show noticeable differences in costs and resource use.

We calculated age- and sex-adjusted costs because glaucoma patients are in average 20 years older than persons without glaucoma. In 2019, the expenditures of health care in Finland were EUR 23.4 billion in total [31]. In the present study, the adjusted direct additional expenditures associated with glaucoma corresponded to 0.86% (EUR 202,094,791) of this cost. The prevalence of glaucoma in Finnish adult population is approximately 2.6% [2], and this figure is likely to increase due to the rapid ageing of the Finnish population. Therefore, the direct costs of glaucoma can be considered significant, and this economic burden is likely to increase in the future with increasing life expectancy and shifting in age distribution in Finland and other developed countries.

While glaucoma care has been organized in different ways around the world, glaucoma is globally considered a major burden for health care resources. In the US, the annual direct medical costs of glaucoma were estimated to be USD 2.9 billion in 2004 [13]. In Australia, the annual direct eye-related costs of glaucoma were estimated to be AUD 144.2 million in 2004 [14]. In both countries, the direct medical costs of glaucoma corresponded to 8% of total medical costs of visual disorders [13, 14]. Furthermore, the costs of glaucoma are usually considered underestimated due to the high percentage of undiagnosed glaucoma [32, 33].

Despite the economic implications of glaucoma, few studies have provided nationwide estimations of all direct and indirect costs of the disease. In 1990 in the UK, the direct medical costs associated with glaucoma were GBP 61 million, direct non-medical costs GBP 25 million

Table 6. Multivariable regression analysis examining the impact of glaucoma, age, sex, and non-eye-related co-morbidities on total annual indirect costs in population aged 30–64 years at the 2019 cost level.

	B coefficient	Marginal mean (EUR)	Marginal mean contrast (EUR)	P value		B coefficient	Marginal mean (EUR)	Marginal mean contrast (EUR)	P value		B coefficient	Marginal mean (EUR)	Marginal mean contrast (EUR)	P value
Constant	12.980			< 0.001	Constant	12.984			< 0.001	Constant	12.954			< 0.001
Age	–0.006			0.10	Age	–0.006			0.10	Age	–0.005			0.13
Male sex	0.091	31,027	2,695	0.023	Male sex	0.091	31,184	2,722	0.022	Male sex	0.088	37,503	3,142	0.030
Glaucoma, all	0.257	33,718	7,647	0.10	Glaucoma, medication	0.263	33,974	7,849	0.15	Glaucoma, operated	0.631	49,204	23,015	0.019
Heart disease	0.248	27,328	6,006	< 0.001	Heart disease	0.251	27,495	6,096	< 0.001	Heart disease	0.251	33,133	7,354	< 0.001
Pulmonary disease	0.097	25,333	2,332	0.037	Pulmonary disease	0.094	25,421	2,277	0.043	Pulmonary disease	0.094	30,628	2,739	0.043
Vascular disease	0.094	25,296	2,261	0.09	Vascular disease	0.097	25,458	2,347	0.08	Vascular disease	0.091	30,583	2,654	0.10
Musculoskeletal condition	0.095	25,309	2,285	0.036	Musculoskeletal condition	0.094	25,422	2,280	0.038	Musculoskeletal condition	0.096	30,658	2,797	0.033
Hypertension	0.012	24,281	282	0.79	Hypertension	0.008	24,356	199	0.85	Hypertension	0.008	29,346	240	0.85
Diabetes	0.171	26,300	4,144	0.021	Diabetes	0.175	26,475	4,252	0.018	Diabetes	0.181	31,988	5,286	0.016
Psychiatric disorder	0.446	30,163	10,846	< 0.001	Psychiatric disorder	0.441	30,240	10,784	< 0.001	Psychiatric disorder	0.453	36,651	13,345	< 0.001
Parkinson's disease	0.152	26,050	3,682	0.52	Parkinson's disease	0.154	26,199	3,742	0.51	Parkinson's disease	0.154	31,560	4,495	0.52
Cancer	0.150	26,025	3,635	0.13	Cancer	0.151	26,158	3,666	0.13	Cancer	0.147	31,462	4,312	0.14

Tweedie distribution using gamma with log link scale response was applied to the model. The analysis was based on participants with information available for all predictors (n = 1688–1710). The age was standardized for the average age of glaucomatous population in Finland under 65 years of age (55.3 years) for the marginal means and contrasts. Marginal mean contrasts equal the difference between those with a medical condition (or of male sex) and those without a medical condition (or of female sex) standardized for all other factors. Statistical significance was calculated for both the B coefficients and marginal mean contrasts.

https://doi.org/10.1371/journal.pone.0295523.t006

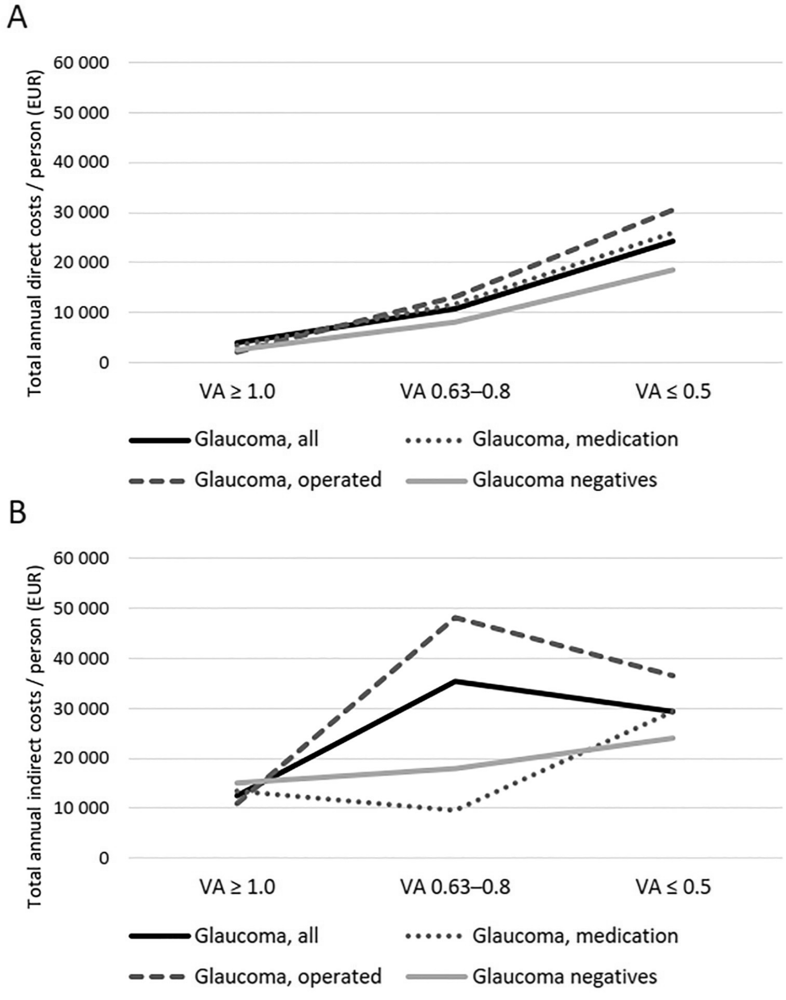

Fig 3. Association between average distance visual acuity (VA) and total annual direct costs (A) and indirect costs (B) among glaucoma patients and glaucoma negatives at the 2019 cost level. Direct costs were evaluated in population aged 30 years and older, and indirect costs in population aged 30–64 years.

https://doi.org/10.1371/journal.pone.0295523.g003

among visually impaired, and indirect costs GBP 45 million [34]. In a more recent study in Nigeria, Adio and Onua reported an annual direct and indirect loss of USD 1,265 per person for treatment of glaucoma, resulting in a total expenditure of USD 4,095,000 [35]. However, both studies only included costs related to glaucoma treatment, which explains why the average costs are lower than in our study. Finally, in a review by Dirani et al., they created a prediction model on primary open-angle glaucoma in Australia that during 2005–2025 direct health system costs will increase from AUD 355 million to AUD 784 million and total costs (direct and indirect) from AUD 1.9 billion to AUD 4.3 billion [36].

Medication represents the major cost of glaucoma treatment. In the US, the cost of glaucoma care for Medicare beneficiaries was USD 748 million in 2009 [15]. In Sweden and France, the respective annual costs of glaucoma treatment were EUR 531 and EUR 390 per patient, with medication costs comprising approximately half of the total costs [9]. In Denmark, the annual treatment cost was EUR 305 per glaucoma patient under their initial regimen, of which 57% was accounted by glaucoma drugs [11]. In Finland, the total cost of glaucoma medication was EUR 25.5 million in 2011 with an average of EUR 352 per patient [37]. When adding the direct eye-related treatment costs in our study (EUR 393 per patient), the average annual glaucoma treatment cost per medicated glaucoma patient at 2019-level would be EUR 745, 47% consisting of medication costs, which is within the range of previous glaucoma resource utilization studies. The high costs associated with glaucoma medicine are likely due to the increased consumption of anti-glaucoma drugs in recent decades and the use of newer and more expensive drugs [36]. Furthermore, the severity of glaucoma has been reported to increase the direct costs of its treatment [38, 39].

There has not been definitive conclusion on whether medical or surgical treatment of glaucoma is more cost-effective [9]. In our study, operated glaucoma patients showed higher use of outpatient care and hospitalization than medicated patients. Although this difference was not statistically significant, it becomes particularly noticeable when costs are considered: even after adjusting for age and sex, the annual total direct costs are EUR 2,210 (31.2%) higher for an operated patient than medicated patient. Still, if the estimated drug costs [37] are added to the expenditures associated with medicated glaucoma, the expenditures for medicated glaucoma patients are higher than reported. The annual indirect costs for an operated patient are EUR 9,656 (49.5%) higher compared with a medicated patient. Patients needing glaucoma surgery are in general more often unable to take care of their medication due to their co-morbidities. This is one of the possible explanations why glaucoma patients only treated with surgery showed higher total direct costs than glaucoma patients only treated with medication. It is also important to remember that glaucoma surgery is in many cases the last option to prevent the progression of glaucoma and consequent visual loss, both of which are associated with additional direct and indirect costs.

Despite the role of treatment in the economic burden of glaucoma observed in previous studies, in our study, majority of the direct health care costs came from non-eye-related services. We also observed a significant increase in the average time spent hospitalized among glaucoma patients in comparison to non-glaucomatous population. This is most likely related to the irreversible vision loss associated with glaucoma and its progression. The severity of visual impairment increases the resource consumption and intensity of care likely due to the increased risk of falls, accidents, and injuries associated with decreased vision [40]. Indeed, glaucoma patients have been reported increased risk of falls and other accidents, which contribute to significant amount of bed days with an economic and operational impact on the hospitals [41–43]. Vision loss is associated with high economic impact [44], and the costs among blinded patients can be twice the amount among patients with normal vision [40]. Also, we observed a strong relationship between decreasing vision and both increasing direct and indirect costs regardless of glaucoma status. Therefore, the role of early intervention in glaucoma care to prevent the progression of visual impairment is vital in alleviating the economic burden of the disease to the society, as well as the detrimental effect on quality of life, independence, and social activity of the patient [17, 45, 46]. In addition, the impact of vision on the societal costs calls for further research.

The indirect costs associated with glaucoma are also considerable. The Finnish gross domestic product was EUR 239.9 billion in 2019 according to the Statistics Finland -database. Additional productivity losses caused by glaucoma alone corresponded to 0.03% (EUR

71,233,046) of the product that year. Loss of productivity among glaucoma patients is likely contributable to vision loss associated with the disease, as visual impairment is associated with nursing home admission, falls, injuries, accidents, and femur fracturs, all of which can lead to work invalidity [40]. Visual impairment and blindness are regarded as major causes of productivity losses worldwide [47]. Therefore, by preventing the progression of vision loss due to glaucoma with early diagnosis and prompt and adhered treatment, significant economic losses could be averted.

Both direct and indirect glaucoma costs showed strong dependency on vision and other co-morbidities. These factors are associated either directly with glaucoma or indirectly through ageing [48–50], which likely explains this effect. However, the indirect additional costs of operated glaucoma are significant even after adjusting for these co-morbidities, which implies the severity and specific surgical indications of the operated glaucoma patients.

The strengths of our study include the representative sample of the Finnish adult population, the multiple data sources, and the long follow-up period that increase the validity and reliability of the results. The Health 2000 Survey addressed public health issue more broadly than national surveys do on average. The survey sample represents the population particularly well due to the comprehensive sampling design and the high participation rate. This allowed us to include a sample of glaucoma patients and negatives at national level rather than from clinical settings. The data design of the national health survey reduces the impact of potential confounding factors, which was further reduced by controlling the co-morbidities and other confounding factors using multivariable modelling. In addition, the applied weighting scheme improves the applicability to population level. Our prevalence-based bottom-up approach aids to avoid the misallocation of costs, which is more likely to occur in top-down approach [51]. Although prevalence-based approach may not accurately quantify the long-term consequences of the study condition leading to underestimation of costs [51], our long, 13-year follow-up time should alleviate the potential bias associated with this approach.

Our study also has limitations that need to be addressed. While our use of multiple data sources can be regarded as a major strength, it also can produce difficulties in processing and integrating data as its availability varied between sources. The time differences between key inputs should be considered, as the data were collected during a 13-year follow-up time during 1999–2011 and the costs were converted to the 2019 level. We could not differentiate eye- and non-eye-related self-reported outpatient health care service visits. While the share of ophthalmologist visits in health centers should be small, the share among private practitioners can be higher, therefore causing bias. We were not able include laboratory costs in private health care in the calculations due to the classified nature of the data. However, laboratory costs are included in public health care unit costs, which should alleviate this deficiency in total cost analyses. We were also unable to include the costs of care outside the health system as well as non-health care costs, for example, those caused by social services, childcare, and housekeeping. Drugs and prescriptions were also not included in the cost analyses, although we discussed their share based on the medication cost estimations by Parkkari and co-workers [37]. While the cost of disability pensions and premature retirement were included, productivity losses might be underestimated because we were not able to get data on sick leaves. Despite this, the estimated costs in this study are generalizable to the Finnish adult population or to a similar setting in terms of population age structure and financial support system from government, such as all Nordic countries and several European countries. Glaucoma classifications were based on register data on observations made by a private ophthalmologist, which can cause biases: for example, high intraocular pressure may have been diagnosed as glaucoma, even though it may not have been the case.

In conclusion, we report annual direct and indirect additional expenditures of EUR 202,094,791 and EUR 71,233,046 among glaucomatous population in Finland. Therefore, glaucoma is a significant economic burden on the health care and society. Majority of the direct expenses come from non-eye-related hospitalizations, and productivity losses comprise most of the indirect expenses. The need for expensive hospitalization is most likely contributable to the progressing vision loss and consequent increase in risk of injuries and accidents among glaucoma patients. The high age and consequent increase in co-morbidities among glaucoma patients are also contributable factors to the additional costs of glaucoma. Moreover, different glaucoma treatments show substantial variability in costs and resource use, most probably due to the uneven distribution of co-morbidities. Given the limited resources available to health care providers, early-stage interventions to prevent glaucoma progression as well as allocating sufficient resources to ophthalmic care are a necessity to avoid economic challenges in the future as the population ages. The increased allocation may pay itself off multiple times with the future savings. Further research in other countries is necessary to address the economic implications of glaucoma in the big picture to confirm our results and to help the prioritizing of health care resources.

Supporting information

S1 Appendix. CHEERS 2022 guidelines followed in this study.
(DOCX)

S1 Table. Direct and indirect costs in Finland in 2011 and 2019.
(DOCX)

S2 Table. Mean annual direct health care costs with 95% confidence intervals (CIs) in the Finnish population aged 30 years and older at the 2019 cost level.
(DOCX)

S3 Table. Mean non-adjusted direct health care costs in glaucoma patients with different treatments at the 2019 cost level.
(DOCX)

S4 Table. Mean indirect costs with 95% confidence intervals (CIs) in the Finnish population aged 30–64 years at the 2019 cost level.
(DOCX)

S5 Table. Multivariable regression analysis examining the impact of glaucoma, age, sex, and non-eye-related co-morbidities on total annual direct health care costs in population aged 30 years and older at the 2019 cost level.
(DOCX)

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ERRATUM TO: PUBLICATION III

Erratum sent to PLOS ONE 24.1.2024

Two of our sources of expenses, annual gross domestic product and travel cost per outpatient visit, were inaccurate, as they were already corrected for inflation. These corrections had only a minor impact on the costs presented in our article and do not have impact on the scientific understanding of the study and conclusions of the article. Following is a list of corrected cost estimates presented in the study.

The annual age- and sex-adjusted additional total direct costs were **EUR 2,658**/glaucoma patient, **EUR 1,768**/glaucoma patient with medication, and **EUR 3,975**/operated glaucoma patient compared with persons without glaucoma. The annual additional total indirect costs were **EUR 4,035**/glaucoma patient, **EUR 3,054**/glaucoma patient with medication, and **EUR 12,141/**operated glaucoma patient compared with persons without glaucoma. The annual direct and indirect additional expenditures were **EUR 201,931,493** and **EUR 67,032,633** among glaucomatous population in Finland, respectively.

The share of eye-related expenses was **12.8%** of the age- and sex-adjusted additional direct expenditure among the glaucomatous population. Most of the direct expenditures came from hospitalizations: **78.9%** (non-adjusted **91.2%**) among glaucoma patients, **81.5%** (non-adjusted **89.5%)** among glaucoma patients treated with medication, and **73.9%** (non-adjusted **90.9%**) among operated glaucoma patients.

Productivity losses comprised majority (**69.1%**) of the total indirect expenditures in all groups.

After adjusting for age, sex, and non-eye-related co-morbidities, only operated glaucoma showed statistically significant association with total indirect costs compared with glaucoma negatives after adjusting for these predictors (additional indirect costs **EUR 21,658**; p = 0.019). When sex and non-eye-related co-morbidities were set constant and age at the average of the glaucomatous population below age of 65 years in Finland (55.3 years), the mean annual total indirect costs were **EUR 31,730 (95% CI 19,628–43,832)** for a glaucoma patient, **EUR 31,971 (95% CI 18,038–45,904)** for a glaucoma patient with medical treatment, and **EUR 46,303 (95% CI 19,912–72,694)** for an operated glaucoma patient.

When adding the direct eye-related treatment costs in our study (**EUR 387** per patient), the average annual glaucoma treatment cost per medicated glaucoma patient at 2019-level would be **EUR 739**, **48%** consisting of medication costs, which is within the range of previous glaucoma resource utilization studies.

Even after adjusting for age and sex, the annual total direct costs are **EUR 2,207 (31.1%)** higher for an operated patient than medicated patient. The annual indirect costs for an operated patient are **EUR 9,087 (49.5%)** higher compared with a medicated patient.

Table 4. Mean annual direct health care costs in the Finnish population aged 30 years and older at the 2019 cost level

	Annual costs per person (EUR)											Population[b]	Annual costs in Finland (EUR)
	Hospitalizations		Outpatient visits		Outpatient health care services	Outpatient travels		Total costs[a]		Additional costs (vs. glaucoma negatives)			Total additional costs
	Eye	Non-eye	Eye	Non-eye	All	Eye	Non-eye	Eye	Non-eye	Eye	Non-eye		All
Non-adjusted costs													
Glaucoma negatives	22	4,001	16	376	434	2	34	39	4,845			3,067,899	
Glaucoma, all	175	14,915	162	511	722	19	43	356	16,191	317	11,346	75,979	886,109,578
Glaucoma, medication	207	12,436	186	508	729	22	44	416	13,718	376	8,873	56,344	521,148,787
Glaucoma, operated	226	17,866	215	672	846	27	53	469	19,437	430	14,593	22,996	345,456,778
Adjusted for age and sex													
Glaucoma negatives	24	4,415	16	379	451	2	34	42	5,279			3,067,899	
Glaucoma, all	152	6,141	209	610	798	23	47	383	7,595	341	2,316	75,979	201,931,493
Glaucoma, medication	178	5,601	209	400	644	24	33	411	6,678	369	1,399	56,344	99,601,029
Glaucoma, operated	154	6,712	177	1,074	1,085	20	74	351	8,945	309	3,666	22,996	91,413,338

All eye- and non-eye-related adjusted and non-adjusted direct annual costs per person were significantly higher in the three glaucoma groups compared with glaucoma negatives ($p < 0.001$), but there were no significant differences within the three glaucoma groups. 95% confidence intervals are provided in S2 Table. [a]Total eye costs consist of eye-related hospitalizations, outpatient visits, and outpatient travels during 1999–2011; total non-eye-related costs consist of non-eye-related hospitalizations, outpatient visits, and outpatient travels during 1999–2011 and all outpatient health care services in 2000. [b]Calculated using population weights in the Health 2000 survey.

Table 5. Mean indirect costs in the Finnish population aged 30–64 years at the 2019 cost level

	Costs per person retired prematurely (EUR)				Annual costs per person retired prematurely (EUR)[a]			Annual costs in Finland (EUR)[a]
	Premature retirement	Productivity loss	Total costs	Additional costs (vs. glaucoma negatives)	Total costs	Additional costs (vs. glaucoma negatives)	Population[b]	Total additional costs
Glaucoma negatives	154,185	344,879	499,063		15,309		2,415,553	
Glaucoma, all	194,823	435,779	630,603	131,539	19,344	4,035	16,613	67,032,633
Glaucoma, medication	184,947	413,687	598,633	99,570	18,363	3,054	12,687	38,749,803
Glaucoma, operated	276,467	618,399	894,866	395,803	27,450	12,141	4,902	59,516,116

No statistical differences were observed in personal indirect costs between the three glaucoma groups and glaucoma negatives and within the three glaucoma groups. Data were collected during 1999–2011. 95% confidence intervals are provided in S4 Table. [a]Annual costs calculated by dividing costs per person by the average years expected to work in a lifetime in Finland (32.6 years in 2011) [24]. [b]Calculated using population weights in the Health 2000 survey.

Table 6. Multivariable regression analysis examining the impact of glaucoma, age, sex, and non-eye-related co-morbidities on total annual indirect costs in population aged 30–64 years at the 2019 cost level

	B coefficient	Marginal mean (EUR)	Marginal mean contrast (EUR)	P value		B coefficient	Marginal mean (EUR)	Marginal mean contrast (EUR)	P value		B coefficient	Marginal mean (EUR)	Marginal mean contrast (EUR)	P value
Constant	12.919			< 0.001	Constant	12.923			< 0.001	Constant	12.893			< 0.001
Age	–0.006			0.10	Age	–0.006			0.10	Age	–0.005			0.13
Male sex	0.091	29,198	2,536	0.023	Male sex	0.091	29,345	2,561	0.022	Male sex	0.088	35,291	2,957	0.030
Glaucoma, all	0.257	31,730	7,196	0.10	Glaucoma, medication	0.263	31,971	7,386	0.15	Glaucoma, operated	0.631	46,303	21,658	0.019
Heart disease	0.248	25,717	5,652	< 0.001	Heart disease	0.251	25,873	5,737	< 0.001	Heart disease	0.251	31,180	6,920	< 0.001
Pulmonary disease	0.097	23,839	2,194	0.037	Pulmonary disease	0.094	23,922	2,143	0.043	Pulmonary disease	0.094	28,822	2,577	0.043
Vascular disease	0.094	23,804	2,127	0.09	Vascular disease	0.097	23,957	2,209	0.08	Vascular disease	0.091	28,780	2,497	0.10
Musculoskeletal condition	0.095	23,816	2,150	0.036	Musculoskeletal condition	0.094	23,923	2,146	0.038	Musculoskeletal condition	0.096	28,850	2,632	0.033
Hypertension	0.012	22,849	266	0.79	Hypertension	0.008	22,919	188	0.85	Hypertension	0.008	27,616	226	0.85
Diabetes	0.171	24,749	3,900	0.021	Diabetes	0.175	24,914	4,001	0.018	Diabetes	0.181	30,102	4,974	0.016
Psychiatric disorder	0.446	28,385	10,206	< 0.001	Psychiatric disorder	0.441	28,457	10,148	< 0.001	Psychiatric disorder	0.453	34,490	12,558	< 0.001
Parkinson's disease	0.152	24,514	3,465	0.52	Parkinson's disease	0.154	24,654	3,521	0.51	Parkinson's disease	0.154	29,699	4,230	0.52
Cancer	0.150	24,490	3,421	0.13	Cancer	0.151	24,616	3,450	0.13	Cancer	0.147	29,606	4,058	0.14

Tweedie distribution using gamma with log link scale response was applied to the model. The analysis was based on participants with information available for all predictors (n = 1688–1710). The age was standardized for the average age of glaucomatous population in Finland under 65 years of age (55.3 years) for the marginal means and contrasts. Marginal mean contrasts equal the difference between those with a medical condition (or of male sex) and those without a medical condition (or of female sex) standardized for all other factors. Statistical significance was calculated for both the B coefficients and marginal mean contrasts.

PUBLICATION
IV

Changes in incidence and severity of visual impairment due to glaucoma during 40 years – a register-based study in Finland

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Acta Ophthalmologica 2022;100:534–540
doi: 10.1111/aos.15030

Changes in incidence and severity of visual impairment due to glaucoma during 40 years – a register-based study in Finland

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ABSTRACT.
Purpose: **To report the incidence and severity of reported visual impairment (VI) due to glaucoma and the changes in them during the past 40 years in Finland.**
Methods: **A register-based study, in which the data were collected from the Finnish Register of Visual Impairment between 1980 and 2019. These data included 5819 visually impaired glaucoma patients, of which 61% were female. Visual impairment (VI) was classified according to the Finnish national definitions. The number of treated glaucoma patients in Finland was calculated using glaucoma medication reimbursement data available between 1986 and 2019 from the Social Insurance Institution of Finland registers.**
Results: **The incidence of reported VI due to glaucoma per 100 000 persons had increased from 2.3 in the 1980s to 3.4 in the 2010s. During the same time period, the incidence of reported VI per 10 000 treated glaucoma patients had decreased from 32 in the 1980s to 21 in the 2010s. Primary open-angle glaucoma (45%) was the main subtype for reported VI due to glaucoma. During the 40 years, the proportion of mild VI and the age at the onset of reported VI had increased.**
Conclusion: **The incidence of reported VI due to glaucoma has increased during the 40 years, but the risk of treated glaucoma patients becoming visually impaired has decreased. Visual impairment (VI) also occurs at an older age. This is likely due to the earlier diagnoses and improved therapy. To prevent the unfavourable development of VI due to glaucoma among the ageing population in the future, all attempts need to be made to improve glaucoma care.**

Key words: glaucoma – incidence – register-based study – visual impairment

We thank Dr. Asko Siitonen for the skilful analyses of the register data. This study was supported by Glaukoomatukisäätiö Lux (A.V), Helsinki and Elsemay Björn Fund, Helsinki. Funding sources did not influence the study design, data collection, analysis, interpretation or writing of the publication. The decision of publishing the results was completely made by the authors.

Acta Ophthalmol. 2022: 100: 534–540

doi: 10.1111/aos.15030

Introduction

Glaucoma contributes significantly to the global causes of visual impairment (VI) and is the leading cause of irreversible blindness (Tham et al. 2014; Flaxman et al. 2017; GBD 2019 Blindness and Vision Impairment Collaborators & Vision Loss Expert Group of the Global Burden of Disease Study 2021). In Finland, glaucoma is the second most common reason for permanent VI after age-related macular degeneration and before diabetic retinopathy in the population aged 65 years or above (Ojamo 2021). These three prominent causes of VI reflect well with the situation in other Western countries with ageing populations. In Finland, the prevalence of glaucoma is approximately 4% among persons over 50 years and increases with age (Social Insurance Institution of Finland 2021).

Even though glaucoma care has improved during the past decades, glaucoma is still a blinding disease. It is estimated that in the follow-up of 15–20 years, approximately 16% of patients in clinical care will become visually impaired (Forsman et al. 2007; Peters et al. 2013). Since VI causes a severe reduction of quality of life (Taipale et al. 2019) and increases the use and costs of health care services (Mikhailova et al. 2018), it is vital to monitor its incidence and changes not only to measure the magnitude of this problem but also to evaluate the effectiveness of glaucoma care over time.

The aim of this register-based study was to report the incidence and severity of reported VI due to glaucoma between 1980 and 2019 and the changes in them during 40 years in Finland. We also assessed the age at the onset of reported VI and the age at death in visually impaired glaucoma patients. The data were collected from the Finnish Register of Visual Impairment. Visual impairment (VI) was classified according to the Finnish national definitions (Ojamo 2021). The number of treated glaucoma patients in Finland was obtained from the Social Insurance Institution of Finland registers (2021), based on persons with reimbursement for glaucoma medication.

Table 1. Finnish definitions of visual impairment (VI, based on the World Health Organization 1973 definitions with a modification of the nomenclature of the names of the VI classes).

Classification of VI	Visual acuity (VA)	Visual field
Mild vision loss	$0.3 > VA \geq 0.1$	
Moderate visual impairment	$0.1 > VA \geq 0.05$	
Severe visual impairment	$0.05 > VA \geq 0.02$	≥5° and <10° from central fixation
Near total blindness	$0.02 > VA - 1/\infty$	<5° from central fixation
Total blindness	VA = 0, no sense of light	

Materials and Methods

Finnish Register of Visual Impairment and definition of VI

The National Board of Health established the Finnish Register of Visual Impairment in 1983. The operation of the Register is regulated by the Act (556/89) and Decree (774/89) on National Personal Records kept under the Health Care System. The register includes data on eye diagnoses, home region, date of birth, year of onset VI and the classification of VI. The classification of VI is based on the examination of ophthalmologists and the Finnish definitions of VI based on the World Health Organization (1973) definitions with a modification of the nomenclature of the names of the VI classes, which are demonstrated in Table 1: (1) mild vision loss, (2) moderate VI, (3) severe VI, (4) near-total blindness and (5) total blindness. In addition, the sixth class of VI, non-defined blindness, is used when the notification data does not include visual acuity or visual field, but the ophthalmologist has notified the blindness of the person. The time of VI is determined based on the notification data, and if it does not exist, the date of registration is used. By the end of 2019, the register included data on 58 822 visually impaired patients, of whom 18 176 were still alive. In this study, we only included visually impaired patients who had glaucoma as the main diagnosis of VI (n = 5819).

We acquired the estimated total number of treated glaucoma patients in Finland from the Social Insurance Institution of Finland registers, based on the number of persons with reimbursement for glaucoma medication (data available from 1986 to 2019). Based on this data, we estimated the incidence of reported VI among the treated glaucoma patients. We also calculated the expected number of years with VI using the age at the onset of reported VI and age at death acquired from the Digital and population data services agency. These figures were compared to the age-specific life expectancies in the general population, provided by Statistics Finland (2021). This study was conducted in line with the tenets of the Helsinki Declaration. As this is a register-based study, the approval of the ethical committee is not needed according to the Finnish legislation.

Statistical analyses

All statistical analyses were performed using R software version 3.5.1 (R Core Team, Foundation for Statistical

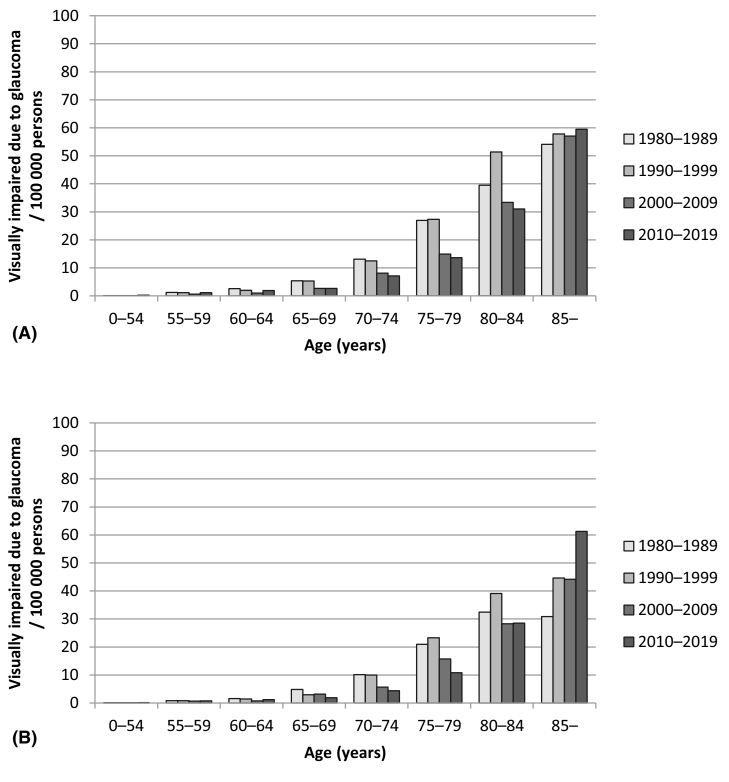

Fig. 1. Incidence of reported visual impairment due to glaucoma per 100 000 Finnish men (A) and women (B) in different decades.

Table 2. Age at the onset of VI in glaucoma patients.

	1980–1989	1990–1999	2000–2009	2010–2019
Men				
n	443	573	513	757
Mean, years (95% CI)	73.9 (72.9–74.9)	75.9 (75.0–76.8)	77.4 (76.4–78.4)	77.5 (76.6–78.4)
Women				
n	661	903	844	1125
Mean, years (95% CI)	76.0 (75.2–76.8)	78.9 (78.3–79.5)	80.7 (80.1–81.3)	82.6 (82.0–83.2)

There was a statistically significant difference in age between sexes in each decade ($p < 0.0001$, Mann–Whitney *U* test).
CI = confidence interval, VI = visual impairment.

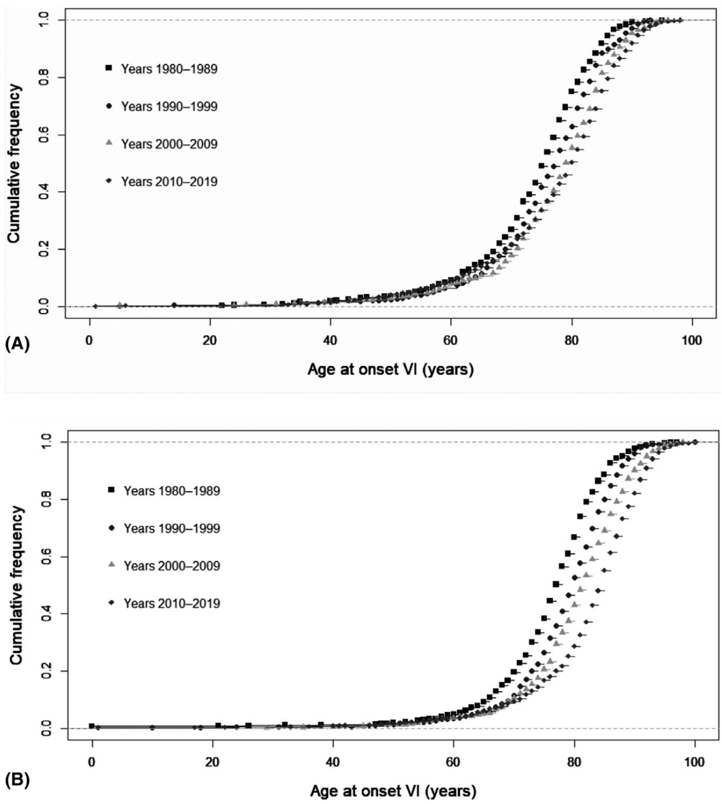

Fig. 2. Cumulative frequency of age at the onset of reported visual impairment (VI) for male (A) and female (B) glaucoma patients in different decades.

Computing, Vienna, Austria). As the distribution of the age data was left-skewed, Mann–Whitney *U* test was used for between-group comparisons and Kruskal–Wallis test to compare multiple groups. A chi-squared test was used for categorical variables when appropriate. A two-tailed p-value of < 0.05 was selected to determine statistical significance.

Results

The Finnish Register of Visual Impairment included altogether 5819 visually impaired persons with glaucoma as the main diagnosis, of whom 3533 (61%) were female and 2286 (39%) male. Of these patients, 1104, 1476, 1357 and 1882 had become visually impaired in the 1980s, 1990s, 2000s and 2010s, respectively. The shares of females were 59.9%, 61.2%, 62.2% and 59.8%, respectively. The calculated incidence of reported VI due to glaucoma in the Finnish population in the four decades by age and sex is shown in Fig. 1. The incidence was higher in women from the 1990s to the 2010s ($p < 0.05$, chi-squared test). The calculated total incidence of reported VI per 100 000 persons were 2.3, 2.9, 2.6 and 3.4 in the four decades, respectively. This increasing trend ($p = 0.0026$) was due to the increase in reported cases in the age group of 85 years and older, especially in women.

The mean age at the onset of reported VI due to glaucoma and the number of glaucoma patients who had become visually impaired in each decade are shown in Table 2 and Fig. S1. The mean age at the onset of reported VI was higher in women compared to men in all decades ($p < 0.0001$, Mann–Whitney *U* test). In addition, the mean age at the onset of reported VI increased with each decade in both sexes ($p < 0.0001$, Kruskal–Wallis test). The mean age at the onset of reported VI had increased by 3.6 years in men and 6.6 years in women between the 1980s and the 2010s. A cumulative age profile of the onset of reported VI in each decade is presented in Fig. 2.

The mean age at death in visually impaired glaucoma patients was investigated in each decade, as shown in Table 3. The mean age at death in women was higher compared to men in all decades ($p < 0.0001$). In addition, the mean age increased with each decade in both sexes ($p < 0.0001$). The development of mean age at the onset of reported VI and age at death between the decades is shown in Fig. 3. The expected number of years with VI had significantly decreased in women from 10.1 years in the 1980s to 7.0 years in the 2010s ($p < 0.0001$, Mann–Whitney *U* test). In men, this decreased from 9.6 years in the 1980s to 8.7 years in the 2010s, but this change was not statistically significant. For both men and women, the number of years with VI did not differ significantly from the life expectancy at the age at the onset of reported VI.

The classifications of reported VI in visually impaired glaucoma patients in the different decades are presented in Fig. 4. The percentage of mild vision

Table 3. Age at death in visually impaired glaucoma patients.

	1980–1989	1990–1999	2000–2009	2010–2019
Men				
n	431	544	443	285
Mean, years (95% CI)	83.5 (82.7–84.3)	84.9 (84.3–85.5)	85.6 (84.9–86.3)	86.2 (85.3–87.1)
Women				
n	647	867	723	442
Mean, years (95% CI)	86.1 (85.6–86.6)	87.7 (87.3–88.1)	88.9 (88.4–89.4)	89.7 (89.1–90.3)

There was a statistically significant difference in age between sexes in each decade ($p < 0.0001$, Mann–Whitney *U* test).
CI, confidence interval.

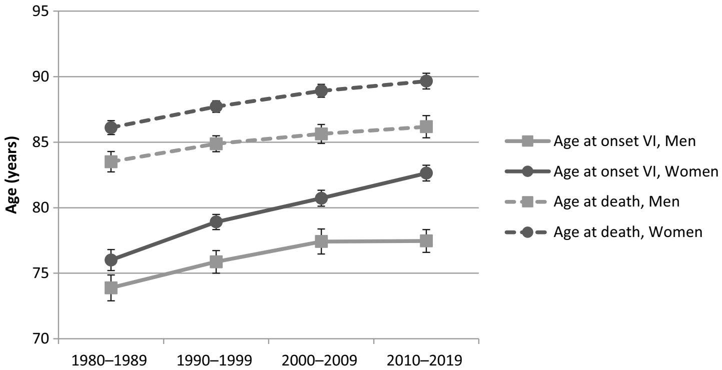

Fig. 3. Age at the onset of reported visual impairment (VI) and age at death (with 95% confidence intervals) in male and female glaucoma patients in different decades.

loss increased from 40% to 51% during the 40 years ($p < 0.0001$). There were no significant differences in the distribution and change of the classifications between sexes.

The percentages of glaucoma subtypes causing VI in Finland are listed in Table 4. During the 40 years, the most common diagnosis has been primary/chronic open-angle glaucoma (44.9%), followed by exfoliative glaucoma (29.8%) and normal-tension glaucoma (7.1%). We also compared this to the data from Purola et al. (2021a), Health 2000 (Aromaa & Koskinen 2004) and Health 2011 (Koskinen et al. 2012), which demonstrate the proportions of various subtypes of glaucoma in Finland. When compared to Health 2000 data, the risk of VI was highest in exfoliative glaucoma, followed by chronic angle-closure glaucoma, primary/chronic open-angle glaucoma and normal-tension glaucoma ($p < 0.0001$).

The mean numbers of treated glaucoma patients with reimbursed glaucoma medication increased by time: 37 475, 51 339, 69 405, and 88 217 in the four decades, respectively (Fig. S2). At the same time, the share of females declined: 68.8%, 68.9%, 67.1%, and

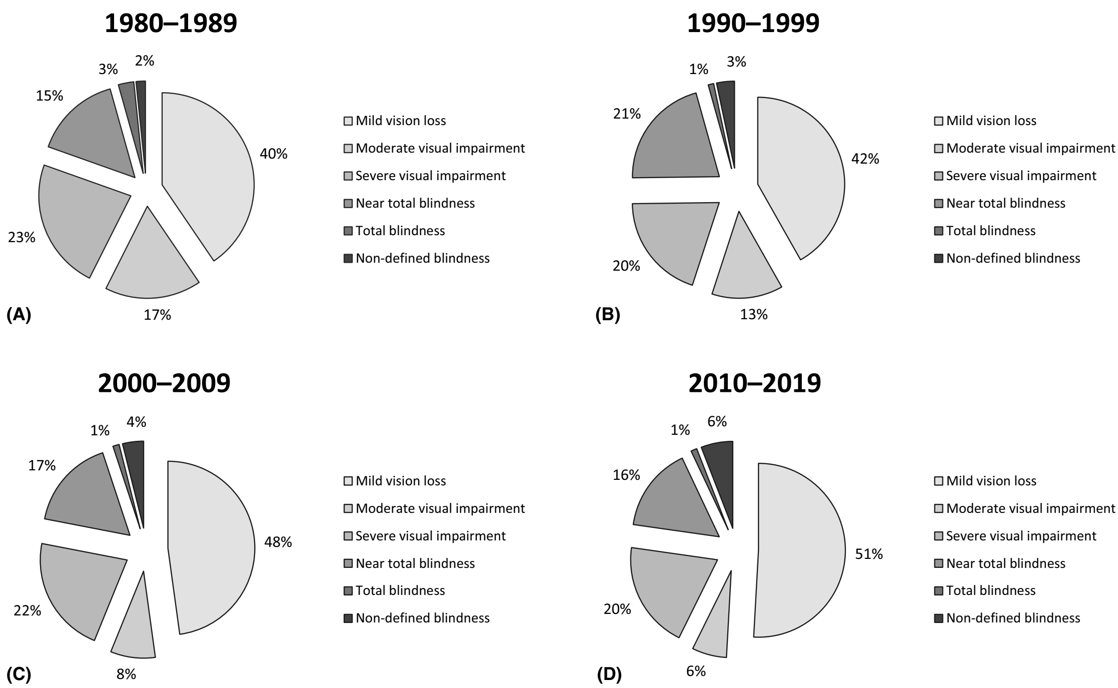

Fig. 4. Classifications of reported visual impairment in glaucoma patients in different decades.

Table 4. Distribution of glaucoma diagnoses in Finland.

	Glaucoma diagnoses associated with VI 1980–2019 (%)	Glaucoma diagnoses in 2000* (%)	Glaucoma diagnoses in 2011* (%)
Primary/chronic open-angle glaucoma	44.9	39.1	36.6
Exfoliative glaucoma	29.8	20.3	22.5
Normal-tension glaucoma	7.1	5.1	9.7
Pigmentary glaucoma	0.5	3.2	1.2
Unspecified open-angle glaucoma	0.5	1.1	3.0
Acute angle-closure glaucoma	0.2	6.6	3.9
Chronic angle-closure glaucoma	5.1	5.1	3.0
Unspecified primary angle-closure glaucoma	0.2	0.4	0.7
Glaucoma secondary to other disorder/factor	4.7	6.3	7.8
Other glaucoma	7.0	12.8	11.6

* Data from Purola et al. (2021b), Health 2000 (Aromaa & Koskinen 2004), and Health 2011 (Koskinen et al. 2012).

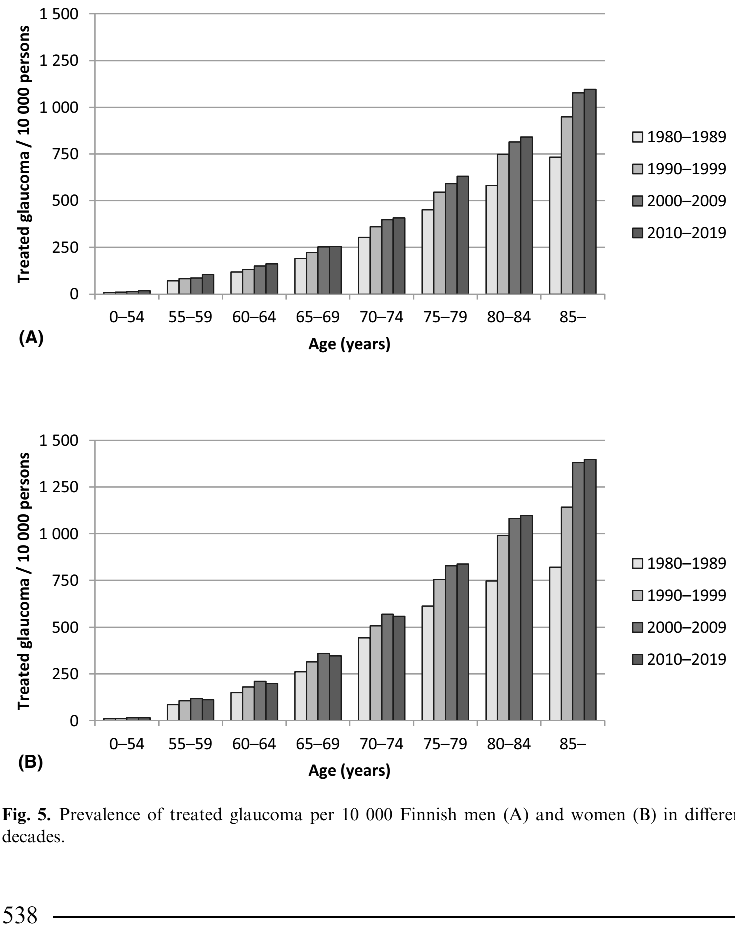

Fig. 5. Prevalence of treated glaucoma per 10 000 Finnish men (A) and women (B) in different decades.

63.3%. The calculated prevalence of treated glaucoma in the Finnish population in the four decades by age and sex is shown in Fig. 5. The prevalence was higher in women from the 1990s to the 2010s ($p < 0.05$). The calculated total prevalence of the treated glaucoma per 10 000 persons was 76, 101, 132 and 161 in the four decades, respectively, showing a significantly increasing trend ($p < 0.0001$). The calculated incidence of reported VI among the treated glaucoma patients is shown in Fig. 6. The calculated total incidence of reported VI per 10 000 treated glaucoma patients was 32, 29, 20 and 21 in the four decades, respectively, showing a significantly decreasing trend ($p < 0.0001$). Although the incidence appeared to be higher in men in all decades, this difference was statistically insignificant (Fig. 6).

Discussion

The number of visually impaired glaucoma patients and the incidence of reported VI due to glaucoma have increased since the 1980s. However, the incidence of reported VI among treated glaucoma patients has decreased in the past four decades in Finland. Similar findings have been presented globally (Flaxman et al. 2017; GBD 2019 Blindness and Vision Impairment Collaborators & Vision Loss Expert Group of the Global Burden of Disease Study 2021). During the same time period, the percentage of mild vision loss among visually impaired glaucoma patients has increased. This positive trend has also been reported globally (Flaxman et al. 2017). These changes suggest that the risk of VI for a glaucoma patient has decreased, probably due to the improved therapeutic options, their availability and earlier diagnosis of glaucoma.

The main subtype of glaucoma causing VI in Finland is primary open-angle glaucoma, followed by exfoliative glaucoma and normal-tension glaucoma. This is in good accordance with the proportions of glaucoma subtypes in Finland (Parkkari et al. 2019; Purola et al. 2021a). As in many other populations of European ancestry (Tham et al. 2014), the prevalence of angle-closure glaucoma and VI due to it is low in Finland (Ojamo 2021). Globally, however, even though open-angle

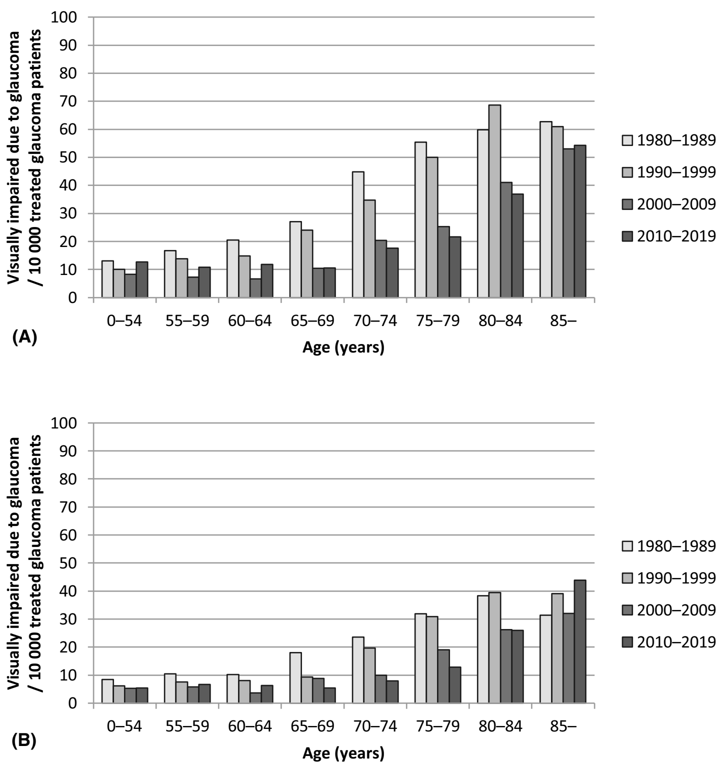

Fig. 6. Incidence of reported visual impairment due to glaucoma per 10 000 Finnish men (A) and women (B) with treated glaucoma in different decades.

glaucoma is substantially more common than angle-closure glaucoma, blindness is more likely to occur in the latter (Quigley & Broman 2006).

The age at the onset of reported VI has increased during the past 40 years. The causes are probably related to better glaucoma care, e.g. improved therapy, their availability and earlier diagnoses. Another explanation could be the increased life expectancy of the population. However, the life expectancy of the glaucoma patients did not significantly differ from that of the general population. Furthermore, the time the glaucoma patients are living visually impaired decreased during the 40 years. This favourable change during the past decades is likely an important factor in the decreasing influence of glaucoma on health-related quality of life (Purola et al. 2021a). This change is also favourable for society because the increased use of health care services and costs are strongly correlated with impaired vision (Köberlein et al. 2013; Mikhailova et al. 2018).

In the Finnish register data, the prevalence and incidence of glaucoma are higher among females (Purola et al. 2021a; Social Insurance Institution of Finland 2021). This is contradictory to many epidemiological findings (Heilj et al. 2013; Flaxman et al. 2017). The reason for this difference is unknown. In our data, the incidence of reported VI is higher among male than female glaucoma patients, which might indicate that the diagnosis of glaucoma and onset of therapeutic measures are happening later in the course of the disease for males. There are indications of gender differences in health behaviour in general (Mahalik et al. 2006; Weber et al. 2019) and in Finland particularly (Koponen et al. 2018), which may explain this difference. In 2019, the life expectancy at birth was still 5.3 years lower for Finnish boys than girls (79.2 versus 84.5 years; Statistics Finland 2021), even though many chronic diseases are more prevalent in women (Koponen et al. 2018).

The prevalence of glaucoma in Nordic countries has been estimated in previous studies. In Reykjavik Eye Study, the prevalence of open-angle glaucoma was 4.0% for those aged 50 years and older (Jonasson et al. 2003). In Sweden, the prevalence of undetected glaucoma was 1.23% (Heijl et al. 2013). There has not been any clear indication on whether the prevalence of glaucoma has changed since the first large population studies were published (Bankes et al. 1968; Kahn et al. 1977). However, the number of treated glaucoma patients has increased during the past 40 years in Finland. This is partly due to the ageing Finnish population (Statistics Finland 2021) and the association of glaucoma with older age (Tielsch et al. 1991; Wolfs et al. 2000; Kapetanakis et al. 2016). Most probably, also the improved awareness of glaucoma and access to health care services during these years explain the trend (Parikka et al. 2018). The increasing number of treated glaucoma patients may also reflect decreasing proportion of undiagnosed glaucoma that has been shown to be high even in Nordic countries with developed public health care (Heijl et al. 2013).

The strengths of our study include the large data based on routinely collected health registers, which ensures that our results are comparable with those from studies in the other Western countries. We had access to data from four decades, giving us a relatively large timescale of 40 years. The notifications of VI due to glaucoma are based on Finnish legislation, and, therefore, the register data covers relatively well the glaucoma cases. The classification of VI is based on the Finnish national definitions and recommendations modified from the World Health Organization 1973 definitions, which cover both decreased visual acuity and visual field constriction.

Our study also has limitations. First, we would like to point out that the prevalence of treated glaucoma does not reflect the prevalence of glaucoma. Therefore, there are several possible biases. As shown previously, there is a large number of undiagnosed even in well-developed countries. Population-based studies in Europe have reported that at least 50% of glaucoma cases remain undiagnosed (Burr et al. 2007;

Topouzis et al. 2008; Heijl et al. 2013). It is also possible that glaucoma diagnoses made for the reimbursement of glaucoma medication can cause misclassification biases. Visual impairment register data, like register data in general, have potential sources of biases, although not as remarkable as those in glaucoma detection. It is difficult to estimate the exact time point at which a person becomes visually impaired, and even more difficult to estimate when the disease itself emerges. In the older population, many of the patients are suffering from more than one vision-threatening disease, such as age-related macular degeneration (Purola et al. 2021b). Therefore, to minimize this bias, we analysed only those patients whose main diagnosis causing VI was glaucoma. Our data included predominantly people with Finnish backgrounds, and, therefore, the results may not be directly applicable to other countries and ethnicities.

In the conclusion, our study demonstrates that whilst the incidence of reported VI due to glaucoma has increased during the past 40 years, the incidence of reported VI has decreased in the glaucomatous population and shifted to older age groups. Furthermore, the percentage of mild vision loss among the visually impaired has increased from the 1980s to the 2010s. This is likely due to better glaucoma care, e.g. improved therapy, their availability and earlier diagnoses. On the contrary, in the future, the number of glaucoma patients is expected to grow with the ageing population. Therefore, all attempts need to be made to prevent VI by further improving glaucoma care.

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Received on April 5th, 2021.
Accepted on August 31st, 2021.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Histogram of age at the onset of reported VI for male (A) and female (B) glaucoma patients in different decades in Finland.

Figure S2. Treated glaucoma patients with reimbursed glaucoma medication in Finland between 1986 and 2019. Data were from the registers of the Social Insurance Institution of Finland.