Title: Association between retinal nerve fibre layer thickness and incident dementia in the European Prospective Investigation into Cancer in Norfolk cohort

Running Title: Incident dementia and retinal nerve fibre layer

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Abstract and Keywords

Background: Retinal nerve fibre layer (RNFL) thickness may reflect cerebral status.

Objective: This study assessed the relationship between RNFL thickness and incident all-cause dementia in the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) Eye Study.

Methods: Glaucoma detection with variable corneal compensation (GDx-VCC) and Heidelberg Retinal Tomograph II (HRT II) derived global mean RNFL thickness from dementia-free participants at baseline within the EPIC-Norfolk Eye Study were analysed. Incident dementia was identified through linkage to electronic medical records. Cox proportional hazard mixed-effects regression models adjusted for key confounders were used to examine the associations between RNFL thickness and incident dementia in 4 separate models.

Results: 6239 participants were included with 322 cases of incident dementia and mean age of 67.5-years old, with 49.7% women (median follow-up 13.2-years, interquartile range (11.7 to 14.6 years). Greater RNFL thickness (GDx-VCC) was not significantly associated with a lower risk of incident dementia in the full adjusted model [HR per quartile increase 0.95; 95% CI 0.82-1.10]. Similarly, RNFL thickness assessed with HRT II was also not associated with incident dementia in any model (full adjusted model; HR per quartile increase: 1.06; [95% CI 0.93-1.19]. Gender did not modify any associations under study.

Conclusion: GDx-VCC and HRT II derived RNFL thickness are unlikely to be useful predictors of incident dementia. Higher resolution optical imaging technologies may clarify whether there are useful relationships between neuro-retinal morphology and brain measures.

Keywords: Retinal ganglion cells; retinal nerve fiber layer; dementia; scanning laser polarimetry.

Introduction

Dementia is one of the most pressing global health issue facing our world today for the significant burden it can place upon patients, their caregivers, and society broadly [1]. The diagnosis of the dementia syndrome depends on clinical features, as it is a clinical syndrome. However, there is significant interest in identifying biomarkers which may strongly correlate with dementia syndrome or hold potential to assist in its diagnosis when interpreted in the context of a patient's presenting symptoms.

Among these potential predictors or biomarkers, there is a growing body of evidence which suggests that retinal neurodegeneration may precede brain dysfunction. The retinal nerve fibre layer (RNFL) is the neuronal sheath formed by the axons of ganglion cells and are a projection of the optic nerve. The RNFL may be accurately and easily measured through optic imaging technologies and is an important parameter that is altered in the preclinical stages of many neurological diseases [2]. For example, RNFL thinning which is detectable on optical imaging technologies often precede symptomatic visual fields loss in glaucoma, making it critical in making an early diagnosis of glaucoma [3-5]. It has been hypothesized that RNFL thinning may specifically reflect neurological injury or pathological axonal atrophy of the optic nerve [6]. Indeed, significant RNFL thinning has been shown to not only be an important diagnostic indicator of glaucoma progression, but also present in a myriad of neurological and degenerative diseases such as multiple sclerosis, Parkinson's disease, and various forms of optic neuropathies [7-9]. In people with Alzheimer's Disease (AD), the same histopathological changes of AD occurring in the hippocampus and temporo-parietal cortex were also seen in their retina [10]. Further, a relationship has been shown between the degree of RNFL thinning and disease severity, supporting the possibility of RNFL thickness as a potential biomarker towards

the diagnosis and prognostication of neurological conditions [7-9]. Thinner macular ganglion cell complex and total macular thickness have also been found to correlate with smaller total brain volume, grey matter volume, and hippocampal volume, supporting the hypothesis that cerebral atrophy and retinal atrophy may share common mechanisms [11].

With high-performance optic imaging tools becoming more widely available over the past decade, it has been discovered that the relationship between RNFL thickness and cognition may be more closely linked than previously thought. In a longitudinal study of 865 participants, having a thinner RNFL at 45-years old was associated with lower cognitive performance, processing speed, and IQ, suggesting that RNFL thickness may be particularly sensitive for detecting changes in cognition in middle life [12]. This is supported by studies which have found strong associations between RNFL thickness and MMSE scores among people with mild cognitive impairment [13]. In the Rotterdam study, patients with a thinner RNFL layer at baseline had a 44% higher risk of developing dementia, and 43% higher risk of developing AD per every RNFL standard deviation increase [14]. With regards to subtypes of dementia such as AD, several studies have suggested that people with AD may have significantly thinner RNFL than their counterparts without AD [15, 16]. Further, pathologic changes in the retina vasculature were associated with increased prevalent and incident AD [17]. Not only might RNFL thickness reflect the presence or absence of dementia, but several studies have also suggested that a gradient may exist between dementia disease severity and RNFL thickness, with a thinner RNFL corresponding to greater disease severity [18, 19]. Together, these findings support the notion that retinal neuronal structure may be a close reflection of cerebral health and function [17]. As there are no known objective stage-specific biomarkers for dementia, neuronal changes as

evidenced through RNFL thinning may offer a promising objective and cost-effective aid in its clinical diagnosis [20].

The aim of this study was to investigate the association between RNFL thickness and incident all-cause dementia in the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) Eye Study Cohort. We hypothesize that thinner global RNFL thickness may be associated with increased incidence of all-cause dementia.

Materials and Methods

Study Population

Between 1993 and 1998, over 30,000 participants were recruited through general practices in Norfolk, UK. A variety of baseline information such as diet, physical activity, blood samples, and anthropometric data were collected. This formed the basis of the EPIC-Norfolk study, a prospective population-based cohort study of residents in East Anglia, United Kingdom (UK). Following enrollment, participants were invited to additional health checks throughout the years and provide consent to electronic medical record linkage to ascertain disease endpoints. A more detailed discussion of the study design of the EPIC-Norfolk study is presented elsewhere [21, 22]. This study is a secondary analysis of the EPIC-Norfolk Eye Study Cohort, which was formed by all living participants still enrolled in the EPIC-Norfolk study by 2004 (n=18,380), who participated in the third health examination (3HE). The 3HE collected a range of covariates with a focus on ocular measurements and cognitive tests. The association between cognitive tests and RNFL thickness within the EPIC-Norfolk Eye Study had previously been explored [23]. For this analysis, ocular measurements, specifically axial length, typical scan score, and RNFL thickness measurements, were derived from the 3HE EPIC-Norfolk Eye Study.

Data Collection

RNFL measures were derived using Glaucoma detection with variable corneal compensation (GDx-VCC; Carl Zeiss Meditec, Inc., Dublin, CA) and Heidelberg Retinal Tomograph II (HRT II; Heidelberg Engineering, Heidelberg, Germany) without pupil dilation. These were carried out by trained nurses following standard operating procedures of Moorfields Eye Hospital which were adapted for the Eye Study after extensive training and validation for staff prior to initiation of the study. Weekly review of data collected was conducted by an ophthalmologist. Both GDx-VCC and HRT II are well validated technologies which use the tissue characteristics of RNFL and the properties of light to ascertain the structure parameters of the optic nerve head and RNFL layer [24-27]. GDx-VCC is a form of scanning laser polarimetry which does not directly measure RNFL thickness [28, 29]. Instead, it derives RNFL thickness based on the birefringence property of the RNFL through measuring the backscattered light from retardation of polarized beams [28, 29]. There is also evidence that GDx-VCC may show changes in the health of the RNFL even prior to thinning [30, 31]. HRT II is a form of laser ophthalmoscopy which measures the height of the retina at the disc margin and uses this as a proxy for RNFL thickness, relying on the surface reflectivity pattern of RNFL to estimate thickness [28, 29]. Although both aim to measure the same construct, the means through which they estimate RNFL thickness are different, and as such, both were included in the analysis to allow comparison and overview. The following controls were implemented to minimise the effect of measurement error on the dataset and ensure that RNFL thickness measurements were of sufficiently high precision. Only eyes with RNFL scan quality score of $\geq$7 on GDx-VCC, and $\leq$ 40µm topography standard deviation from HRT II were included. A highly significant level of

'atypical retardation' can occur in the retinal measurements of eyes which have other comorbidities (such as glaucoma, which is common among older adults) [32, 33]. Within published studies using RNFL data, the typical scan score (TSS) derived from GDx-VCC is frequently deployed to account for this distortion and differentiate healthy eyes from others [33, 34]. In our analysis, the TSS was accounted for as a quality control metric by incorporating it as a variable into the regression model.

Cases of incident all-cause dementia were derived from linkage to electronic medical records (EMR) of patients with available 3HE data through the International Classification of Diseases (ICD) 10 coding system. Electronic medical record linkages with local and national organisations within the UK also aided in capturing diagnosed cases of incident dementia. A systematic review of studies evaluating the validity of routinely collected EMRs within the UK found that validity estimates of diagnosed dementia are generally high [35]. A list of included codes used to capture cases of incident dementia are included in Supplementary Table 4.

Covariates data were pooled from the baseline visit or the 3HE. Age, sex, smoking status, alcohol consumption and quantity, employment status, education level, social class, and family history of dementia were all collected through participant self-disclosed questionnaires. Smoking history was derived from yes/no responses to the questions: "have you ever smoked as much as one cigarette a day for as long as a year?", and "do you smoke cigarettes now?". Responses were then categorized into smoking status of "ever" and "never" smokers for this analysis. Alcohol consumption was derived from the question: "how many alcoholic drinks do you have each week?". Total alcohol consumption was estimated as the total units of drinks consumed in a

week, and categorized into no intake, >0 to <7 units/week, ≥ 7 units to <14 units/week, ≥ 14 units to <21 units/week, and ≥ 21 units/week. Employment status was determined from the question "do you have a paid job at present?". Education level represents the highest level attained, and was categorized into education less than age 16, education to age 16, education to age 18, and degree. Social class was self-reported by participants and then classified based on the Registrar General's occupation-based classification scheme based on their own, or their partner's current occupation. If the participants were retired, then their last employment or their partner's last employment was used. Family history of dementia was also self-reported, and determined as yes or no overall based on if any one of the participant's immediate family had a known diagnosis of dementia, specifically: mother, father, brother, or sister. BMI was calculated as the weight in kilograms divided by the square of height. Height was measured to the nearest 0.1kg using digital scales, and height measured to the nearest millimeter using free-standing stadiometer by a nurse. Axial length as a covariate was measured by a trained nurse following standard operating procedures of Moorfields Eye Hospital which were adapted for the Eye study using non-contact partial coherence interferometry (IOLMaster V.4, Carl Zeiss Meditech Ltd, Welwyn Garden City, UK).

Statistical Analysis

All statistical analysis were carried out using the software R (version 2022.02.3+492) with a significance level of p-value <0.05. Patients who had prevalent dementia at time of recruitment into the EPIC-Norfolk Eye Study were excluded from this analysis. A complete-case analysis was carried out and patients with missing covariate data of interest included in the primary analysis, such as RNFL thickness measurements or missing quality control variables,

were excluded from the study. If only one eye met the inclusion criteria, that eye was included in the analysis with the other excluded. Figure 1 summarizes this with a flow diagram of the study population after applying inclusion and exclusion criteria. To investigate the survival and hazard probabilities of incident dementia based on mean RNFL thickness, three mixed-effects Cox proportional hazard models were built as the primary analysis. To reduce the effect of skewing by outliers, mean RNFL thickness was stratified into quartiles. Model one included adjusting for TSS and clustering between eyes of the same person. Model two further adjusted for age and sex. Model three further adjusted for BMI, education level, employment status, smoking status, alcohol consumption and axial length. As TSS is only applicable to GDx-VCC derived measurements, TSS was not included as a covariate in HRT II models. The proportional hazards assumption was checked for each covariate within a model in addition to the global test for each model by testing for significance between scaled Schoenfeld residuals and time using a significance threshold of $p=0.05$. As such, the beta can be considered valid during the entire follow-up period. Following, secondary analysis examined the same associations with patients stratified by sex. Interaction analysis by age and sex were also carried out in addition to sensitivity analysis of GDx-VCC and HRT II as continuous variables. Further sensitivity analysis including all covariates additionally adjusted for glaucoma status, presence or absence of age-related macular degeneration (AMD), and presence or absence of diabetic retinopathy (DR). Glaucoma status was derived from a combination of various systematic ocular examinations, including visual acuity, tonometry, optic nerve head assessment, peripapillary nerve fiber layer assessment, 24-2 central threshold visual field, and clinical examination by a consultant ophthalmologist with expertise in glaucoma. Following, participants were stratified into no glaucoma, suspected glaucoma, and glaucoma. Where two eyes of the same participant differed

in glaucoma status, the more clinically serious designation was assumed for that participant. The presence of absence of AMD were determined from standardized grading of fundus photographs by independent reviewers, based on the Wisconsin protocol [36]. DR grading were derived from these same fundus photographs of the optic disc and macula, taking into account photo quality and lesion grading to derive an overall grade of DR based on the National Health Service (NHS) Diabetic Eye Screening Programme grading definitions [37].

Results

Data were available from 17,246 eyes of 8623 participants within the EPIC-Norfolk Eye Study. After removing participants that did not meet inclusion criteria, had quality control values outside the threshold of acceptability, or had missing data in variables of interest, 10,949 eyes from 6239 participants were included in the final analysis.

Table 1 summarizes the baseline characteristics of those included. Among those included in the final analysis, the mean age was 67.53-years old, and 56.0% were women. The median follow-up period was 13.2-years, interquartile range (11.7 to 14.6 years). GDx-VCC derived quartiles are as follows: 1st quartile, <52.54 µm; 2nd quartile, 52.54-56.35µm; 3rd quartile, 56.36-60.36µm; and 4th quartile, >60.36µm. HRT II derived quartiles are as follows: 1st quartile, <0.17mm; 2nd quartile, 0.17-0.22mm; 3rd quartile, 0.22-0.27mm; 4th quartile, >0.27mm. Regression results for each model built for the primary analysis are captured in Table 2. Descriptive characteristics of eyes included stratified by GDx-VCC and HRT II derived RNFL quartiles are available in Supplementary Tables 3 and 4 respectively.

Among those included in the analysis, people with diagnosed dementia were more likely to be older, have history of smoking, score lower on the SF-MMSE, and lower on the Hopkins

Verbal Learning Test (HVLT) than those without diagnosed dementia. Throughout all models, the Cox proportional hazards assumption was not violated.

Survival Analysis for GDx-VCC Derived RNFL Thickness

Within model 1 which adjusted for TSS and clustering between eyes of the same patient, mean RNFL quartile was significantly associated with diagnosed dementia later in life (p=0.003) with a hazard ratio of 0.84 (95% CI 0.72-0.98) per RNFL thickness quartile increase. However, once age and sex were adjusted for in model 2, the association between RNFL quartile and diagnosed dementia was no longer statistically significant (hazard ratio per quartile increase 0.96 [95% CI 0.85-1.08]; p=0.46). This association remained statistically insignificant when further covariates were adjusted for in model 3 (hazard ratio per quartile increase 0.95 [95% CI 0.82-1.10]; p=0.52). Table 2 summarizes the hazard ratios of all-cause dementia per increase in RNFL quartile for GDx-VCC derived RNFL thickness. Figure 2 summarizes the Kaplan-Meier survival curve for all-cause incident dementia by GDx-VCC derived RNFL quartiles.

Survival Analysis for HRT II Derived RNFL Thickness

Within model 1, the association between mean RNFL quartile as measured through HRT II was statistically non-significant (p=0.13). Similarly, when age, sex, BMI, employment status, smoking status, alcohol consumption, and axial length were adjusted for in models 2 and 3, the association continued to remain statistically non-significant (p=0.47, and p=0.39 respectively). Similar to findings from GDx-VCC derived RNFL thickness, age remained a significantly associated with diagnosed dementia throughout all models (p<0.05). Figure 2 outlines the Kaplan-Meier survival curve for survival from diagnosed dementia by HRT II derived RNFL

quartiles. Table 3 summarizes the hazard ratios of all-cause dementia per increase in RNFL quartile for HRT II derived RNFL thickness. Figure 3 summarizes the Kaplan-Meier survival curve for all-cause incident dementia by GDx-VCC derived RNFL quartiles.

After stratifying by sex, no significant associations were found in either the GDx-VCC or HRT II derived cohort. Interactions by sex also found similar results of non-significance for GDx-VCC (p=0.06) and HRT II (p=0.06). Interactions by age was also non-significant for both GDx-VCC (p=0.06) and HRT II (p=0.07). After considering RNFL as a continuous variable, no significant associations were found after all covariates were accounted for. Results of the regression analysis for GDx-VCC derived RNFL thickness and HRT II derived RNFL thickness are available in supplementary tables 1 and 2, respectively. Additional sensitivity analysis adjusting for all covariates included in model 3 in addition to glaucoma status, AMD, and DR also supported the primary analysis of no significant associations for both GDx-VCC (p=0.94), and HRT II (p=0.41). An overview of descriptive characteristics of glaucoma, AMD, and DR by dementia status is available in supplementary table 5.

Discussion

Within this cohort, GDx-VCC or HRT II derived RNFL thickness was not significantly associated with incident all-cause dementia. This study raises the hypothesis that some optic imaging technologies may not be precise or accurate enough to detect a significant enough difference in RNFL thickness for accurate dementia prognosis and supports the potential superiority of the OCT in further investigating this association. Considering that all regression models merely act as approximations of some underlying truths within the dataset, further studies

of this association in different populations and using a range of optical imaging technologies are necessary.

The novelty of this study stems from i) the use of GDx-VCC and HRT II to measure RNFL thickness, and ii) having the largest number of incident cases of dementia reported within the present literature. The Mutlu et al. (2018) analysis embedded within the Rotterdam Study similarly examined the association between RNFL thickness and incident dementia [14]. In comparing findings, our result of null effect differs from the embedded Rotterdam Study which found that having a thinner RNFL at baseline was significantly associated with an increased risk of incident dementia [HR 1.44; 95% CI 1.19-1.75] in a cohort of 5065 Dutch adults. Notably, the Rotterdam Study used OCT to obtain RNFL measurements, which may have a higher sensitivity for discriminating RNFL thickness than GDx-VCC and HRT II. Optical coherence tomography (OCT) is a more advanced imaging technology which offers higher resolution 3D images of the retina of at least 100 times that of its predecessors [38, 39]. Results of this study may be highlighting the importance of access to high-resolution imaging technologies, such as the OCT, in further examining this association. As each optical imaging technology derives the RNFL thickness measurement through different techniques, it could be the case that the GDx-VCC and HRT II systems were unable to pick up the subtleties available on OCT to detect a statistically significant trend. For this reason, our results may differ due to regression dilatation bias from a less precise measurement of RNFL thickness, leading to a measured association which may be weaker than the true association. However, the value of understanding their utility in detecting a difference is still pertinent, as they are more likely to be available in lower-middle income countries than OCTs which is a newer technology and generally more expensive to acquire [40, 41]. The Rotterdam Study's exclusion of all participants with pre-existing eye pathologies may

have further increased an ability to detect a difference through increasing the accuracy of RNFL thickness measurements by reducing potential measurement variabilities introduced by these pathologies. In considering additional variables of interest, neither sets of analysis were able to account for the role of genetic factors, such as APOE or polygenic risk scores, in investigating a possible association. In looking to future areas of research within the realm of RNFL thickness and incident dementia, synthesis of genetic factors into the discussion could offer meaningful insights. Future studies directly comparing the sensitivity and association of RNFL thickness as measured by HRT II, GDx-VCC, and OCT with incident dementia may be of interest.

We hypothesised we would detect an association between RNFL thickness and incident dementia based on the following. Embryonically, the retina is developed from the neural tube and shares the same neuronal and vascular components as the central nervous system [15, 17, 42]. Anatomically, it is a layered structure at the back of the eye and synapses into the optic nerve, which forms a direct connection between the retina and subcortical nuclei of the brain [42]. Thinning of the RNFL reflects retinal ganglion cell axon loss and is thought to be an index of neurodegeneration and cerebral atrophy [43-45]. Damage to the optic nerve can also directly cause reciprocal responses in CNS axons alongside alterations in neurotransmitter levels, and a growing body of literature suggests that factors leading to CNS degeneration may be similar in the brain and the retina [15, 17, 46-49]. Breakdown of the blood-brain barrier (BBB) including disruption of the blood-retina barrier has been postulated as a mechanism contributing towards neurodegeneration, cognitive impairment, and dementia [50, 51]. Research regarding the potential utility of BBB breakdown as an early biomarker of dementia is ongoing.

Strengths, Limitations, and Next Steps

There are several notable strengths inherent to the EPIC-Norfolk Eye Study. First, its large sample size lends to increased statistical power to detect associations and increased precision. Second, its long period of follow-up and electronic linkage to the medical health records of participants minimizes loss to follow-up while maximizing the number of cases of diagnosed dementia captured [21, 22] As most residents within the United Kingdom (UK) are registered with a general practitioner, recruitment through this method minimizes selection bias. Finally, demographic and ophthalmic data collected within the study were detailed and extensive, allowing inclusion of key covariates and RNFL thickness analysis.

The cohort of participants within the EPIC-Norfolk Eye Study are predominantly white (99.7%) [22, 52]. While this may be representative of the resident population within the wider older population in the UK, investigation in other populations may be necessary to validate these findings. Given the observational nature of the study, residual confounding also remains a possibility despite accounting for potential confounders in the analysis. Given the relative health of participants enrolled, healthy volunteer bias and loss to follow-up of the most cognitively impaired may also bias results.

Dementia is a complex, multi-factorial syndrome with many shared risk factors between sub-types. It has been previously demonstrated that although the validity of ascertaining all-cause dementia through routinely collected healthcare datasets is good, it is worse for Alzheimer's type dementia, and very poor for vascular type dementia [53]. It is possible that retinal thinning may be specific to certain dementia subtypes, and unlikely to occur in others. However, it was not possible to examine this, given the risk of misclassification bias of subtypes through our ascertainment methods of electronic medical records linkage. First, the incidence of

mixed pathologies of dementia types are high, as such, the granularity of data available and accuracy of differential diagnosis of dementia subtypes may be challenging [54-56]. Further, this method of identifying primary endpoint may lead to an underestimation of the true incidence – particularly for cases at the milder end of the dementia spectrum, and cases in which a firm dementia diagnosis may place the patient at higher risk of rapid decline [57, 58]. For this reason, the focus of our study remained on "all-cause" dementia. Future studies investigating whether retinal thinning is only a biomarker for primary neurodegeneration rather than secondary causes, such as those due to vascular compromise, may be of interest.

Summary and Conclusion

The prevalence of dementia is expected to triple from 57 million people in 2019 to 152.8 million people by 2050 [59], making the care of persons with dementia a global health priority [60]. Any potential predictor of dementia requires rigorous testing with existing data and other evidence before adoption. We have contributed to this process with testing of RNFL thickness in the EPIC-Norfolk Eye Study. Overall, while RNFL thickness may be a biomarker for the early pathobiology of neurodegenerative diseases such as dementia, its clinical utility as a potential diagnostic tool in the routine work-up of dementia requires further research. Although some clinical applications of RNFL thickness in the early detection of dementia may be possible, RNFL thickness as a standalone proxy may be insufficient. Consideration for combining RNFL thickness with another non-invasive test, such as amyloid beta measurements, microvascular dysfunction measurement, adaptive optics, fundus photos, and genetics information (e.g., APOE status or a polygenic risk score) may yield greater utility. At present, a focus on primary

prevention at the population level may still be the most effective strategy for preventing morbidity and improving quality of life for people with dementia.

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Conflicts of Interest Disclosure

GSY was supported by the Cambridge Trust as an HRH Prince of Wales Commonwealth Scholar and was a graduate student at the University of Cambridge while conducting this research. EK was supported by the Nicolaus and Margrit Langbehn Foundation. APK has acted as a consultant

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Data Availability Statement

The data supporting the findings of this study are available within the article and/or its supplementary material.

Table 1. Descriptive characteristics by dementia status

	All	Incident Dementia		
		Yes	No	p-value
Total Patients, n (%)	6239 (100)	322 (5.2)	5917 (94.8)	
Total Eyes, n (%)	10949 (100)	534 (4.9)	10415 (95.1)	
Age, years, mean (SD)	67.53 (7.5)	75.2 (5.8)	67.5 (7.5)	**<0.0001**
Sex, n (%)				
Women	3493 (56.0)	170 (52.8)	3323 (56.2)	0.23
BMI, kg/m^2, mean (SD)	26.8 (4.3)	26.7 (4.3)	26.8 (4.3)	0.86
Family History of Dementia[1], n yes (%)	861 (13.8)	39 (12.1)	822 (13.9)	
Social Class[2], n (%)				0.63
Professional	373 (6.0)	20 (6.2)	353 (6.0)	
Managerial/technical	2345 (37.8)	114 (35.5)	2231 (38.0)	
Skilled, non-manual	1670 (26.9)	86 (26.8)	1584 (27.0)	
Skilled, manual	842 (13.6)	54 (16.8)	788 (13.4)	
Semi-skilled	782 (12.6)	39 (12.1)	743 (12.6)	
Nonskilled	185 (3.0)	8 (2.5)	177 (3.0)	
Education Level				**0.004**
Degree	1148 (18.4)	46 (14.3)	1102 (18.6)	
Education to Age 18	2809 (45.0)	137 (42.5)	2672 (45.2)	
Education to Age 16	736 (11.8)	33 (10.2)	703 (11.9)	
Education less than age of 16	1546 (24.8)	106 (32.9)	1440 (24.3)	
Alcohol Intake, n (%)				**0.01**
No intake	1798 (28.8)	120 (37.3)	1678 (28.4)	
>0 to <7 units/week	2289 (36.7)	105 (32.6)	2184 (36.9)	
>/= 7 to <14 units/week	1245 (20.0)	53 (16.5)	1192 (20.1)	
>/=14 to <21 units/week	508 (8.1)	26 (8.1)	482 (8.1)	
>/= 21 units/week	399 (6.4)	18 (5.6)	381 (6.4)	
Smoking Status				0.002
Never	3122 (50)	138 (60.2)	2984 (49.6)	
Ever	3117 (50)	194 (39.8)	2933 (50.4)	
Employment Status[3], n yes (%)	1813 (29.1)	21 (6.5)	1792 (30.3)	
Axial Length, mm; mean (SD)	23.5 (1.1)	23.4 (1.1)	23.5 (1.1)	**0.0006**

[1]First-degree relatives;

[2]Derived from participant self-reported own and partner's last occupation based on the Registrar General's occupation based classification scheme

[3]Employed with paid job at time of 3rd health examination;

SD, standard deviation; BMI, body mass index; GDx-VCC, Glaucoma detection with variable corneal compensation; HRT II, Heidelberg Retinal Tomography II; RNFL, retinal nerve fiber layer, P<0.05 in bold.

Table 2. Regression Results with GDx-VCC Derived Mean RNFL Thickness Stratified by Quartiles and Incident All-Cause Dementia as Outcome of Interest

	Hazard Ratio	95% Confidence Interval	p-value
Model 1[1]	0.84	0.72-0.98	**0.03**
Model 2[2]	0.96	0.85-1.08	0.46
Model 3[3]	0.95	0.82-1.10	0.52

Hazard ratio for all-cause dementia per quartile increase in RNFL thickness.
[1]Model adjusted for clustering between eyes of the same patient and the typical scan score
[2]Model adjusted for clustering between eyes of the same patient, the typical scan score, age, and sex
[3]Model adjusted for all covariates, including clustering between eyes of the same patient, the typical scan score, age, sex, body mass index, employment status at time of 3rd health examination, highest education level completed, smoking status, amount of alcohol consumed, and axial length.
GDx-VCC, Glaucoma detection with variable corneal compensation; RNFL, retinal nerve fiber layer. P<0.05 in bold.

Table 3. Regression Results with HRT II Derived Mean RNFL Thickness Stratified by Quartiles and Incident All-Cause Dementia as Outcome of Interest

	Hazard Ratio	95% Confidence Interval	p-value
Model 1[1]	0.92	0.83-1.02	0.13
Model 2[2]	1.04	0.93-1.18	0.47
Model 3[3]	1.06	0.93-1.19	0.39

Hazard ratio for all-cause dementia per quartile increase in RNFL thickness.
[1]Model adjusted for clustering between eyes of the same patient
[2]Model adjusted for clustering between eyes of the same patient, age, and sex
[3]Model adjusted for all covariates, including clustering between eyes of the same patient, age, sex, body mass index, employment status at time of 3rd health examination, highest education level completed, smoking status, amount of alcohol consumed, and axial length.
HRT II, Heidelberg Retinal Tomography II; RNFL, retinal nerve fiber layer. P<0.05 in bold.

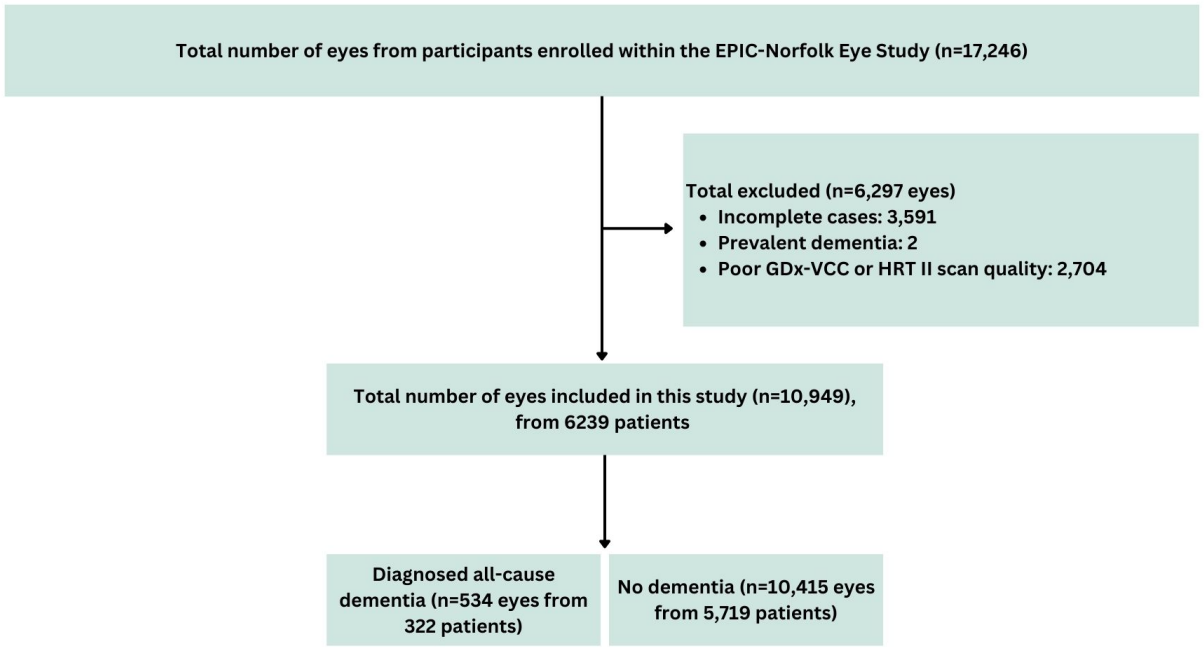

Figure 1. Flow diagram of study population after applying inclusion and exclusion criteria.

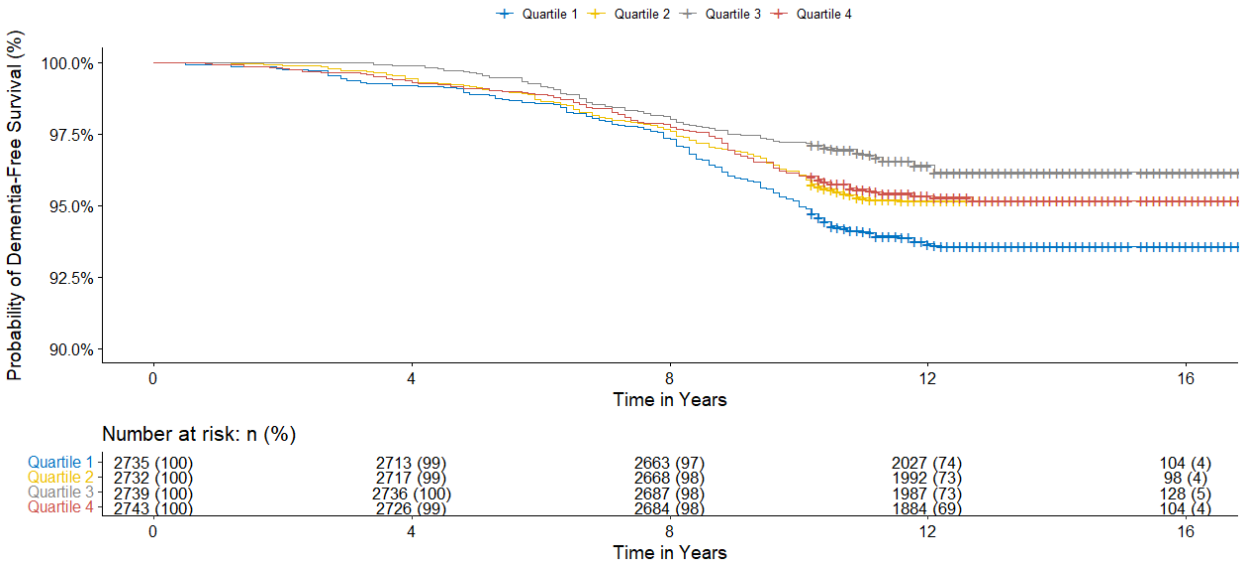

Figure 2. Kaplan-Meier Survival Curve for All-Cause Incident Dementia by GDx-VCC derived RNFL quartiles.

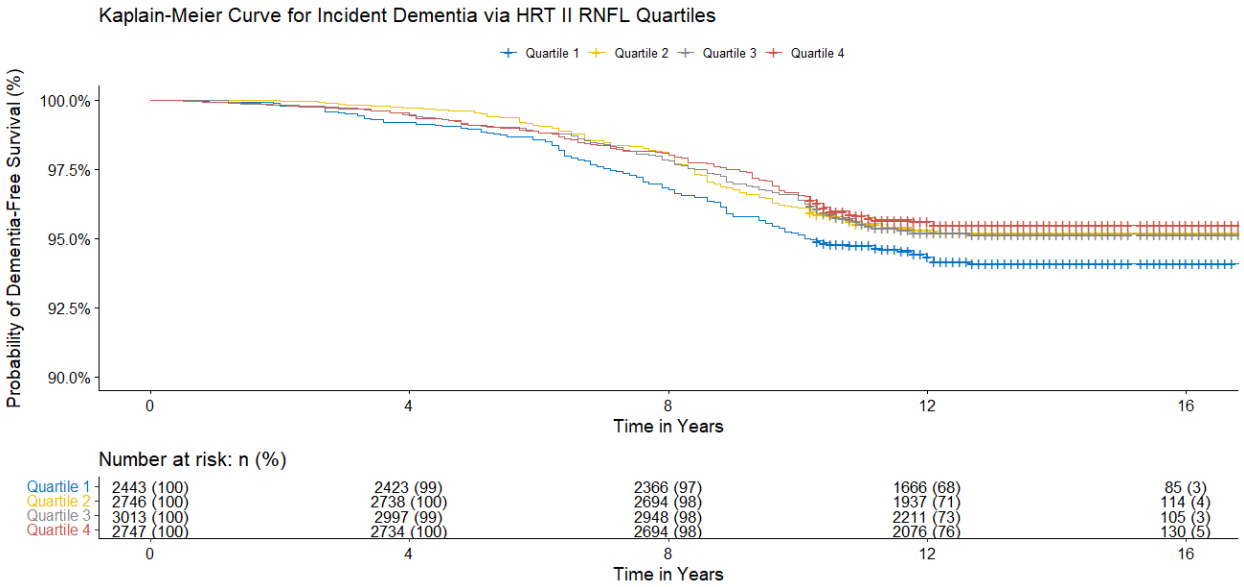

Figure 3. Kaplan-Meier Survival Curve for All-Cause Incident Dementia by HRT II derived RNFL quartiles.

Supplementary Tables

Supplementary Table 1. Regression Results with GDx-VCC Derived Mean RNFL Thickness Stratified as a Continuous Variable and Incident All-Cause Dementia as Outcome of Interest

	Hazard Ratio	95% Confidence Interval	p-value
Model 1[1]	0.98	0.96-0.99	**0.04**
Model 2[2]	0.99	0.98-1.02	0.87
Model 3[3]	0.99	0.97-1.02	0.76

Hazard ratio for all-cause dementia per quartile increase in RNFL thickness.
[1]Model adjusted for clustering between eyes of the same patient and the typical scan score
[2]Model adjusted for clustering between eyes of the same patient, the typical scan score, age, and sex
[3]Model adjusted for all covariates, including clustering between eyes of the same patient, the typical scan score, age, sex, body mass index, employment status at time of 3rd health examination, highest education level completed, smoking status, amount of alcohol consumed, and axial length.
GDx-VCC, Glaucoma detection with variable corneal compensation; RNFL, retinal nerve fiber layer. P<0.05 in bold.

Supplementary Table 2. Regression Results with HRT II Derived Mean RNFL Thickness Stratified as a Continuous Variable and Incident All-Cause Dementia as Outcome of Interest

	Hazard Ratio	95% Confidence Interval	p-value
Model 1[1]	0.26	0.07-0.98	**0.04**
Model 2[2]	1.48	0.39-4.49	0.56
Model 3[3]	1.43	0.30-6.78	0.65

Hazard ratio for all-cause dementia per quartile increase in RNFL thickness.
[1]Model adjusted for clustering between eyes of the same patient
[2]Model adjusted for clustering between eyes of the same patient, age, and sex
[3]Model adjusted for all covariates, including clustering between eyes of the same patient, age, sex, body mass index, employment status at time of 3rd health examination, highest education level completed, smoking status, amount of alcohol consumed, and axial length.
HRT II, Heidelberg Retinal Tomography II; RNFL, retinal nerve fiber layer. P<0.05 in bold.

Supplementary Table 3. Descriptive characteristics of all included eyes stratified by GDx-VCC derived RNFL measurements.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value
Total Eyes, n (%)	2735 (100)	2732 (100)	2739 (100)	2743 (100)	
Age, mean (SD)	68.9 (7.7)	67.3 (7.6)	66.9 (7.3)	67.1 (7.5)	**<0.0001**
Sex, n (%)					
Female	1505 (55)	1529 (60.0)	1582 (57.8)	1582 (57.7)	0.11
BMI, mean (SD)	26.8 (4.2)	26.7 (4.4)	26.7 (4.4)	26.8 (5.3)	0.72
Family History of Dementia[1], No. yes (%)	397 (14.5)	368 (13.4)	362 (13.2)	387 (14.1)	0.49
Social Class[2], No. (%)					**0.004**
Professional	152 (5.6)	163 (6.0)	165 (6.1)	165 (6.0)	
Managerial/technical	982 (36.2)	998 (36.8)	1033 (38.0)	1098 (40.2)	
Skilled, non-manual	757 (27.9)	748 (27.6)	725 (26.7)	724 (26.5)	
Skilled, manual	420 (15.5)	379 (14.0)	346 (12.7)	322 (11.8)	
Semi-skilled	328 (12.1)	338 (12.5)	352 (13.0)	360 (13.2)	
Nonskilled	75 (2.8)	88 (3.2)	96 (3.5)	64 (2.3)	
Education Level					
Degree	465 (17.0)	487 (17.8)	559 (20.4)	515 (18.8)	**0.006**
Education to Age 18	1260 (46.1)	1224 (44.8)	1201 (43.8)	1255 (45.8)	
Education to Age 16	306 (11.2)	317 (11.6)	317 (11.6)	353 (12.9)	
Education less than age of 16	704 (25.7)	704 (25.8)	662 (24.2)	620 (22.6)	
Alcohol Intake, No. (%)					
No intake	793 (29.0)	788 (28.8)	748 (27.3)	815 (29.7)	0.82
>0 to <7 units/week	1012 (37.0)	992 (36.3)	1021 (37.3)	992 (36.2)	
>/= 7 to <14 units/week	555 (20.3)	535 (19.6)	562 (20.5)	531 (19.4)	
>/=14 to <21 units/week	214 (7.8)	232 (8.5)	228 (8.3)	228 (8.3)	
>/= 21 units/week	161 (5.9)	185 (6.8)	180 (6.6)	177 (6.5)	
Smoking Status					
Never	1375 (50.3)	1346 (49.3)	1396 (51.0)	1396 (50.9)	0.57
Ever	1360 (49.7)	1386 (50.7)	1343 (49.0)	1347 (49.1)	
Employment Status[3], No. yes (%)	713 (26.1)	851 (31.1)	883 (32.2)	845 (30.8)	**<0.0001**
Axial Length, mm; mean (SD)	23.4 (0.9)	23.4 (1.0)	23.5 (1.0)	23.8 (1.3)	**<0.0001**

Number of All-Cause Dementia Cases, n (%)	173 (7.1)	131 (4.7)	101 (3.4)	129 (4.7)	**<0.0001**

[1]First-degree relatives;
[2]Derived from participant self-reported own and partner's last occupation based on the Registrar General's occupation-based classification scheme
[3]Employed with paid job at time of 3rd health examination;
SD, standard deviation; BMI, body mass index; P<0.05 in bold.

Supplementary Table 4. Descriptive characteristics of all included eyes stratified by HRT II derived RNFL measurements.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value
Total Eyes, n (%)	2443 (100)	2746 (100)	3013 (100)	2747 (100)	
Age, mean (SD)	69.7 (7.6)	67.7 (7.3)	67.1 (7.2)	65.9 (7.5)	**<0.0001**
Sex, n (%)					
Female	1263 (51.7)	1528 (55.6)	1751 (58.1)	1656 (60.3)	**<0.0001**
BMI, mean (SD)	26.7 (4.3)	26.8 (4.3)	26.7 (4.2)	26.8 (4.5)	0.58
Family History of Dementia[1], No. yes (%)	354 (14.5)	363 (13.2)	416 (15.3)	381 (13.9)	
Social Class[2], No. (%)					
Professional	166 (6.8)	139 (5.1)	169 (5.7)	171 (6.3)	**0.0001**
Managerial/technical	917 (37.7)	1035 (37.9)	1113 (37.4)	1046 (38.3)	
Skilled, non-manual	617 (25.4)	701 (25.7)	868 (29.2)	758 (27.8)	
Skilled, manual	375 (15.4)	404 (14.8)	358 (12.0)	330 (12.1)	
Semi-skilled	282 (11.6)	357 (13.1)	383 (12.9)	356 (13.0)	
Nonskilled	75 (3.1)	94 (3.4)	86 (2.9)	68 (2.5)	
Education Level					
Degree	436 (17.8)	467 (17.0)	548 (18.2)	575 (20.9)	**<0.0001**
A level	1114 (46.0)	1263 (46.0)	1370 (45.5)	1193 (43.4)	
O level	263 (10.8)	298 (10.9)	351 (11.6)	381 (13.9)	
No qualifications	630 (25.9)	718 (26.1)	744 (24.7)	598 (21.8)	
Alcohol Intake, No. (%)					
No intake	723 (29.6)	808 (29.4)	832 (27.6)	781 (28.4)	0.16
>0 to <7 units/week	861 (35.2)	1032 (38.6)	1121 (37.2)	1003 (36.5)	
>/= 7 to <14 units/week	509 (20.8)	497 (18.1)	614 (20.4)	563 (20.5)	
>/=14 to <21 units/week	204 (8.4)	242 (8.8)	249 (8.3)	207 (7.5)	
>/= 21 units/week	146 (6.0)	167 (6.1)	197 (6.5)	193 (7.0)	
Smoking Status					
Never	1234 (50.5)	1356 (49.4)	1546 (51.3)	1377 (50.1)	0.53
Ever	1209 (49.5)	1390 (50.6)	1467 (48.7)	1370 (49.9)	
Employment Status[3], No. yes (%)	580 (23.7)	799 (29.1)	930 (30.9)	983 (35.8)	**<0.0001**
Axial Length, mm; mean (SD)	23.7 (1.2)	23.5 (1.0)	23.4 (1.1)	23.4 (1.1)	**<0.0001**

Number of All-Cause Dementia Cases	140 (5.7)	129 (4.7)	143 (4.7)	122 (4.4)	0.15

[1]First-degree relatives;
[2]Derived from participant self-reported own and partner's last occupation based on the Registrar General's occupation based classification scheme;
[3]Employed with paid job at time of 3rd health examination;
SD, standard deviation; BMI, body mass index; P<0.05 in bold.

Supplementary Table 5. Descriptive characteristics of glaucoma, age-related macular degeneration, and diabetic retinopathy by dementia status

	All	Incident Dementia		
		Yes	No	p-value
Glaucoma Status, n eyes (%)				0.23
No glaucoma	5669 (91.1)	283 (88.4)	5386 (91.3)	
Glaucoma suspect	400 (6.4)	23 (7.2)	377 (6.4)	
Glaucoma	153 (2.5)	14 (4.4)	139 (2.4)	
Age-related Macular Degeneration, n eyes (%)	656 (18.6)	50 (35.5)	606 (17.9)	<0.001
Diabetic Retinopathy, n eyes (%)	129 (1.2)	7 (1.3)	122 (1.2)	<0.001

References

[1] van der Flier WM, Scheltens P (2005) Epidemiology and risk factors of dementia. *Journal of Neurology, Neurosurgery & Psychiatry* **76**, v2-v7.

[2] Lamirel C (2014) Optical Coherence Tomography In *Encyclopedia of the Neurological Sciences (Second Edition)*, Aminoff MJ, Daroff RB, eds. Academic Press, Oxford, pp. 660-668.

[3] Harwerth RS, Carter-Dawson L, Shen F, Smith EL, 3rd, Crawford ML (1999) Ganglion cell losses underlying visual field defects from experimental glaucoma. *Invest Ophthalmol Vis Sci* **40**, 2242-2250.

[4] Sommer A, Katz J, Quigley HA, Miller NR, Robin AL, Richter RC, Witt KA (1991) Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol* **109**, 77-83.

[5] Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, 2nd, Wilson MR, Gordon MO (2002) The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* **120**, 701-713; discussion 829-730.

[6] Cettomai D, Hiremath G, Ratchford J, Venkatesan A, Greenberg BM, McGready J, Pardo CA, Kerr DA, Frohman E, Balcer LJ, McArthur JC, Calabresi PA (2010) Associations between retinal nerve fiber layer abnormalities and optic nerve examination. *Neurology* **75**, 1318-1325.

[7] Khanifar AA, Parlitsis GJ, Ehrlich JR, Aaker GD, D'Amico DJ, Gauthier SA, Kiss S (2010) Retinal nerve fiber layer evaluation in multiple sclerosis with spectral domain optical coherence tomography. *Clin Ophthalmol* **4**, 1007-1013.

[8] Kirbas S, Turkyilmaz K, Tufekci A, Durmus M (2013) Retinal nerve fiber layer thickness in Parkinson disease. *J Neuroophthalmol* **33**, 62-65.

[9] Lee TH, Ji YS, Park SW, Heo H (2017) Retinal ganglion cell and axonal loss in optic neuritis: risk factors and visual functions. *Eye (Lond)* **31**, 467-474.

[10] Koronyo-Hamaoui M, Koronyo Y, Ljubimov AV, Miller CA, Ko MK, Black KL, Schwartz M, Farkas DL (2011) Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. *Neuroimage* **54 Suppl 1**, S204-217.

[11] Chua SYL, Lascaratos G, Atan D, Zhang B, Reisman C, Khaw PT, Smith SM, Matthews PM, Petzold A, Strouthidis NG, Foster PJ, Khawaja AP, Patel PJ (2021) Relationships between retinal layer thickness and brain volumes in the UK Biobank cohort. *Eur J Neurol* **28**, 1490-1498.

[12] Barrett-Young A, Ambler A, Cheyne K, Guiney H, Kokaua J, Steptoe B, Tham YC, Wilson GA, Wong TY, Poulton R (2022) Associations Between Retinal Nerve Fiber Layer and Ganglion Cell Layer in Middle Age and Cognition From Childhood to Adulthood. *JAMA Ophthalmol* **140**, 262-268.

[13] Ascaso FJ, Cruz N, Modrego PJ, Lopez-Anton R, Santabárbara J, Pascual LF, Lobo A, Cristóbal JA (2014) Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. *Journal of neurology* **261**, 1522-1530.

[14] Mutlu U, Colijn JM, Ikram MA, Bonnemaijer PWM, Licher S, Wolters FJ, Tiemeier H, Koudstaal PJ, Klaver CCW, Ikram MK (2018) Association of Retinal Neurodegeneration

on Optical Coherence Tomography With Dementia: A Population-Based Study. *JAMA Neurol* **75**, 1256-1263.
[15] Cheung CY, Chan VTT, Mok VC, Chen C, Wong TY (2019) Potential retinal biomarkers for dementia: what is new? *Curr Opin Neurol* **32**, 82-91.
[16] Marziani E, Pomati S, Ramolfo P, Cigada M, Giani A, Mariani C, Staurenghi G (2013) Evaluation of retinal nerve fiber layer and ganglion cell layer thickness in Alzheimer's disease using spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci* **54**, 5953-5958.
[17] Cheung CY, Ikram MK, Chen C, Wong TY (2017) Imaging retina to study dementia and stroke. *Prog Retin Eye Res* **57**, 89-107.
[18] Moreno-Ramos T, Benito-León J, Villarejo A, Bermejo-Pareja F (2013) Retinal nerve fiber layer thinning in dementia associated with Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease. *J Alzheimers Dis* **34**, 659-664.
[19] Kim JI, Kang BH (2019) Decreased retinal thickness in patients with Alzheimer's disease is correlated with disease severity. *PLoS One* **14**, e0224180.
[20] Geldmacher DS (2004) Differential diagnosis of dementia syndromes. *Clin Geriatr Med* **20**, 27-43.
[21] Hayat SA, Luben R, Keevil VL, Moore S, Dalzell N, Bhaniani A, Khawaja AP, Foster P, Brayne C, Wareham NJ, Khaw KT (2014) Cohort profile: A prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of men and women in Norfolk (EPIC-Norfolk 3). *Int J Epidemiol* **43**, 1063-1072.
[22] Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N (1999) EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer* **80 Suppl 1**, 95-103.
[23] Khawaja AP, Chan MP, Yip JL, Broadway DC, Garway-Heath DF, Luben R, Hayat S, Matthews FE, Brayne C, Khaw KT, Foster PJ (2016) Retinal Nerve Fiber Layer Measures and Cognitive Function in the EPIC-Norfolk Cohort Study. *Invest Ophthalmol Vis Sci* **57**, 1921-1926.
[24] Bathija R, Zangwill L, Berry CC, Sample PA, Weinreb RN (1998) Detection of early glaucomatous structural damage with confocal scanning laser tomography. *J Glaucoma* **7**, 121-127.
[25] Weinreb RN, Dreher AW, Coleman A, Quigley H, Shaw B, Reiter K (1990) Histopathologic validation of Fourier-ellipsometry measurements of retinal nerve fiber layer thickness. *Arch Ophthalmol* **108**, 557-560.
[26] Weinreb RN (1999) Evaluating the retinal nerve fiber layer in glaucoma with scanning laser polarimetry. *Arch Ophthalmol* **117**, 1403-1406.
[27] Hoh ST, Greenfield DS, Mistlberger A, Liebmann JM, Ishikawa H, Ritch R (2000) Optical coherence tomography and scanning laser polarimetry in normal, ocular hypertensive, and glaucomatous eyes. *Am J Ophthalmol* **129**, 129-135.
[28] Stoor K, Karvonen E, Leiviskä I, Liinamaa J, Saarela V (2022) Comparison of imaging parameters between OCT, GDx and HRT in the Northern Finland birth cohort eye study. *Acta Ophthalmol* **100**, e1103-e1111.
[29] Belyea DA, Alhabshan RN, Mahesh SP, Gertner GS, Ibisevic MM, Habib AS, Dan JA (2014) Utility of Heidelberg retinal tomography as a screening tool for analyzing retinal nerve fiber layer defects. *Clin Ophthalmol* **8**, 2409-2414.

[30] Fortune B, Burgoyne CF, Cull G, Reynaud J, Wang L (2013) Onset and progression of peripapillary retinal nerve fiber layer (RNFL) retardance changes occur earlier than RNFL thickness changes in experimental glaucoma. *Invest Ophthalmol Vis Sci* **54**, 5653-5661.
[31] Fortune B, Burgoyne CF, Cull GA, Reynaud J, Wang L (2012) Structural and functional abnormalities of retinal ganglion cells measured in vivo at the onset of optic nerve head surface change in experimental glaucoma. *Invest Ophthalmol Vis Sci* **53**, 3939-3950.
[32] Hoesl LM, Tornow RP, Schrems WA, Horn FK, Mardin CY, Kruse FE, Juenemann AG, Laemmer R (2013) Glaucoma diagnostic performance of GDxVCC and spectralis OCT on eyes with atypical retardation pattern. *J Glaucoma* **22**, 317-324.
[33] Bagga H, Greenfield DS, Feuer WJ (2005) Quantitative assessment of atypical birefringence images using scanning laser polarimetry with variable corneal compensation. *Am J Ophthalmol* **139**, 437-446.
[34] Khawaja AP, Chan MP, Garway-Heath DF, Broadway DC, Luben R, Sherwin JC, Hayat S, Khaw KT, Foster PJ (2013) Associations with retinal nerve fiber layer measures in the EPIC-Norfolk Eye Study. *Invest Ophthalmol Vis Sci* **54**, 5028-5034.
[35] McGuinness LA, Warren-Gash C, Moorhouse LR, Thomas SL (2019) The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: A systematic review. *Pharmacoepidemiol Drug Saf* **28**, 244-255.
[36] Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, de Jong PT, Klaver C, Klein B, Klein R (1995) An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Survey of ophthalmology* **39**, 367-374.
[37] England PH, Guidance: NHS Diabetic Eye Screening Programme grading definitions for referable disease,Public Health England https://www.gov.uk/government/publications/diabetic-eye-screening-retinal-image-grading-criteria/nhs-diabetic-eye-screening-programme-grading-definitions-for-referable-disease, Accessed June 19.
[38] Podoleanu AG (2012) Optical coherence tomography. *Journal of microscopy* **247**, 209-219.
[39] Drexler W, Fujimoto JG (2008) State-of-the-art retinal optical coherence tomography. *Prog Retin Eye Res* **27**, 45-88.
[40] Yadav H, Shah D, Sayed S, Horton S, Schroeder LF (2021) Availability of essential diagnostics in ten low-income and middle-income countries: results from national health facility surveys. *Lancet Glob Health* **9**, e1553-e1560.
[41] Fujimoto J, Swanson E (2016) The Development, Commercialization, and Impact of Optical Coherence Tomography. *Invest Ophthalmol Vis Sci* **57**, Oct1-oct13.
[42] Gregg RG, McCall MA, Massey SC (2013) Function and anatomy of the mammalian retina In *Retina* Elsevier, pp. 360-400.
[43] van der Heide FCT, Steens ILM, Geraets AFJ, Foreman YD, Henry RMA, Kroon AA, van der Kallen CJH, van Sloten TT, Dagnelie PC, van Dongen M, Eussen S, Berendschot T, Schouten J, Webers CAB, van Greevenbroek MMJ, Wesselius A, Koster A, Schaper NC, Schram MT, Köhler S, Stehouwer CDA (2021) Association of Retinal Nerve Fiber Layer Thickness, an Index of Neurodegeneration, With Depressive Symptoms Over Time. *JAMA Netw Open* **4**, e2134753.

[44] Shi Z, Zheng H, Hu J, Jiang L, Cao X, Chen Y, Mei X, Li C, Shen Y (2019) Retinal Nerve Fiber Layer Thinning Is Associated With Brain Atrophy: A Longitudinal Study in Nondemented Older Adults. *Front Aging Neurosci* **11**, 69.
[45] Mutlu U, Bonnemaijer PWM, Ikram MA, Colijn JM, Cremers LGM, Buitendijk GHS, Vingerling JR, Niessen WJ, Vernooij MW, Klaver CCW, Ikram MK (2017) Retinal neurodegeneration and brain MRI markers: the Rotterdam Study. *Neurobiol Aging* **60**, 183-191.
[46] Levkovitch-Verbin H, Quigley HA, Kerrigan-Baumrind LA, D'Anna SA, Kerrigan D, Pease ME (2001) Optic nerve transection in monkeys may result in secondary degeneration of retinal ganglion cells. *Invest Ophthalmol Vis Sci* **42**, 975-982.
[47] Yoles E, Schwartz M (1998) Degeneration of spared axons following partial white matter lesion: implications for optic nerve neuropathies. *Exp Neurol* **153**, 1-7.
[48] Lim JKH, Li QX, He Z, Vingrys AJ, Chinnery HR, Mullen J, Bui BV, Nguyen CTO (2020) Retinal Functional and Structural Changes in the 5xFAD Mouse Model of Alzheimer's Disease. *Front Neurosci* **14**, 862.
[49] Chang LY, Ardiles AO, Tapia-Rojas C, Araya J, Inestrosa NC, Palacios AG, Acosta ML (2020) Evidence of Synaptic and Neurochemical Remodeling in the Retina of Aging Degus. *Front Neurosci* **14**, 161.
[50] Hussain B, Fang C, Chang J (2021) Blood-Brain Barrier Breakdown: An Emerging Biomarker of Cognitive Impairment in Normal Aging and Dementia. *Front Neurosci* **15**, 688090.
[51] Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, Sepehrband F, Nelson AR, Buennagel DP, Harrington MG, Benzinger TLS, Fagan AM, Ringman JM, Schneider LS, Morris JC, Chui HC, Law M, Toga AW, Zlokovic BV (2019) Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med* **25**, 270-276.
[52] Khawaja AP, Chan MP, Hayat S, Broadway DC, Luben R, Garway-Heath DF, Sherwin JC, Yip JL, Dalzell N, Wareham NJ, Khaw KT, Foster PJ (2013) The EPIC-Norfolk Eye Study: rationale, methods and a cross-sectional analysis of visual impairment in a population-based cohort. *BMJ Open* **3**.
[53] Wilkinson T, Schnier C, Bush K, Rannikmäe K, Henshall DE, Lerpiniere C, Allen NE, Flaig R, Russ TC, Bathgate D, Pal S, O'Brien JT, Sudlow CLM (2019) Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol* **34**, 557-565.
[54] Mc Cord KA, Hemkens LG (2019) Using electronic health records for clinical trials: Where do we stand and where can we go? *Cmaj* **191**, E128-e133.
[55] Schneider JA, Arvanitakis Z, Bang W, Bennett DA (2007) Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* **69**, 2197-2204.
[56] Rahimi J, Kovacs GG (2014) Prevalence of mixed pathologies in the aging brain. *Alzheimer's Research & Therapy* **6**, 82.
[57] Maki Y (2021) Reconsidering the overdiagnosis of mild cognitive impairment for dementia prevention among adults aged ≥80 years. *J Prim Health Care* **13**, 112-115.
[58] Stites SD, Karlawish J, Harkins K, Rubright JD, Wolk D (2017) Awareness of Mild Cognitive Impairment and Mild Alzheimer's Disease Dementia Diagnoses Associated

With Lower Self-Ratings of Quality of Life in Older Adults. *J Gerontol B Psychol Sci Soc Sci* **72**, 974-985.

[59] Collaborators GDF (2022) Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* **7**, e105-e125.

[60] Organization WH (2017) Global action plan on the public health response to dementia 2017–2025. *Geneva: World Health Organization*.