Working title: Finding Ophthalmic Risk and Evaluating the Value of Eye exams and their predictive Reliability (FOREVER). A cohort study in a Danish high street optician setting: design and methodology.

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Abstract

Purpose: To describe the rationale and design of Project FOREVER (Finding Ophthalmic Risk and Evaluating the Value of Eye exams and their predictive Reliability).

Design: Project FOREVER will build a comprehensive database of clinical eye and vision data collected from approximately 280,000 adults at 100 optician stores across Denmark with a nested longitudinal study cohort of 30,000. The FOREVER database (FOREVERdb) includes detailed data from refraction, visual acuity, intraocular pressure, corneal thickness, visual field assessments and retinal fundus images. Linkage to comprehensive Danish national registries with systemic health and prescribing data permits investigation of rare associations and risk factors. In addition, the subpopulation of 30,000 individuals over 50 also provide a saliva sample for later genetic studies, blood pressure measurements and Optical Coherence Tomography (OCT) nerve and retinal scans. This subpopulation data is reviewed by ophthalmologists for disease detection. All participants will be asked to complete a questionnaire assessing lifestyle, self-perceived eye health and general health. Enrolment of participants began in April 2022.

Perspective: The FOREVERdb is a powerful tool ~~that can be utilized~~ to answer a wide range of research questions that can pave the way for better eye health. This database will provide valuable insights for future studies investigating the correlations between eye and systemic health in a Danish population cohort, enabling research to identify potential risk factors for a range of diseases.

Keywords: Eye and vision Cohort, Project FOREVER, Optometry, eye health

Introduction

The elderly population aged above 70 has increased worldwide in the last 30 years and age-related diseases account for 51.3% (95 % CI 48.5-53.9%) of the global disease burden among adults (1). This also applies to ophthalmology, where the number of visually impaired people is also increasing (2, 3). Projections for the most common sight-threatening diseases estimate that the number of glaucoma patients will increase from 64.3 million in 2013 to 111.8 million in 2040 (4), while the number of people in Europe with age-related macular degeneration in 2040 will range between 14.9 and 21.5 million (5). The global prevalence of diabetic retinopathy is also expected to increase from 103.12 million patients (95% CI 91.34–115.90 million) in 2020 to 160.50 million (95% CI 143.70–178.60 million) in 2045 (6). With these increases in affected populations we shall also see a huge increase in the demand for ophthalmologists. The estimated global number of ophthalmologists in 2015 was 232,866, a figure based on data from 94% of the population worldwide, and only 13 countries had more than one ophthalmologist per 10,000 inhabitants (7). In recent years, the number of persons visiting an ophthalmologist in Denmark has increased by 30% from approximately 500,000 patients in 2007 to 700,000 in 2017, while the number of private ophthalmologists (visits covered by the public health insurance) has increased only by 4.5 % (from 155 to 162) over the same period (8). A similar increase in the visually impaired population will bring greater need for social care and support, with attendant costs. The loss of sight has profound personal as well as societal consequences (9-12) and as societal resources are limited, it has been suggested, that screening programs should be targeted at high-risk populations (2, 3). As the demographic shift continues to put a strain on healthcare, and the number of individuals suffering from age-related diseases increases, it is crucial to ensure that resources are used efficiently and effectively. Careful stratification and quantification of risk to help target scarce resource to those most in need will be vital.

High street optician chains have been increasingly offering comprehensive eye health checks, which have led to the accumulation of large amounts of eye health data and images, including fundus photographs, Optical Coherence Tomography (OCT) scans and visual field tests (perimetry). Most visits are due to refractive alterations that may be corrected with glasses or contact lenses, but more recently, optometrists have advocated advanced imaging techniques as part of routine eye exams to detect early signs of future sight-threatening ocular pathology. Patients with abnormal findings may be referred on to ophthalmologists for further evaluation

and treatment, however, the details of these extensive clinical case-finding examinations have not been validated systematically for e.g. sensitivity, specificity, cost or potential harm (e.g. over-treatment, anxiety). Given the limited societal resources and number of ophthalmologists, such validation is vital to target sight-threatening eye diseases effectively.

Previous studies, using eye and vision cohorts, have investigated potential risk factors for developing eye diseases, e.g., lifestyle, systemic diseases, and alterations in the vascular system (13-17). The UK Biobank Eye and Vision sub-cohort is the world's largest prospective eye cohort including a total of 502,665 participants with data collected between January 2006 and October 2010 (18). Smaller cohorts in the USA, Australia, Europe, Asia, and the Middle East have also been established (19-23). Project FOREVER (Finding Ophthalmic Risk and Evaluating the Value of Eye exams and their predictive Reliability) will collect data on eye health, blood pressure and genetic profiles from customers visiting 100 Danish high street optician shops. The database will include data from extensive eye examinations, including refraction, visual acuity, intraocular pressure (IOP), corneal thickness, use of contact lenses, visual field and image data such as fundus photographs and OCT retinal scans. The FOREVER database (FOREVERdb) linkage with the Danish national registers forms a unique cohort that will permit risk-profiling algorithms to help target those at greatest risk. Furthermore, FOREVER will validate and help refine the extensive optometric eye exams to minimise false positive and negative findings.
In this paper, we describe the study design, methodology and data collected in Project FOREVER.

Methods

Project consortium

The Project FOREVER team includes experienced clinicians and researchers from a wide range of disciplines including ~~genetics, epidemiology and data science. The consortium has been assembled to accommodate the diverse data types and analyses being conducted in Project FOREVER. The research disciplines include~~ experts in ophthalmology, epidemiology, statistics, data science, machine learning, questionnaire methodology, genetics, and data management. Patients have been involved in development from the earliest stages with help

from Fight for Sight, Denmark who are an integral part of the consortium. A detailed overview of the consortium is available on the projects website (24).

Ethics

Project FOREVER has been approved by the National Committee on Health Research Ethics, Denmark (project ID H-21026000). All participants give informed, written consent before enrolment in the study.

Study Design

Study Location

A total of 100 optician shops in Denmark compromise the study locations. All Danish regions will be represented, with 50 sites located in Zealand, 37 in Jutland, 8 on Funen and 6 on the smaller islands.

Recruitment

Eligible and consenting individuals will be enrolled for either of two populations, denoted as the selected population and the extended population. The inclusion criteria are listed in Table 1 below. As all project materials, such as informational material and consent forms, are written in Danish, participants must be able to read and understand Danish. The recruitment of the extended population participants began in April 2022, and the recruitment of the selected population participants began in July 2022.

Population	Criteria
Selected population	1. Subjects must have had at least one extensive eye examination carried out by the optician chain three years previously 2. ≥ 50 years 3. Must read and understand Danish
Extended population	4. ≥ 18 years 5. Must read and understand Danish

Table 1: Inclusion criteria of the two populations; the selected and the extended population

Subjects in the selected population will have ~~retrospective follow-up~~ data from at least three years prior to enrolment and will be re-invited for additional follow-up examinations three years after their second eye examination, giving three assessments over six years. Participants in the extended population will be examined once when recruited to the project and will be asked to fill out a questionnaire. There are no plans for follow-up examinations in the extended population (Figure 1).

Recruitment selected population

Potential participants intended for the selected population are identified in the optician chain's customer database. Eligible subjects who have consented to receive information from the optician chain are invited to participate in Project FOREVER by e-mail. The e-mail will contain information material in written form and a link to an information video, a link to schedule an appointment in the optician shop, and a link to the FOREVER questionnaire (FOREVERQ). When visiting the optician store, an employee informs the customer about Project FOREVER. Before enrolment in the study, the subject fill out and sign a consent form. Recruitment will continue until a total of 30,000 consenting participants have been enrolled.

Recruitment extended population

Subjects in the extended population are invited to participate in Project FOREVER when visiting the optician shop on their own initiative. With oral consent, participant contact information (name and social security number) is shared exchanged with FOREVER at the University of Copenhagen (UCPH). The official Danish authorities communication “Digital Post” linked to social security numbers is used to send invitations to participants including written and video explanations and links to a digital consent form the FOREVERQ. Recruitment will continue until a minimum of 250,000 consenting participants have been enrolled.

In total, extensive data from a minimum of 280,000 Danish citizens will be collected in the selected population and EP.

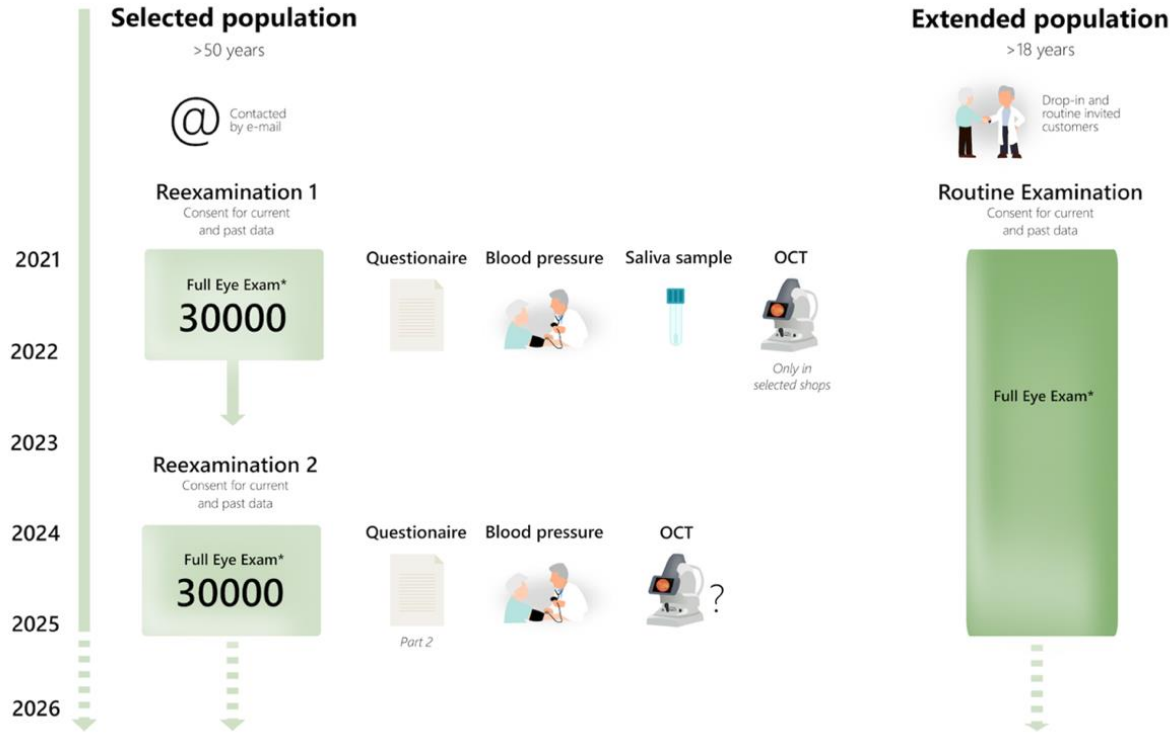

Figure 1: Overview of recruitment in the two study populations. A: The selected population is contacted by e-mail and invited to participate in Project FOREVER. Upon written consent, data collected from the visit is included in the FOREVER database. Data include full eye exam +/- OCT, questionnaire, blood pressure measurement and saliva samples. Three years after enrolment in the FOREVER cohort, participants in the selected population are reinvited for follow-up examinations; full eye exam +/- OCT, questionnaire, and blood pressure measurements. B: The extended population is invited to participate in Project FOREVER when visiting the optician shop. Upon written consent, data collected from the visit is included in the FOREVER database. Data include a full eye exam and questionnaire. The participants in the extended population do not have follow-up examinations.

Data in the FOREVERdb

Data in the FOREVERdb will originate from several sources. Both populations will have the following assessments: refraction, visual acuity, IOP, corneal thickness, visual field tests and fundus photographs. In addition, subjects in the selected population will provide a saliva sample and have blood pressure measured. A subset (approximately 10,000) in the selected population will also have OCT scans of the optic nerve and the retina. Both populations are

moreover encouraged to complete the FOREVERQ with %% rounds of reminders via &?&. See Table 2 for details about the various data available in the FOREVERdb.

	Examination	Equipment
Refraction	Auto kerato-refractometer. Outcome: Spherical refractive power: -25D to +22D (0.12D/0.25D steps) Cylindrical refractive power: OD to ±10D (0.12D/0.25D steps) Astigmatic axial angle: 0 to 180° (in 1°or 5°steps) Minimal measurable pupil diameter: 2 mm Corneal curvature radius: 5.00 to 10.00mm (0.01mm step) Corneal refractive power: 67.50D to 33.75D (0.12D/0.25D steps) (where, corneal refractive power =1.3375) Corneal astigmatic refractive power: OD to ±10D (0.12D/0.25 D steps) Corneal astigmatic axial angle: 0 to 180° (1°/ 5°steps) PD Measurement Range: 20mm to 85mm (0.5mm step)	TopCon KR-800
Visual acuity	Phoroptor Spherical power: +27.00 to -27.00D (0.25D/ 1.00D/ 2.00D/ 3.00D steps) Cylinder power: +8.00 to -8.00D (0.25D/1.00D steps) Cylinder axis: 0 to 180° (1°/5°/15° steps) Prism: 0 to 20Δ, all direction (0.1Δ/ 0.2Δ /0.5Δ/1.0Δ) Pupillary distance: 48 to 80mm (0.5mm/1.0mm) Cross cylinder: ±0.25D/±0.50D Test lens (aux lens): Red-Green filter, Polarizing filter (45°/135°), Prism (6Δ /10Δ), Red Maddox (horizontal/ vertical), Lens for retinoscopy (+1.5D/+2.0D), Cross cylinder for measuring presbyopia (±0.50D), Occluding plate, Pinhole, and Cross hairs glass.	Topcon CV5000, CV5000S, CV5000Pro
Intraocular pressure (IOP)	Non-contract tonometry Outcome: IOP (mmHg), range 0-60 mmHg	Canon Tx20-P
Corneal thickness	Non-contact pachymeter Outcome:	Canon Tx20-P

	Thickness (μm), range 150-1300 μm	
Visual field	Computer-assisted visual field examination. Qualitative screening test Outcome: Report with visual field evaluation	OCTOPUS 600 – pulsar perimetry test, Haag-Streit
Retinal image	Macular-centred 45-degree field of view retinal fundus images without mydriasis. Outcome: Fundus image, BMP format	Canon CR-2 AF incorporating Canon EOS 70D and Canon EOS 80D cameras
Retinal scan	OCT Outcome: Automated OCT: • 2mmx9mm widefield scan (with macula and optic disc) and Hood report. • Retinal nerve fiber layer (RFNL) Thickness Map • RNFL Circular Tomogram/Thickness including Average, total, Superior and inferior thickness (μm). • Disc Topography rim and disc Area (mm2), linear and vertical CDR and Cup volume mm^3 • RNFL probability and visual field test points (Field View) • Ganglion cell layer (GCL) thickness Macular 6sector Grid • GCL thickness (Retina View) • GCL probability and visual field test points (field view) • Color fundus photography Automated OCT Angiography: visualising the vascular flow and vascular segmentation.	Topcon Maestro2

Table 2: Overview of types of data in the FOREVER database.

Upon obtaining signed consent, all data will be securely transferred from the optometrist site to the UCPH via a Secure File Transfer Protocol (SFTP) server. The data will be stored on a scalable and secure cloud server owned by the UCPH.

FOREVER Questionnaire

A web-based questionnaire specifically designed for project FOREVER has been developed and validated, “FOREVERQ”. Validation included four in-depth face-to-face interviews and evaluating responses from 20 representative individuals with different educational backgrounds and ages with further refinement of language and layout for clarity and ease of use. The final questionnaire, FOREVERQ is listed in Table 3. The two populations, ES and SL, are recruited differently, with some additional data in the selected population (e.g. the option to specify their gender as "man," "woman," "non-binary," or "other" not available in the national security records).

~~When accessing the questionnaire, only basic information is required, i.e., height and weight. If this information is not filled out, the respondent will not be able to proceed. All other questions are optional, and some can be answered with "do not know."~~

The FOREVERQ is divided into three categories of questions: primary, secondary, and tertiary. A primary question is visible to all respondents. A secondary question is a follow-up question, that appears based on the answer given to the primary question. A tertiary question is a further follow-up question to the secondary question and will only appear if relevant. An example of a primary question could be: "Has a physician informed you that you have one or more eye diseases?". When answering “Yes” the responder will subsequently be asked to select the relevant eye disease(s) from a predefined list (secondary question). If the respondent selects glaucoma as one of the known eye diseases, a new list of various glaucoma subtypes will appear, and the respondent is asked to select the specific glaucoma subtype (tertiary question).

In rare cases, we ask the respondent to enter text themselves. For example, if the respondent is diagnosed with an eye disease that is not listed, the name of the disease can be entered. There are a total of five free text fields in the FOREVERQ.

In total, the questionnaire entails 270 questions including secondary and tertiary questions.

Section	**Examples of questions**	**Number of questions in the section**

Basic Data	How tall are you (without shoes)?	6
Eye surgery and disease	Have you had surgery to correct myopia, hyperopia, or astigmatism in one or both eyes? Has a physician told you that you have one or more eye diseases?	77
Self-reported eye health	How would you describe your vision with both eyes right now (with glasses or contact lenses, if you wear them)?	12
Use of eye medication	Are you using medication for eye diseases? Do you use prescribed medication for eye diseases? Do you use artificial tears/moisturizing eye drops?	19
Smoking habits	Do you smoke? How much do you smoke on average per day?	16
Alcohol consumption	How many drinks do you typically have in a week (7 days)?	11
Coffee habits	How many cups of coffee do you drink a day?	3
Sleeping position	What is your typical sleeping position?	1
Snoring and sleep apnea	How often do you snore? Have you consulted a physician regarding sleep apnea?	5

Physical activity	How do you rate your physical fitness?	6
Self-reported health	How do you rate your overall health?	12
Long-term diseases and after-effects	Do you suffer from one or more of the following diseases?	53
Disease among close family members	Do any of your close relatives suffer from one or more of the following diseases?	25
Mental and emotional health	Have you been upset by something that happened unexpectedly?	10
Contact to health authorities	Have you visited a general practitioner in the last 12 months? How many times have you visited your general practitioner?	14

Table 3: Questionnaire sections in FOREVERq

FOREVERQ data are collected and managed using the electronic data capture tool denoted Research Electronic Data Capture (REDCap) hosted at hospitals in the Capital Region of Denmark (RegionH). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (25, 26).

Blood pressure

Blood pressure and heart rate is measured using a BP B6 Connect blood pressure monitor (Microlife®), showing the heart rate (beats per minute), systolic and diastolic blood pressure (mmHg). The blood pressure output is listed as the average of three continuous measurements, using the Microlife® Average Mode (MAM) function on the monitor.

Saliva samples

A volume of 2 ml saliva will be collected using a saliva collection kit (Wuxi NEST Biotechnology Co., Ltd®), containing 2 ml ITM inactivated solution consisting of 88.706% water, 10% buffer solution (pH 7), 1% foam-free powder WX-110, and 0.294% sodium citrate.

The saliva samples are stored at room temperature before shipment from the optician shop to UCPH. Hereafter, saliva samples are stored in a biobank on UCPH at 5 ^{o}C for up to two years. DNA will be extracted from the samples latest two years after collection.

Management of consents

The consents given in the selected population are filled out with the customer number (generated by the optician chain) and full name and signature, after which it is sent to UCPH together with the saliva samples. The consents are scanned and archived in both digital and physical form. The consents given in the extended population are digital and stored securely in REDCap.

Definition of disease

All participants in the selected population will have their eye examinations evaluated by an ophthalmologist, and relevant diagnoses will be listed in their individual records in the FOREVERdb (see Table 4 for an overview of diagnoses). Two ophthalmologists will individually evaluate the first 50 records in the selected population. Hereafter, the agreement of their assessment regarding diagnosis and follow-up plan is compared. In case of disagreement between the two ophthalmologists, the case will be discussed. In case of continued disagreement between the two ophthalmologists, a third ophthalmologist will be asked to review the record, and the third ophthalmologist's decision will overrule and constitute the ground truth. The ophthalmologists' assessments will be compared with the optometrist's follow-up plan to validate and optimize the correct referral to ophthalmologists.

If new signs of pathology are detected by the ophthalmologists that were not previously detected by the optometrist, the participant will be informed and instructed on any further necessary actions.

Disease	Subtype	Degree	
Insight (Indirect measure of cataract)	NA	Clear Slightly blurred Moderately blurred Very blurred	
Glaucoma	NA	Suspect (ISNT rule not met, Cup-disc ratio >0.6), Mild (MD <6, autoperimetry) Moderate >6 MD <12, autoperimetry) Severe (MD >12, autoperimetry)	
Optic neuropathy,	NA	Mild Moderate Severe	
Choroidal nevus	Benign	Small (diameter <1 papillary diameter (PD)) Medium (diameter]1; 2[ ) Drusen and/or changes in pigmentation	
	Suspicious of Malignancy	Size > 2 PD Thickness (>2 mm) Localisation near the optic nerve Orange pigmentation and/or detachment	
Age-related Macular Degeneration (AMD)	Dry AMD	Small drusen Medium drusen Large drusen Drusen of variable types and size Geographic atrophy	Mild Moderate Severe
	Wet AMD	Exudative Fibrotic Mixed type +VEGF-inhibitor treatment - VEGF-inhibitor treatment	
Diabetic retinopathy	Non-proliferative	Mild Moderate	Grade (DOS guideline) 1 2 3 4
	Maculopathy	Non-CSME CSME	
	Proliferative	NA	
Other types of retinopathies	Epiretinal fibrose	NA	Mild Moderate Severe
	Macula hole	Lamellar Full thickness	
	Central Serous Chorioretinopathy	NA	
	Congenital/hereditary	Retinitis pigmentosa Tap dystrophy	
	White dot syndrome	NA	
	Retinitis	NA	

	Toxoplasmosis	Active Inactive	
Hypertensive retinopathy	NA	Grading 1 2 3 4	
Other vascular retinopathies	Arterial	Central retinal artery occlusion Branch retinal artery occlusion	
	Venous	Central retinal venous occlusion Branch retinal venous occlusion	
Retinal detachments	Rhegmatogenous	Fovea not included Fovea included	
	Exudative		
	Traction		
Vitreous body	Asteroid hyalosis/ Synchysis scintillans	Mild Moderate severe	
	Vitritis		

Table 4: Overview of the diagnostic choices and action plan.

Patient and public involvement

To ensure that project status, research results and news are regularly disseminated to project participants, the scientific community, the public and other interested parties, we will update the FOREVER website regularly (24). In addition, we will use social media to share relevant news and updates. Contact details for the UCPH research teams are also available on the website.

Collaboration

The FOREVERdb is available for interested researchers with defined research projects. Researchers must formally apply online at the FOREVER website, where application requirements can be found. All applications will be processed by the FOREVER steering committee. To ensure the anonymity and confidentiality of data from FOREVER participants,

strict guidelines apply. If research projects are approved, pseudo-anonymized data extraction from the FOREVERdb will be made available to the researchers during the project period (24).

Analysis and statistics

~~The statistical analyses of data in Project FOREVER will follow standard practices and utilize new, more accurate methods~~. Descriptive data will primarily use non-parametric analysis, with comparisons made using rank-sum statistics for continuous and ordinal data and chi-square for categorical data. The initial analysis of cross-sectional data for the analysis of outcomes will use logistic regression. The final analyses will employ causal inference methods as described in the book by Hernan and Robins (27). To maximize the potential for demonstrating relevant associations, we will utilize the newer methods of Targeted Maximum Likelihood Estimation. These methods are "double robust," ensuring optimal results if either adjustment for confounders or a correct association between confounders and parameters of interest is achieved.

The main analyses of the FOREVER data will be longitudinal and focus on the relationship between data observed in the study and long-term outcomes. Unadjusted analyses will use survival-type estimates such as Kaplan-Meier estimates (and log-rank tests) for survival and Nelson-Aalen estimators and Gray's test when addressing competing risks. The preliminary multivariable analysis will use Cox regression, and the main analyses will again employ causal inference methods and Targeted Maximum Likelihood Estimation.

It is expected that the various parts of the study will have issues with missing values. If this is minimal, the main analyses will only include complete cases. However, if the problem is significant, multiple imputations will be applied when the missing data can be assumed to be randomly missing.

Before analyses are performed, a detailed statistical analysis plan will be pre-specified for each part of the project. These plans will address which data should be included in a particular analysis, which analyses will address the main outcomes, and how the data will be presented. Each of these plans will also address issues with misclassification and missing data. We will continuously investigate how the applied methods can be optimized.

Discussion

Strengths and weaknesses

To our knowledge, Project FOREVER is the largest eye and vision cohort in Scandinavia as it will entail extensive clinical data from a minimum of 280,000 individuals. We recognize that all study populations have limitations. Below we highlight the most important strengths and weaknesses of Project FOREVER.

Study design

Project FOREVER entails two populations with different aims. The selected population is designed as a longitudinal study cohort, enrolling subjects examined three years before enrolment and with a three-year follow-up period, allowing for the detection of changes in clinical outcomes over time. Hence, the selected population cohort will provide retrospective and eventually also prospective data. As participants from the selected population are over 50 years old, it is expected that many participants have been affiliated with the optician chain for more than three years, and consequently, their datasets will compromise data from several years. With state-of-the-art examination and analysis methods, we aim to identify early signs of disease and monitor progression in the selected population. The FOREVERdb do not allow further evaluation of the specific subtypes of eye diseases, and therefore we may not be able to fully understand the nuances and complexities of different eye conditions in the dataset.

In the selected population, participants have been selected because they have had an extended eye examination with a fundus image at least three years ago. However, it is expected that only a portion of invited individuals will enrol in the study, potentially introducing bias to the FOREVERdb. In addition, there may be a bias towards the exclusion of healthier individuals without a need for refractive correction and hence have not visited an optician shop.

~~The datasets from both populations are incredibly robust and provide a wealth of information for research. The quality of the data is high, which strengthens the validity of the dataset.~~ It is ~~in addition also possible to apply automated computer-assisted analysis methods to help efficiently analyse the high-volume data and extract valuable insights.~~

The extended population includes some limitations. Specifically, we will not be able to conduct systematic case finding by a trained ophthalmologist due to the volume of data. Also, the extended population dataset is comprised of retrospective data without the possibility to include

clinical eye examination follow-up data, although we shall obtain follow-up information through the Danish health registries.

Despite these limitations, we believe that the FOREVERdb provide unique and valuable insights into eye health and disease. We are confident that our robust data and comprehensive analyses will enable us to make significant contributions to the field of ophthalmology.

Study population

The characteristics of the FOREVER population may not be fully comparable to the general Danish population. A brief overview of potential biases is listed below.

Age distribution

Since the inclusion criteria regarding age vary between the two populations, we expect the selected population to be older than the extended population. Also, the FOREVER population in general is expected to be older based on data from the optician chain (Figure 2). Hence, the prevalence of eye diseases in the FOREVER cohort is assumed to be higher compared to the general Danish population, but this will generate an enriched sample of those most at risk: a higher mean age in the FOREVER populations makes the FOREVERdb a valuable resource for studying age-related diseases.

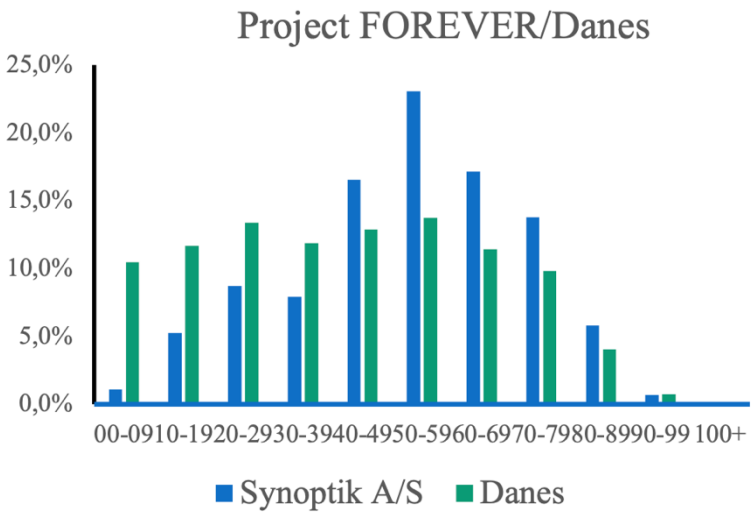

Figure 2: The age distribution in the Synoptik A/S population (green bars) compared to the Danish population (blue bars). The figure outlines that the majority of customers visiting an optician are above 40 years. Source: Synoptik A/S and Statistics Denmark.

Geography

Participants from across Denmark are represented in the FOREVERdb. The density of optician shops is higher near the capital and larger cities compared to rural areas. Consequently, subjects living in urban areas may be overrepresented in the FOREVER populations. Although this could potentially distort findings, the large number of participants from both demographic areas enables studies in urban/rural lifestyles as potential risk factors for certain eye diseases.

Economics

The specific optician chain is perceived to have a medium price range, attracting customers from the middle class. This could introduce various biases, as certain diseases might be more prevalent in different socio-economic strata (28-31). Since Denmark has a universal health care system, substantial income redistribution, and little inequality in the standard of living, we assume that some of these confounders will be mitigated. Moreover, this potential challenge can be addressed by comparing FOREVER data with information from the Danish registers and examining the extent of any differences observed.

Ethnicity

Approximately 14% of the general Danish population are immigrants or descendants of which 57 % are of non-western ethnic origin (32). Hence, we expect the FOREVERdb to consist primarily of Caucasians. The potential findings of risk factors and associations examined in the FOREVERdb are only generalizable across countries with a similar ethnical distribution.

Potentials

In Denmark, each person has a unique social security number known as a Central Personal Register (CPR) number (33), which enables comprehensive epidemiological research using the national registers. The national registers contain routinely collected data on prescribed medication, hospitalizations, and other health-related information (34). However, these registers are sparse when it comes to eye and vision data, and only contain diagnoses from the secondary sector. Most patients with eye diagnoses in Denmark do not visit hospitals, but rather consult private ophthalmologists. These visits are covered by the public health insurance, but the examination data are usually not captured in the national registers.

The FOREVERdb can provide valuable insights into the potential associations between eye health and general health data, as it can be linked to these registers. The potential for future research projects using the FOREVERdb is vast. For instance, the high-quality retinal fundus photographs and perimetries in the entire FOREVER cohort can be used for studies on potential biomarkers of diseases, and the selected population cohort will be of interest for studies on risk factors for eye diseases in an elderly population due to addition of blood pressure measurements, OCTs, genetics and the evaluation by trained ophthalmologists. Lastly, there is a great opportunity to follow study subjects further into the future for both the selected population and the extended population. This means that Project FOREVER will not be limited by the current plan to re-invite participants in three years, but potentially continue for years. In this context, the number of participants could potentially be far beyond the planned 280,000.

Conclusion

Project FOREVER is a Danish eye and vision study that collects data on eye examinations from customers of 100 optician shops in Denmark aiming at including at least 280,000 persons. A subpopulation aged above 50 will have additional data on blood pressure, DNA from saliva +/- OCT scans, and be followed for a minimum of six years. The FOREVERdb will be linked to comprehensive data from national registries in Denmark, allowing studies on potential associations between eye health, general health, and the Scandinavian lifestyle. This unique dataset offers a wealth of information and opportunities for research in the field of ophthalmology.

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Competing Interests:

The authors have declared no competing interests concerning Project FOREVER.

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