Statistical modelling for prediction of diabetes complications

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Para mi familia y Belén.

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Work derived from this thesis has been published (Chapter 3 to 5) and the corresponding declaration forms are located in Appendix F.

I used R Markdown and the bookdown package to write this thesis.[1] The format is based on the oxforddown template.[2]

Key support: I am ever so grateful to my PhD supervisors Professors Adnan Tufail, Catherine Egan, Alicja Rudnicka, and Christopher Owen for their continued support and guidance. I am also extremely grateful for the confidence and support

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Abstract

Background:

Diabetes is a major health issue affecting 10% of the population, causing significant morbidity and healthcare costs, with NHS expenditures exceeding £1.5 million per hour. Diabetic retinopathy (DR), a common microvascular complication of diabetes, doubles healthcare costs compared with people living with diabetes (PLD) but no DR. In 2021, there were 6.7 million global diabetes-related deaths, a third among working-age individuals. Notably, not all PLD develop complications, and times-to-progression vary. Accurate risk stratification at the point of care could improve resource allocation, recruitment for clinical trials, and outcomes, yet current approaches remain limited.

Objectives:

To utilise diabetic eye screening (DES) and electronic health records (EHR) data to: i) quantify visual impairment in people with DR, ii) identify sociodemographic factors associated with DES non-attendance and sight-threatening DR, and iii) develop predictive models for sight-threatening DR and all-cause mortality.

Methods and results:

Visual impairment prevalence and certification rates among people with DR were quantified using ophthalmic EHR data (aim i). Sociodemographic factors linked to DES non-attendance were identified, and prognostic factors for sight-threatening diabetic retinopathy (STDR) were examined within a large, ethnically diverse cohort from DES using multivariable logistic regression. Transition probabilities to STDR were calculated (aim ii). I linked EHR data to an identified cohort undergoing DES in the North East of London between 01/01/2012 to 31/12/2021 to develop and rigorously evaluate 5-year Cox regression predictive models for sight-threatening DR and mortality (aim iii).

Conclusion:

I have shown visual impairment in people with DR remains a significant public health problem, underscoring a need of continued resource allocation. By integrating DES and EHR data, this work provides valuable insights into critical

points in the diabetes disease course. It aims to identify high-risk individuals early, enabling targeted interventions and improved strategies for clinical trial recruitment, ultimately enhancing diabetes care and outcomes.

Impact statement

My work has provided critical insights into key stages in the journey of a person with diabetes, from diagnosis and attendance at diabetic eye screening (DES) to referral to hospital eye services (HES) or death.

First, I have assessed the prevalence of visual impairment and certification of visual impairment (CVI) in people with diabetic retinopathy (DR) at eye hospital services to shed light into the magnitude of visual impairment. Although DR is no longer the leading cause of certifiable blindness in the UK, I have demonstrated that visual impairment is significantly underestimated at HES when relying on CVI data alone, implying STDR remains a serious public health issue. Approaches to improve the mechanism of CVI aiming to address under-registration have been disseminated at HES, in a peer reviewed publication, and presented in the 2024 annual Royal College of Ophthalmologists meeting.

Second, I have assessed demographic determinants of attendance to DES, where despite pre-conceptions that non-white ethnic groups being less likely to attend DES appointments, no associations in non-white ethnic groups with non-attendance were evidenced in an established systematic DES programme (DESP) when compared with white people. Importantly, I confirmed that high levels of deprivation, younger age, and longer duration of diabetes, were associated with non-attendance in the setting were all of my analyses were conducted.

Third, I have comprehensively provided transition STDR probabilities by subgroups of the population which are not frequently represented in diabetes and STDR research. And identified ethnic disparities in STDR progression rates. Findings from this work are relevant for future STDR research, for power calculations for clinical trials, and health economic modelling. This work was published in a peer reviewed journal.

Fourth, I have shown that in the context of transitioning to two-year interval DES for people with two subsequent DES episodes with no retinopathy, a remarkable 66% of incident STDR cases would experience a 1 year delay in diagnosis, highlighting the need for personalised medicine in sociodemographically diverse populations. This work was published in a peer reviewed journal alongside a commentary and received media coverage.

Lastly, I have developed prediction models for STDR, as well as mortality in people with diabetes, providing evidence of how my research can impact on patient outcomes beyond ophthalmology. Importantly, work derived from this thesis has contributed to the creation of an observational data resource of unprecedented scale with deep characterisation including retinal fundus photographs for future diabetes research and creation of tools for personalised medicine. As noted in the Acknowledgements section, significant contributions from a multidisciplinary team in the form of data extraction, data management, and production of summary statistic measures, facilitated the analyses in this work.

Publications arising from this PhD

Research paper declaration forms of work included in this thesis are in Appendix F.

First authored publications:

1. **Olvera-Barrios A**, Rudnicka AR, Anderson J, Bolter L, Chambers R, Warwick AN, et al. Two-year recall for people with no diabetic retinopathy: a multi-ethnic population-based retrospective cohort study using real-world data to quantify the effect. Br J Ophthalmol. 2023; 107(12):1839–45.
2. **Olvera-Barrios A**, Owen CG, Anderson J, Warwick AN, Chambers R, Bolter L, et al. Ethnic disparities in progression rates for sight-threatening diabetic retinopathy in diabetic eye screening: a population-based retrospective cohort study. BMJ Open Diabetes Res Care. 2023; 11(6):e003683.
3. **Olvera-Barrios A**, Mishra AV, Schwartz R, Khatun M, Seltene M, Rutkowska C, Rudnicka AR, Owen CG, Tufail A, and Egan C. Formal registration of visual impairment in people with diabetic retinopathy significantly underestimates the scale of the problem: a retrospective cohort study at a tertiary care eye hospital service in the UK. Br J Ophthalmol. 2022 Oct 14;0:1-6.
4. **Olvera-Barrios A**, Kihara Y, Wu Y, N Warwick A, Müller PL, Williams KM, Rudnicka AR, Owen CG, Lee AY, Egan C, Tufail A, on behalf of the UK Biobank and Eyes Vision Consortium. Foveal Curvature and Its Associations in UK Biobank Participants. Invest Ophthalmol Vis Sci. 2022 Jul 8;63(8):26. **Joint first author.**
5. **Olvera-Barrios A**, Seltene M, Heeren TFC, Chambers R, Bolter L, Tufail A, Owen CG, Rudnicka AR, Egan C, and Anderson J. Effect of ethnicity and other sociodemographic factors on attendance at diabetic eye screening: a 12-month retrospective cohort study. BMJ Open. 2021 Sep 17;11(9):e046264.
6. **Olvera-Barrios A**, Heeren TF, Balaskas K, Chambers R, Bolter L, Egan C, Tufail A, and Anderson J. Diagnostic accuracy of diabetic retinopathy grading by an artificial intelligence-enabled algorithm compared with a human standard for wide-field true-colour confocal scanning and standard digital retinal images. Br J Ophthalmol. 2021 Feb;105(2):265–70.
7. **Olvera-Barrios A**, Heeren TF, Balaskas K, Chambers R, Bolter L, Tufail A, Egan C, and Anderson J. Comparison of true-colour wide-field confocal scanner imaging with standard fundus photography for diabetic retinopathy screening. Br J Ophthalmol. 2020 Nov;104(11):1579–84.
8. Rajesh AE, **Olvera-Barrios A,** Warwick AN, Wu Y, Stuart KV, Biradar M, et al. Ethnicity is not biology: retinal pigment score to evaluate biological variability from ophthalmic imaging using machine learning. medRxiv. 2023; 2023.06.28.23291873. **Accepted in Nature Communications. Joint first author.**

Co-authored publications

1. Yang Q, Yasvoina M, **Olvera-Barrios A**, Mendes J, Zhu M, Egan C, et al. Deciphering the Connection Between Microvascular Damage and Neurodegeneration in Early Diabetic Retinopathy. Diabetes. 2024; 73(11):1883–94.
2. Fajtl J, Welikala RA, Barman S, Chambers R, Bolter L, Anderson J, **Olvera-Barrios A**, et al. Trustworthy Evaluation of Clinical AI for Analysis of Medical Images in Diverse Populations. NEJM AI. Massachusetts Medical Society; 2024; 1(9):AIoa2400353.
3. Huemer J, Heeren TF, **Olvera-Barrios A,** Faes L, Casella AMB, Hughes E, et al. Sight threatening diabetic retinopathy in patients with macular telangiectasia type 2. Int J Retina Vitreous. 2024; 10(1):28.
4. Wu Y, Egan C, **Olvera-Barrios A**, Scheppke L, Peto T, Issa PC, et al. Developing a continuous severity scale for MacTel type 2 using Deep Learning and implications for disease grading. Ophthalmology. 2024 Feb;131(2):219-226.
5. Willis K, Chaudhry UAR, Chandrasekaran L, Wahlich C, **Olvera-Barrios A,** Chambers R, et al. What are the perceptions and concerns of people living with diabetes and National Health Service staff around the potential implementation of AI-assisted screening for diabetic eye disease? Development and validation of a survey for use in a secondary care screening setting. BMJ Open. 2023; 13(11):e075558.
6. Peng CL, **Olvera-Barrios A**, Schwartz R, Grimaldi G, Egan C, Tufail A. Novel Outer Retinal Columnar Abnormalities (ORCA) and Non-Vasogenic Cystoid Macular Edema in Dense Deposit Disease. Retin Cases Brief Rep. 2023.
7. Wu Y, **Olvera-Barrios A**, Yanagihara R, Kung T-PH, Lu R, Leung I, et al. Training Deep Learning Models to Work on Multiple Devices by Cross-Domain Learning with No Additional Annotations. Ophthalmology. 2022; S0161-6420(22)00749-7.
8. Thomas DS, Warwick A, **Olvera-Barrios A**, Egan C, Schwartz R, Patra S, et al. Estimating excess visual loss from neovascular age-related macular degeneration in the UK during the COVID-19 pandemic: a retrospective clinical audit and simulation model. BMJ Open. 2022; 12(4):e057269.
9. Müller PL, Kihara Y, **Olvera-Barrios A**, Warwick AN, Egan C, Williams KM, et al. Quantification and Predictors of OCT-Based Macular Curvature and Dome-Shaped Configuration: Results From the UK Biobank. Invest Ophthalmol Vis Sci. 2022; 63(9):28.
10. Thomas DS, Lee AY, Müller PL, Schwartz R, **Olvera-Barrios A**, Warwick AN, et al. Contextualizing single-arm trials with real-world data: An emulated target trial comparing therapies for neovascular age-related macular degeneration. Clin Transl Sci. 2021; 14(3):1166–75.

11. Schwartz R, Warwick A, **Olvera-Barrios A**, Pikoula M, Lee AY, Denaxas S, et al. Evolving Treatment Patterns and Outcomes of Neovascular Age-Related Macular Degeneration Over a Decade. Ophthalmol Retina. 2021; 5(8):e11–22.
12. Müller PL, Liefers B, Treis T, Rodrigues FG, **Olvera-Barrios A**, Paul B, et al. Reliability of Retinal Pathology Quantification in Age-Related Macular Degeneration: Implications for Clinical Trials and Machine Learning Applications. Transl Vis Sci Technol. 2021; 10(3):4.
13. Liefers B, Taylor P, Alsaedi A, Bailey C, Balaskas K, Dhingra N, Egan C, Gomes Rodrigues F, González Gonzalo C, Heeren TFC, Lotery A, Müller P, **Olvera-Barrios A**, et al. Quantification of Key Retinal Features in Early and Late Age-Related Macular Degeneration Using Deep Learning. Am J Ophthalmol. 2021; 226:1–12.

Other outputs

1. Runner-Up in University College London Doctoral School Images as Art Competition 2021/2022 with the image entitled: *The doors of perception* (Figure A.1, `https://bit.ly/ucl-research-image-competition2021-2022`)
   Image description: "Cataracts are a clouding of the naturally transparent lens of the eye and are amongst the leading causes of blindness worldwide. Cataract surgery is one of the most common performed surgeries in the world. During surgery, patients may experience unique visual phenomena which may be perceived as pleasant or distressing. Few actual visual representations of these experiences are available in the literature. The image shows 45 digitised drawings donated by 38 patients who experienced visual perceptions during their cataract surgery. The result is a unique piece of artwork which represents a resource of importance for pre and postoperative patient counselling in ophthalmology".

I, Abraham Olvera Barrios, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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List of Abbreviations

AIC . . . . . Akaike Information Criterion.

ARIAS . . . . Automated retinal image assessment software.

CCG . . . . . Clinical Commissioning Group.

csv . . . . . Comma delimited values.

CVI . . . . . Certification of visual impairment.

CWS . . . . . Cotton-wool spots.

DES . . . . . Diabetic eye screening.

DESP . . . . . Diabetic eye screening programme.

DR . . . . . Diabetic retinopathy.

DRS . . . . . Diabetic Retinopathy Study.

EHR . . . . . Electronic Health Record.

ETDRS . . . . Early Treatment Diabetic Retinopathy Study.

FBG . . . . . Feature-based grading.

FP . . . . . Fibrovascular proliferation.

FPD . . . . . Fibrovascular proliferation at the disc.

FPE . . . . . Fibrovascular proliferation elsewhere.

GDPR . . . . . General Data Protection Regulations.

HDL-C . . . . High-density lipoprotein cholesterol.

HE . . . . . Hard exudates.

HES . . . . . Hospital eye service.

HR . . . . . Hazard ratio.

ICDR . . . . . International Clinical Diabetic Retinopathy Severity System.

IMD . . . . . Index of multiple deprivation.

IR . . . . . Incidence rate.

IRMA . . . . . Intraretinal microvascular abnormalities.

LASSO . . . . Least absolute shrinkage and selection operator.

LDL-C . . . . Low-density cholesterol.

LSOA . . . . . Lower Layer Super Output Area.

MA . . . . . Microaneurysm.

MEH-DRS . . Moorfields Eye Hospital Diabetic Retinopathy Service.

MEH . . . . . Moorfields Eye Hospital.

NHS . . . . . National Health Service.

NICE . . . . . National Institute for Health and Care Excellence.

NSC . . . . . National Screening Committee.

NV . . . . . New vessels.

NVD . . . . . New vessels at the disc.

NVE . . . . . New vessels elsewhere.

ONH . . . . . Optic nerve head.

ONS . . . . . Office for National Statistics.

PDR . . . . . Proliferative diabetic retinopathy.

PH . . . . . Proportional hazards.

PRH . . . . . Pre-retinal haemorrhage.

PRP . . . . . Pan-retinal photocoagulation.

PTAL . . . . . Public Transport Accessibility Level.

RCT . . . . . Randomised controlled clinical trial.

STDR . . . . . Sight-threatening diabetic retinopathy.

STRATOS . . STRengthening Analytical Thinking for Observational Studies.

TC . . . . . Total cholesterol.

TG . . . . . Triglycerides.

TRD . . . . . Tractional retinal detachment.

TRE . . . . . Trusted Research Environment.

TRIPOD . . . Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis.

TRUD . . . . . Technology Reference Data Update Distribution.

UKPDS . . . . United Kingdom Prospective Diabetes Study.

VA . . . . . Visual acuity.

VEGF . . . . . Vascular endothelial growth factor.

VH . . . . . Vitreous haemorrhage.

WebCAT . . . Web-based Connectivity Assessment Toolkit.

Introduction

Diabetes mellitus is a major global health issue affecting approximately 1 in 10 adults worldwide.[3,4] Complications from diabetes are leading contributors to morbidity, premature mortality, sight impairment and blindness.[5–7] Given not all people develop diabetes-related complications, and the time to adverse events are highly variable among different individuals, frequent contacts with health services are recommended by national and international organisations.[8–11] An accurate stratification of people at risk is therefore challenging and currently lacking at the point of care. In this context, clinical decision tools which allow identification of people at-risk early in the course of diabetes can reap the benefits of secondary prevention to improve quality of life and reduce healthcare costs.

Aim

The aim of this thesis was to integrate routinely collected clinical data to gain insights into the development of diabetes complications to improve outcomes in people with diabetes.

Specific objectives were:

1. To examine the proportion of visual impairment in people with diabetes referred from population diabetic eye screening to hospital eye services.
2. To examine determinants of non-attendance at diabetic eye screening (DES).
3. To examine incidence and associations of sight-threatening diabetic retinopathy (STDR) in diabetic eye screening by sociodemographic characteristics.
4. To develop prediction models for:

- STDR, and
- All-cause mortality.

Data sources

With the appropriate ethical approvals in place, I utilised large datasets derived from DES and electronic health records (EHR), briefly described below:

0.1 Data sources

0.1.1 The North East London Diabetic Eye Screening Programme Data

The North East London DES Programme (NELDESP) is a large ethnically diverse DES programme (DESP) provided by the Homerton Healthcare NHS Foundation Trust, and serves approximately 125,000 people with diabetes living in inner-city areas with multi-ethnic populations.[12] The NELDESP operates in accordance with English NHS DESP standards.[13] All people with diabetes aged 12 years or over are invited to attend DES yearly.

I identified a cohort comprising all people registered in the NELDESP between 01/01/2012 to 31/12/2021. Data include demographic characteristics (age, sex, self-reported ethnicity), type and duration of diabetes, visual acuity, structured multilevel human DR severity grading,[14] index of multiple deprivation (IMD), date of death, and linked EHR (including primary, secondary care, and medication data).[15,16]

0.1.2 Moorfields Eye Hospital Diabetic Retinopathy Service (MEH-DRS)

Moorfields Eye Hospital is the major centre for treatment of ophthalmic diseases in England, and receives referrals of people diagnosed with STDR from 5 main DESPs (i.e. North Central London, North East London, North West London, South East London, and South West London DESP). Data include demographic

characteristics (age, sex, self-reported ethnicity), type and duration of diabetes, visual acuity, diabetic retinopathy (DR) severity grading, IMD, and Certification of Visual Impairment (CVI) status.

Thesis outline

- Chapter 1 is a review of the literature on diabetes, the breadth and depth of the public health problem, DR and the burden to DESPs and eye hospitals, the excess mortality in people with diabetes, and the potential of prediction models to improve patient outcomes or clinical pathways.
- Chapter 2 describes the methods followed for results in Chapters 3 to 6. Subsections of the methods correspond to each results Chapter.
- Chapter 3, is the first of the results chapters. Here, I used the MEH-DRS data to estimate visual impairment prevalence and incidence in people with DR attending Eye Hospital Services, and show the proportion of patients registered with visual impairment at various time points during their hospital care.
- In Chapter 4, I identified sociodemographic determinants of non-attendance to DES using a one year cycle of NELDESP data.
- In Chapter 5, I examine sociodemographic associations with STDR development to assess disparities in DR progression rates. I also present DR and STDR incidence rates (IR).
- In Chapter 6, I followed rigorous prediction modelling strategies to develop survival predictive models for the development of STDR and all-cause mortality in people with diabetes.
- Chapter 7 brings together results from Chapters 3 to 6 and discusses avenues for future work deriving from this thesis.

Part I

Background

"...there are to be perceived a considerable number of apparently uniformly distributed blood-red flecks, some punctate, some striate or otherwise shaped, of the most various size, which seem to lie in the plane of the retinal vessels,... there also appear numerous irregular, rounded, light yellow spots whose brightness makes them very obvious."

— Eduard Jaeger's first description of diabetic retinopathy/maculopathy in *"Beiträgen zur Pathologie des Auges"* (1855-1856).

1 Background

Contents

This chapter examines diabetes complications, focusing on diabetic retinopathy (DR) and diabetes-related mortality, two major complications for the working-age population worldwide. It reviews DR classification systems, key associations, risk factors for both DR and mortality, and explores prediction models with their potential utility for risk stratification in diabetic eye screening programmes or hospital eye services.

1.1 Diabetes mellitus

Diabetes is an increasing public health problem affecting 1 in 10 adults globally and a major cause of premature death and morbidity.[3,4] The number of people

with diabetes worldwide has almost quadrupled in the last two decades, from 151 million in the year 2000, to 537 million in 2021, and is projected to rise to 1.31 billion in 2045, fuelled by sizeable increases in developing countries.[3,4] About half of patients with diabetes remain undiagnosed (from 54% in Africa to 24% in North America and the Caribbean).[17] And an estimated 352 million people have impaired fasting glucose or impaired glucose tolerance, which progresses to type 2 diabetes at a 5-10% rate per year.[18,19]

From all people with diabetes, 90% and 5 to 10% are affected by type 2 and type 1 diabetes, respectively.[20,21] Type 2 diabetes is recognised as a complex, cardio-renal-metabolic disease driven by a chronic positive energy balance.[21] Type 1 diabetes is due to an autoimmune destruction of beta cells in the pancreas causing insulin deficiency.[22,23] Table 1.1 lists the other less frequent forms of diabetes, which are increasingly recognised, and are referred to as: "*Other types of diabetes*".[22]

Disturbances in glucose and lipid metabolism, along with systemic arterial hypertension, have detrimental effects on vascular integrity and supply, which leads to micro- (i.e., DR, nephropathy, and neuropathy) and macrovascular complications (i.e. ischaemic heart disease, cerebrovascular disease, stroke, peripheral vascular disease [PVD]).[24] Vascular complications represent a substantial proportion of the diabetes burden for individuals and health systems.[20,25,26] Diabetes is estimated to consume 10% of the National Health Service (NHS) budget for England and Wales, and 80% of these costs are destined for the treatment of diabetes complications.[27,28]

1.2 Diabetic retinopathy

Diabetic retinopathy is one of the most common complications of diabetes and a leading cause of visual impairment (VI) and blindness in the working age population (16-64 years of age).[29]

The overall prevalence of DR in people living with diabetes is 30%.[6,30] After 20 years of diabetes, nearly 100% of people with type 1 diabetes will develop some form of DR. In people with type 2 diabetes, about 50% of the people treated

Table 1.1: Other specific types of diabetes.

Other types of diabetes
Genetic defects of beta-cell function
MODY 3 (Chromosome 12, HNF-1alpha); accounts for 2/3 of all MODY
MODY 1 (Chromosome 20, HNF-4alpha)
MODY 2 (Chromosome 7, glucokinase)
Other very rare forms of MODY: MODY 4 (PDX1), MODY 5 (HNF-1beta), MODY 6 (neuroD1), MODY 7 (corboxyl ester lipase)
Mitochondrial DNA
Others
Genetic defects in insulin action
Type A insulin resistance
Leprechaunism
Rabson-Mendenhall syndrome
Lipoatrophic diabetes
Others
Diseases of the exocrine pancreas
Endocrinopathies
Drug or chemical induced
Other genetic syndromes sometimes associated with diabetes
Down syndrome
Klinefelter syndrome
Turner syndrome
Wolfram syndrome
Others

MODY; maturity-onset diabetes of the young, HNF; hepatic nuclear factor, PDX1; pancreatic duodenal homeobox 1.

with non-insulin hypoglycaemic therapy and more than 80% of people on insulin therapy will develop some form of DR.[31]

Health care costs are almost doubled for patients with diabetic retinopathy when compared with individuals without the disease. In the UK, the lifetime cost of dealing with a diabetic retinopathy case was estimated to be up to £237,000 per person in the working age group, from which half the costs accounted for lack of productivity due to visual complications.[25]

1.2.1 Classification

Since the first histopathological evidence of DR was reported in 1872,[32] landmark studies have show that DR can affect all cell types in the retina, leading to cellular dysfunction or injury which can occur even before clinically visible vascular changes.[24] Nevertheless, clinically, the presence and severity of DR is defined by visible retinal microvascular lesions.

Classic retinal lesions are well described and consist of microaneurysms (MA), intraretinal haemorrhages, hard exudates, cotton wool spots, venous beading, venous loops/reduplications, intraretinal microvascular abnormalities (IRMA), and retinal neovascularisation (NV).[33] Broadly, the overlapping spectrum of DR can be divided in non-proliferative DR (NPDR), defined as eyes with any of the DR features but NV, and proliferative DR (PDR), defined by the presence of NV. Diabetic macular oedema (DMO), is broadly defined as the presence of exudation within the central macula and can occur with any stage of NPDR or PDR.[34,35] Advanced forms of DR can affect the vision. Classification systems have been introduced to stage DR with more precision.

Apollinaire Bouchardat, considered the founder of modern diabetology, reported for the first time a case of visual decline associated with diabetes in 1846.[36] Nearly a decade later, in 1854, Charles Babbage's direct ophthalmoscope invention was described,[37] enabling retinal examination and paving the way for Eduard Jaeger to describe the first case of diabetic maculopathy in 1856.[38] Table 1.2 provides an overview on the progress of understanding DR and its treatment over the years.

1. Background

Different classification systems have arisen from attempts to classify DR severity stages, however, a unified classification (useful for research, clinical practice, and screening) has not been developed. Given the evidence behind these systems add perspective to our current thinking and approaches, a review of DR classification systems follows.

Table 1.2: A brief history of diabetic retinopathy.

Year	Historical landmark	Reference
	Diabetic retinopathy	
1846	Appolinaire Bouchardat reported visual loss in the absence of anterior segment changes, and absence of cataract	Bouchardat A. Nouveau mémoire sur la glycosurie. Ann de Thérap Suppl. 1846;162–311.
1847	Charles Babbage invents the direct ophthalmoscope	Jones W. British and Foreign Medico-Chirurgical Review. 1854; (XIV):549.
1856	Eduard Jaeger's first description of diabetic maculopathy	Jaeger E. Beitr zur Pathol des Auges. Wien: 1856; p.33 Fig.12)
1869	Henry Noyes's "Retinitis in glycosuria"	Noyes HD. Retinitis in glycosuria. Trans Am Ophthalmol Soc. 1869; 4:71–75
1872	Edward Nettleship provides first histopathological proof of diabetic maculopathy	Nettleship G. On oedema or cystic disease of the retina. Roy Ophth Lond Hosp Rep. 1872; VII(3):343–351
1875	Appolinaire Bouchardat describes a "glucose-induced amblyopia"	Bouchardat A. De la glycosurie ou diabète sucré. Paris: Librairie Germer Baillière. 1875
	Theodor Leber published a series of "glycosuric retinitis"	Leber T. Ueber die Erkrankungen des Auges bei Diabetes mellitus. Graefes Arch Clin Exp Ophthalmol. 1875; 21(3):206–253
1876	Wilhelm Manz describes fibrovascular proliferations of the retina: "retinitis proliferans"	Manz W. Retinitis proliferans. Graefes Arch Clin Exp Ophthalmol. 1876; 22:229
1890	Julius Hirschberg attempts the first DR classification	Hirschberg J. Über diabetische Netzhautentzündung. Dtsch Med Wochenschr. 1890;13:1181

DR; Diabetic retinopathy

Table 1.2: A brief history of diabetic retinopathy.

Year	Historical landmark	Reference
1943	Arthur James Ballantyne shows for the first time the role of capillary alterations in DR development	Ballantyne AJ, Loewenstein A. Exudates in diabetic retinopathy. Trans Ophthalmol Soc. UK 1943; 63:95.
1965	Norman Ashton began research at endothelial cell level	Ashton N, Cunha-Vaz JG. Effect of histamine on the permeability of the ocular vessels. Arch Ophthalmol. 1965;73: 211–223.
	The treatment of diabetic retinopathy	
1798	John Rollo's first monograph on diabetes recommending a meat-based diet	Rollo J. Cases of the diabetes mellitus. London: C. Dilly. 1798
1921	Charles H. Best and Frederick C. Banting discover the Insulin	Banting FG, Best CH. The internal secretion of the pancreas. J Lab Clin Med. 1922; 7:251–266
1950	Gerd Meyer-Schwickerath reports treatment of retinal diseases with light coagulation	Meyer-Schwickerath G. Koagulation der Netzhaut mit Sonnenlicht. Berl Dtsch Ophthalmol Ges. 1950; 55:256–259
1953	J. E. Poulsen describes regression of retinopathy following haemorrhagic infarct of the pituitary post-partum	Poulsen JE. Recovery from retinopathy in a case of diabetes with Simmonds' disease. Diabetes. 1953;2:7
1964	Charles Campbell and Christian Zweng use for the furst time the ruby laser in a clinical setting	Wetzig PC, Worlton JT. Treatment of diabetic retinopathy by light-coagulation: a preliminary study. Br J Ophthalmol. 1963; 47:539–541 Campbell CJ, Rittler MC, Koester CJ. The optical maser as a retinal coagulator: an evaluation. Trans Am Acad Ophthalmol Otolaryngol. 1963; 67:58–67

DR; Diabetic retinopathy

Table 1.2: A brief history of diabetic retinopathy.

Year	Historical landmark	Reference
1968	Francis L'Esperance and Arnall Patz establish treatment protocols with argon laser	L'Esperance FA. An ophthalmic argon laser photocoagulation system: design, construction, and laboratory investigations. Trans Am Ophthalmol Soc. 1968; 66:827–904
1970	William Beetham and Lloyd Aiello recognised the effectiveness of retinal photocoagulation	Beetham WP, Aiello LM, Balodimos MC, Koncz L. Ruby laser photocoagulation of early diabetic neovascular retinopathy: preliminary report of a long-term controlled study. Arch Ophthalmol. 1970; 83:261–272
1971	Robert Machemer describes the pars plana vitrectomy for vitreous haemorrhages	Machemer R, Buettner H, Norton WE, Parel JM. Vitrectomy: a pars plana approach. Trans Am Acad Ophthalmol Otolaryngol. 1971; 75:813–820

DR; Diabetic retinopathy

Historical classifications

The first comprehensive DR classification was attempted by Julius Hirschberg in 1890,[39] distinguishing 3 types of retinopathy: i) retinitis centralis punctate, ii) a haemorrhagic form, iii) and rare forms of retinal inflammation and degeneration like retinal infarction and haemorrhagic glaucoma. Hirschberg's classification did not include PDR as a category, however, possible proliferative changes were described in his haemorrhagic DR stage. In 1934, Henry Wagener distinguished between hard exudates and cotton wool spots, started to emphasize venous changes, and distinguished PDR as a specific category.[40] Wagener's classification presented a theory of the natural history of DR, progressing in a five-step fashion. Almost a decade later, in 1943, Ballantyne's hallmark study showed for the first time the role of capillary wall alterations in the development of DR, and discovered MA's.[41] This led him later to the development of another classification which emphasised the role of MA's as distinctive, early lesions of retinopathy.[42]

Full-disease classifications

The Airlie House classification, was the first standardised full-disease DR classification. This system was a result of the joint effort of the UK and the United States of America to find a generally accepted severity system. The expert committee meeting took place in 1968 in Airlie House, Virginia, USA.[43] This work from more than five decades ago, provided a standardisation of clinical variables that became the foundation which was then modified and used by the DR Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) groups.[34]

Based on a modification of the Airlie House classification, the ETDRS severity scale followed. Even though this classification system dates more than three decades back, it has remained the reference standard for DR grading, and the foundation for the evidence related to disease severity, progression rates to high-risk disease, vision loss, and for the efficacy of retinal laser supported with a strong evidence base.[34] The ETDRS was based on the natural history of untreated eyes using non-simultaneous 30-degree stereoscopic colour fundus photographs in seven

standard fields for evaluation. Fields 1 and 2 are centred in the optic disc and macula, respectively. Field 3 is temporal to the macula, and fields 4-7 surround fields 1-3 (Figure 1.1). Imaging and evaluation of the images has to be carried out by trained photographers and graders. Over 30 lesions are individually graded using a set of standard photographs to define the thresholds for scoring and a summary grade is then assigned.[34] The ETDRS classification made the analysis of clinical trials endpoints, progression of DR, and treatment assessments possible. Image acquisition and assessment are however time-consuming for patients, technicians, and graders.

The International Clinical Diabetic Retinopathy (ICDR) disease severity scale was published by the Global Diabetic Retinopathy Project Group as a reduced version of the ETDRS classification to be a method to improve communication among clinicians regarding DR staging, to be deployed in countries without systematic screening programmes, and to be used in clinical trials.[35] This meaningful and functional system overcame the time-consuming nature of the ETDRS system and its need for cooperative patients and trained graders (Table 1.3).

UK-based population screening classifications

In the UK, a further effective simplification of the ETDRS severity classification system was produced to fulfil the requirement for quality control and minimise the potential for error by non-expert screening staff within a population-based Diabetic Eye Screening Programme (DESP). The programme consists of one field (Scotland), and two field (England, Wales, Northern Ireland) photographic screening (macula-centred, and macula- and disc-centred, respectively).[14,15,44] Of the 8 possible steps in the grading of the UK-based classification systems, pre-proliferative DR (R2), PDR (R3), diabetic maculopathy (M1), and ungradable (U) levels are referred to hospital eye services for further assessment or treatment. Table 1.3 shows an overview of the most widely used DR classification systems, and their approximate equivalences based on retinal features.[14,34,35]

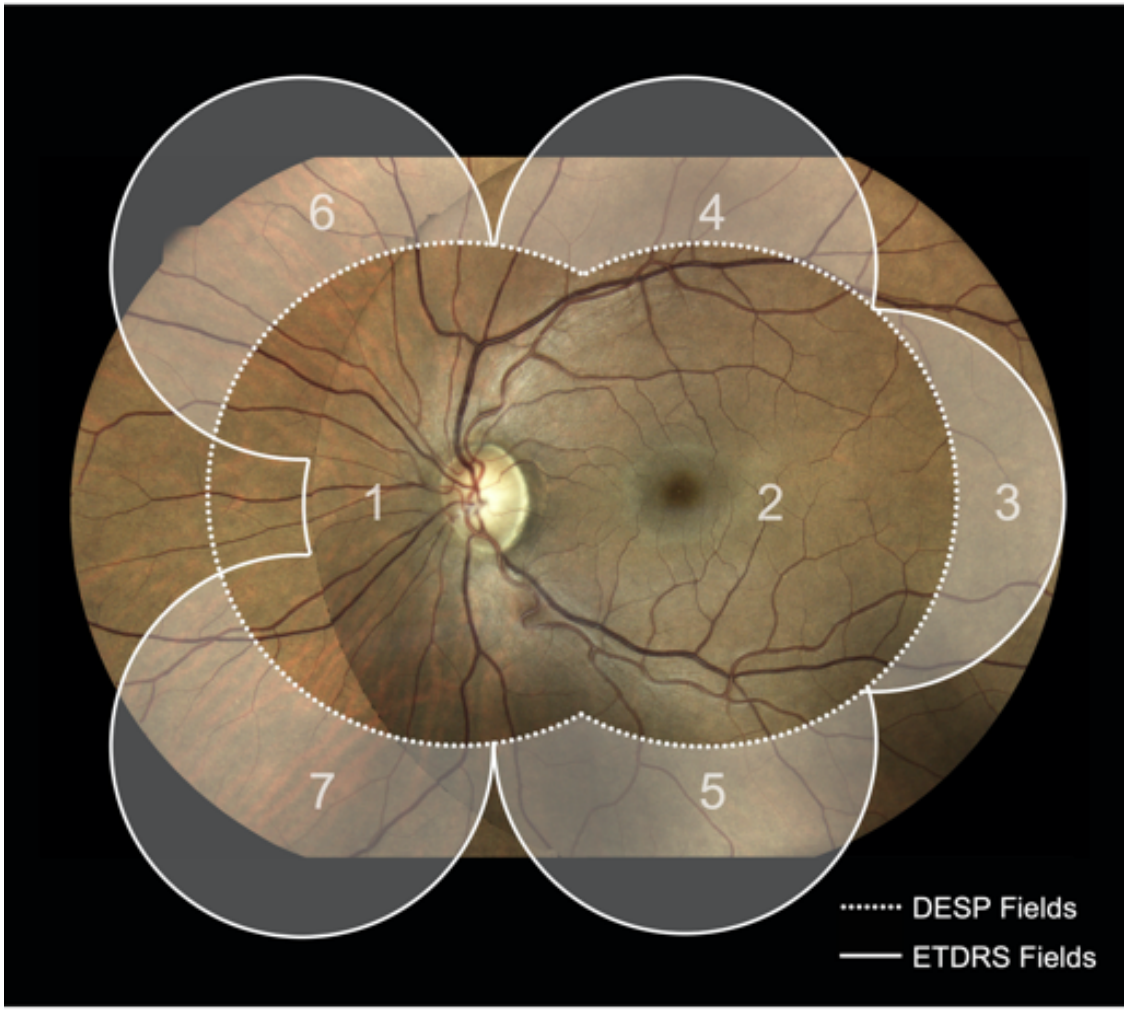

Figure 1.1: Montage of macula- and disc-centred 60-degree true-colour wide-field scanning laser ophthalmoscopy image of a left eye showing a comparison of the different fields of view obtained with different imaging protocols and imaging systems. Solid lines show the 7 Early Treatment Diabetic Retinopathy Study (ETDRS) fields (30-degree fundus cameras), dashed lines show the 2 Diabetic Eye Screening Programme (DESP) fields (45-degree fundus cameras).

Automated retinal image analysis classifications

The introduction of high-resolution digital retinal imaging systems in the 1990's, combined with major improvements in computing power, allowed the development of computer algorithms capable of computer-aided detection and diagnosis of DR cases.[45] Broadly, the approach to automated retinal image analysis system (ARIAS) can be categorised in two components: i) image quality assessment and ii) image analysis. The image quality assessment is essential to obtain images with sufficient quality for the currently available algorithms. Alteration of the optic

media transparency, patient movement and positioning, result in the presence of artefacts in 3 to 30% of retinal images, impeding correct grading.[46] Regarding image analysis, computer-aided diagnosis of DR broadly stratifies patients into the following categories: i) disease or no disease, and ii) refer or no refer.[45,47–49] Additional outputs providing ICDR severity classification system and/or UK-based classifications are also available within different algorithms.[48]

Table 1.3: Comparison of the most widely used diabetic retinopathy severity classification systems.

ETDRS	ICDR	NSC-UK
Level 10 DR absent	No aparent retinopathy No abnormalities	R0 No retinopathy
Level 14 DR Q; HE, CWS, or IRMA. MA A	No aparent retinopathy No abnormalities	R0 No retinopathy
Level 20 MA only	Mild NPDR MA only	R1 Background retinopathy Any of: MA, HA, exudate, VL
Level 35 Mild NPDR. One of more of: VL >= D/1, CWS, IRMA, or VB = Q, HA present, HE >= D/1, CWS >= D/1	Moderate NPDR > MA but < severe NPDR	R1 Background retinopathy Any of: MA, HA, exudate, VL
Level 43 Moderate NPDR HA/MA = M/4-5 - S/1 or IRMA = D/1-3 (not both)	Moderate NPDR > MA but < severe NPDR	R2 Pre-proliferative retinopathy Any of: VB, VRD, IRMA, multiple dot or blot HA

ETDRS, Early treatment diabetic retinopathy study; ICDR, International classification of diabetic retinopathy; NSC-UK, National Screening Committee UK; DR, diabetic retinopathy; HE, hard exudates; CWS, cotton-wool spots; IRMA, intraretinal microvascular abnormalities; MA, microaneurysm; D, definite; A, absent; VL, venous loops; VB, venous beading; Q, questionable; HA, haemorrhages; NPDR, non-proliferative DR; M, moderate; S, severe; VRD, venous reduplication; FPD, fibrovascular proliferation at the disc; FPE, fibrovascular proliferation elsewhere; NVD, new vessels at the disc; NVE, new vessels elsewhere; PDR, proliferative DR; PRH, pre-retinal haemorrhage; VH, vitreous haemorrhage; U, ungradable.

Table 1.3: Comparison of the most widely used diabetic retinopathy severity classification systems.

ETDRS	ICDR	NSC-UK
Level 47 Moderately severe NPDR Both Level 43 features and/or one (only) of the following: IRMA = D/4-5, HA/MA = S/2-3, VB = D/1	Moderate NPDR > MA but < severe NPDR	R2 Pre-proliferative retinopathy Any of: VB, VRD, IRMA, multiple dot or blot HA
Level 53 Severe NPDR One or more of: >= 2 of the L47 features, HA/MA >= S/4-5, IRMA >= M/1, VB >= D/2-3	Severe NPDR Any of: > 20 HA in each quadrant, VB >= 2 quadrants, IRMA in >= 1 quadrant	R2 Pre-proliferative retinopathy Any of: VB, VRD, IRMA, multiple dot or blot HA
Level 61 Mild PDR FPD or FPE present with NVD and NVE absent, or NVE = D	PDR >= 1 of: NVD, NVE, PRH, VH	R3 Proliferative retinopathy Any of: NVD, NVE, PRH, VH, FP, TRD
Level 65 Moderate PDR Either: i) NVE >= M/1 or NVD = D, and PRH = A or Q, ii) VH or PRH = D and NVE < M/1 and NVD absent	PDR >= 1 of: NVD, NVE, PRH, VH	R3 Proliferative retinopathy Any of: NVD, NVE, PRH, VH, FP, TRD
Levels 71 and 75 High risk PDR Any of: VH or PRH >= M/1, NVE >= M/1 and VH or PRH >= D/1, NVD = 2 and VH or PRH >= D/1, NVD >= M and VH or PRH >= D/1	PDR >= 1 of: NVD, NVE, PRH, VH	R3 Proliferative retinopathy Any of: NVD, NVE, PRH, VH, FP, TRD

ETDRS, Early treatment diabetic retinopathy study; ICDR, International classification of diabetic retinopathy; NSC-UK, National Screening Committee UK; DR, diabetic retinopathy; HE, hard exudates; CWS, cotton-wool spots; IRMA, intraretinal microvascular abnormalities; MA, microaneurysm; D, definite; A, absent; VL, venous loops; VB, venous beading; Q, questionable; HA, haemorrhages; NPDR, non-proliferative DR; M, moderate; S, severe; VRD, venous reduplication; FPD, fibrovascular proliferation at the disc; FPE, fibrovascular proliferation elsewhere; NVD, new vessels at the disc; NVE, new vessels elsewhere; PDR, proliferative DR; PRH, pre-retinal haemorrhage; VH, vitreous haemorrhage; U, ungradable.

Table 1.3: Comparison of the most widely used diabetic retinopathy severity classification systems.

ETDRS	ICDR	NSC-UK
Level 81 Advanced PDR Fundus partially obscured, centre of macula attached NVD = cannot grade, or NVD < D and NVE = cannot grade in >= 1 field and absent in all others; and retinal detachment at centre of macula < D	PDR >= 1 of: NVD, NVE, PRH, VH	R3 Proliferative retinopathy Any of: NVD, NVE, PRH, VH, FP, TRD
Level 85 Advanced PDR; posterior fundus obscured, or centre of macula detached. VH = VS in fields 1&2, or retinal detachment at centre of macula = D	PDR >= 1 of: NVD, NVE, PRH, VH	R3 Proliferative retinopathy Any of: NVD, NVE, PRH, VH, FP, TRD
Level 90 Cannot grade, even sufficiently for level 81 or 85		U Ungradable

ETDRS, Early treatment diabetic retinopathy study; ICDR, International classification of diabetic retinopathy; NSC-UK, National Screening Committee UK; DR, diabetic retinopathy; HE, hard exudates; CWS, cotton-wool spots; IRMA, intraretinal microvascular abnormalities; MA, microaneurysm; D, definite; A, absent; VL, venous loops; VB, venous beading; Q, questionable; HA, haemorrhages; NPDR, non-proliferative DR; M, moderate; S, severe; VRD, venous reduplication; FPD, fibrovascular proliferation at the disc; FPE, fibrovascular proliferation elsewhere; NVD, new vessels at the disc; NVE, new vessels elsewhere; PDR, proliferative DR; PRH, pre-retinal haemorrhage; VH, vitreous haemorrhage; U, ungradable.

1.2.2 Risk factors for diabetic retinopathy

Longer duration of diabetes, higher haemoglobin A1c (HbA1c), and systemic arterial hypertension are established risk factors associated with DR and blindness.[30,50–52]. The evidence available for dyslipidaemia, on the other hand, remains controversial.[53–55]

Duration of diabetes

In the context of diabetes chronicity, duration of the disease is a clear unmodifiable risk factor for DR incidence. A meta-analysis revealed an 8.69-fold

greater risk of STDR in individuals with type 1 diabetes and a 6.27-fold greater risk in people with type 2 diabetes for diabetes durations exceeding 20 years, compared with individuals with type 1 and type 2 diabetes with less than 10 years duration of diabetes, respectively.[30] A cohort study with a 10-year follow-up in the UK evidenced that each 5-year increase in the duration of diabetes among people with type 2 diabetes was associated with a 17% increase in DR risk, and a 42% risk increase of severe DR (defined as retinopathy requiring laser or advanced retinopathy).[6] Similarly, a 10% risk increase for DR and 26% risk increase for severe DR was found per each 5-year rise in the duration of diabetes in people with type 1 diabetes.[6]

Hyperglycaemia

Epidemiologic studies and randomised controlled clinical trials (RCTs) have consistently shown that poor glycaemic control is associated with DR incidence and progression.[51,56–59] A recent meta-analysis of individual participant data of 4 large-scale RCTs (United Kingdom Prospective Diabetes Study [UKPDS], Action to Control Cardiovascular Risks in Diabetes [ACCORD], Action in Diabetes and Vascular Disease [ADVANCE] and Veterans Administration Diabetes Trial [VADT] studies) evidenced a relative risk reduction of 13% for diabetic eye complications with intensive glucose control over 5 years.[60] The beneficial effects of intensive glycaemic control have been evidenced to persist years after intensive interventions are stopped,[61,62] and highlight the importance of early identification of people at risk of complications and the potential role of optimal glucose control for secondary prevention of diabetes complications.

Systemic arterial hypertension

The UKPDS showed that intensive treatment of systemic arterial hypertension reduced the incidence of DR with a 10 mmHg reduction in systolic blood pressure being associated with an 11% reduction in photocoagulation or vitreous haemorrhage.[52,63] Evidence from the ACCORD Eye Study lowering systemic blood

pressure did not show an effect on DR progression.[64] In a systematic review and meta-analysis, it was evidenced that intensive blood pressure control had preventive effects on 4-5-year incidence of DR, but the evidence is less supportive when looking at progression if retinopathy was already present.[65] Importantly, legacy effects seen after interventions for glucose control, were not equally present with blood pressure, highlighting a potential benefit of targeted interventions to continue an intensive control of blood pressure to avoid diabetes micro and macrovascular complications.[66,67]

Dyslipidaemia

While small studies examining the effects of statin use on DR risk have found beneficial effects,[53,55] no benefits have been found on large RCTs.[54,68] A recent large population-based cohort study in people with type 2 diabetes found that statin use was significantly associated with reduced DR (hazard ratio [HR] 0.86; 95% CI, 0.81-0.91), PDR (HR 0.64; 95% CI, 0.58-0.70), and diabetic macular oedema (DMO) hazards (HR 0.60; 95% CI, 0.46-0.79), and was associated with a reduced the rate of DR-related interventions (retinal laser, intravitreal injections, and vitrectomy).[69] Fenofibrate use has been associated with lower risk of DR progression and the need for pan-retinal photocoagulation (PRP) in people with diabetes.[64,70,71] Recent results from a Scottish RCT which included 1151 participants randomly assigned to treatment with 145mg fenofibrate over a median of 4 years showed a 27% reduction in STDR hazards, and a 42% reduction in hazards of DR-related treatments.[72] Nevertheless, accumulating evidence suggests that the mechanism of action of fenofibrate is directly mediated within the eye rather than through a reduction in circulating blood lipids.[72]

A systematic review and meta-analysis which included 7 observational studies did not show differences in tryglicerides (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) in patients with and without DR.[73] Low-density lipoprotein cholesterol (LDL-C) were discretely higher in patients with DR

(3.74mg/dl, 95% CI 0.13-7.35, p = 0.04), but the estimate was unstable and no longer significant on sensitivity analysis.[73]

1.2.3 Diabetic eye disease screening

Early detection and a timely intervention for STDR, once clinically defined criteria are met, can prevent blindness, limit healthcare costs, and indirectly reduce mortality.[74] Diabetic eye screening (DES) is different across countries and depends on available resources and public health policies. Since 2008, the UK offers nationwide annual photographic diabetic eye screening (two fundus images per eye obtained under mydriasis, one macula-centred and one disc-centred image) to all people living with diabetes aged 12 years and older.[8,74] As a possible result of this measure, since at least 2009-2010, DR no longer ranks as the leading cause of certifiable blindness in the UK for the first time in almost 50 years, and was superseded by hereditary retinal dystrophies.[29]

Interval recommendations for diabetic eye screening

Regular DES for people with diabetes is recommended, however, frequency of screening and subsequent monitoring for progression in clinical guidelines can differ across healthcare settings. The National Institute for Health and Care Excellence (NICE) recommends annual diabetic eye screening,[75] and since October 2023, people attending DESP with two consecutive screening episodes with no evidence of DR in both eyes are eligible for biennial DES.[76] Annual screening is accepted, with some organisations allowing less frequent intervals (screening every 2 or 3 years) for people at low risk (No diabetic retinopathy, or type 2 diabetes).

Models of DES using personalised risk-stratification have been developed,[25,77–83] however, the implications of deployment of longer than annual DES intervals with respect to STDR in multi-ethnic populations with more deprived profiles has not been formally quantified.

1.3 Diabetes-related mortality

Diabetes is a major cause of mortality worldwide. People diagnosed with diabetes typically have shorter life expectancies than people without diabetes, with heart disease being a major underlying cause of death.[84,85] Differences in mortality rates between people with diabetes is an indicator of the quality of and access to health-care. Approximately 6.7 million adults are estimated to have died as a result of diabetes or its complications in the year 2021. Importantly, a third (32.6%) of diabetes-related deaths occur in the working age population (<60 years of age). In the same year, a staggering 37.8 million years of life were estimated to have been lost due to diabetes, and 94% of these were attributed to type 2 diabetes.[3,7]

Despite systematic review data showing that all-cause mortality rates have declined 80% among people with diabetes from a population of predominantly European background since 2000,[86] similar patterns are not to be expected in low- and middle-income countries where 3 out of 4 people with diabetes live.[7,86] The burden of diabetes remains high, as evidenced by the inclusion of diabetes as one of three target diseases in the World Health Organisation Global Action Plan for the Prevention and Control of non-communicable disease.[87] Moreover, the United Nations has established a target of reducing rates of premature death due to diabetes by a third by 2030.[88]

Few data are available in the literature to examine mortality in people with diabetes at population DES by age, sex, type of diabetes, ethnicity, and sociodemographic deprivation.

1.4 Risk prediction models for diabetes-related complications

Although early identification of people at risk of diabetes-related visual loss or cardiovascular complications is key to limiting complications by emphasising on lifestyle modifications and targeting a more intensive systemic control, accurate identification of people with diabetes at high-risk of complications remains a challenge.[25,77]

The use of risk prediction models in a healthcare setting could support and inform decision-making, emphasising early measures for secondary prevention in individuals at high risk of complications.[89]

A number of studies have sought to estimate the risk of STDR or death in people with diabetes,[90–92] however, predictive performance is not routinely evaluated or reported, studies show modest levels of agreement which varies considerably between studies, and there is a tendency to overestimate mortality[93,94] and underestimate DR risk.[90]

Equity in prognostic modelling needs to be emphasised since most of the data comes from high-income countries, models predominantly include people with type 2 diabetes, there is insufficient representation of non-white ethnic groups, and the levels of sociodemographic deprivation are not routinely reported.[92]

1.5 Summary

It is clear that diabetes is a major public health problem that is rising in prevalence. The complications that people with diabetes may develop along the course of their disease are a major burden at an individual level, a significant cause of disability, and generate significant costs to health care systems. It is because of these reasons that I aim to: i) quantify the rate of visual impairment of people with DR to inform on the current status of the problem, ii) describe sociodemographic variations in incidence rates, and identify associations for complications of diabetes (DR, STDR and all-cause mortality) in population-based cohorts and ii) develop, validate, assess, and compare performance of prediction models for diabetes-related complications (STDR and all-cause mortality).

With this work, I aim to create a method to identify individuals at high risk of diabetes-related complications with the potential to integrate within the current DES infrastructure (i.e. early in the course of the disease where people can benefit from early interventions), and with potential to generalise to other settings.

Part II

Methods

2 Methods

Contents

This chapter details the methodology followed for each result Chapter. Each designated subsection corresponds to the results Chapters 3 to 6.

2.1 Ethics statement

Data approvals were secured for all relevant analyses. The work detailed in Section 2.2.1 and results Chapter 3 was registered as an audit and approved by Moorfields Eye Hospital NHS Foundation Trust research governance. Professor Catherine Egan was the registered lead auditor and data custodian. Michael Seltene from the diabetic retinopathy screening service at Moorfields NHS Foundation Trust performed the identification and extraction of pseudonymised data. Work described in Section 2.3 and results Chapter 4 was registered and approved as part of a Health Equity Audit (cycle 2018-2018) through the research governance process at the Homerton Healthcare NHS Foundation Trust. Dr John Anderson was the registered lead auditor and data custodian. Ryan Chambers, the North East London Diabetic Eye Screening (NELDESP) data manager, conducted participant identification, pseudonymisation, and data extraction. For work outlined in Sections 2.4 to 2.5 and results Chapters 5-6 ethical approval was obtained from the NHS Health Research Authority and Health and Care Research Wales (IRAS project ID 265637). Approval from the head of research governance at the Homerton Healthcare was also secured. Individual consent forms were not deemed necessary for ethics approval, as the study was confined to the utilisation of retrospective anonymised data. A data protection impact assessment form was

completed and ratified by the Homerton Healthcare Information Governance Team to allow installation of the Trusted Research Environment (TRE) in the Trust Network. All research was conducted in accordance with the ethical principles of the Declaration of Helsinki. The management and handling of all patient data adhered to the UK Policy Framework for Health and Social Care Research, the Data Protection Act 2018, the common law duty of confidentiality, the Caldicott Principles, and the principles of Good Clinical Practice (GCP).

2.2 Visual impairment in patients with diabetes and diabetic retinopathy at hospital eye services

2.2.1 Moorfields Eye Hospital Diabetic Retinopathy Service (MEH-DRS) data source

The data source is described in Section 0.1.2. In 2019, a total of 5,173 diabetic retinopathy (DR) referrals from five main Diabetic Eye Screening Programmes (DESP) were reviewed at Moorfields Eye Hospital. Certification of visual impairment (CVI) data is collected regularly by the Performance Audit & Failsafe Service at Moorfields Eye Hospital from the eye clinic liaison officers via the Trust's clinical letter database from all of the hospital's clinical sites. This is the basis of the annual CVI audit which is shared with the local DESP in line with national requirements.

2.2.2 Design

This was a retrospective study which included consecutive people referred to the MEH-DRS with a diagnosis of referrable DR from the NHS DESP between 04/01/2016 to 01/08/2019. The main outcome measure was the prevalence of patients with visual impairment.

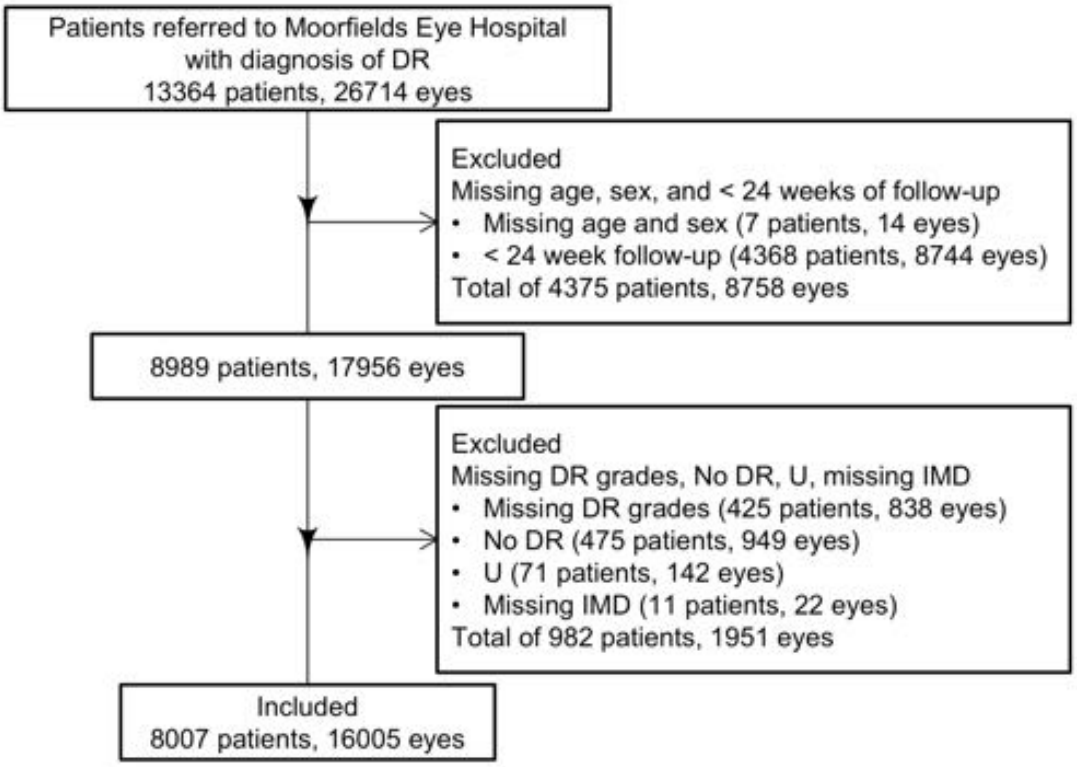

Figure 2.1: Diagram of exclusions. DR, diabetic retinopathy; IMD, index of multiple deprivation; U, ungradable.

2.2.3 Visual impairment definition

Visual impairment was defined as best corrected visual acuity (VA) in the better eye worse than 6/24 (0.6 logarithm of the minimum angle of resolution (logMAR) equivalent) following the UK CVI Guidance definition.[95]

2.2.4 Exclusion criteria

Patients with missing data on age, sex, less than 24 weeks of follow-up, missing diabetic retinopathy (DR) grades (severity graded as per National Screening Committee DR classification),[14] and patients with no DR (R0M0) at the time of their clinical examination, were excluded from the analysis (Figure 2.1).

2.2.5 Variables

Visual acuity

Visual acuity data was measured and recorded in Snellen fractions, Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores, and as logMAR at three different time points: i) baseline, ii) year one, and iii) at the end of follow-up. All VA measurements were converted to logMAR based on work from Holladay et al.,[96] Beck et al.[97] and Gegori et al.[98] To align with UK CVI guidance,[95] the eye with best VA at each visit was selected for analysis.

Index of Multiple Deprivation

The English indices of deprivation are composed of 39 post-code-derived indicators arranged in 7 different domains of deprivation, which are combined and weighted to create the index of multiple deprivation (IMD), the nationally recognised measure of relative deprivation in England.[16] The measure is calculated for every neighbourhood or small area (lower-layer super output area [LSOA]) in England. There are 32,844 LSOAs with an average population of 1,500, and each of them is ranked from 1st, the most deprived area, to the 32,844th, least deprived area. Patients' postcodes were linked to their IMD scores before data extraction, and only the IMD scores were used for analysis. Rank scores of the IMD were split into quintiles following Office for National Statistics (ONS) data of the English indices of deprivation 2019, where the 1st quintile was the most deprived and the 5th quintile the least deprived.[16]

Only for the purpose of this analysis, IMD quintiles 4 and 5 were pooled due to small numbers with visual outcome.

Self-reported ethnicity

Ethnicity was categorised in 4 main groups; white (white British, Irish, any other white background), South Asian (Indian, Pakistani, Bangladeshi), black (African, Caribbean, any other black background), and other (white and black Caribbean, white and black African, white Asian, any other mixed background,

Chinese, any other Asian background and any other Ethnic group). Missing data points on ethnicity were categorised as a 'Missing' group.

Diabetic retinopathy severity

Diabetic retinopathy grades (grading classification in order of increasing severity: R1, R2, M1, and R3)[14] were included as follows: a) the DR grade corresponding to the eye with the best baseline VA was selected for analysis, b) if VA was the same in both eyes at baseline, the worst DR grade was included. Diabetic retinopathy grades were further categorised as non-sight-threatening DR (comprising R1M0 grades), and sight-threatening DR (STDR), which comprises R2, R3, and M1 grades. Treatment of DR-related complications was recorded at patient level as intravitreal injections (anti-Vascular endothelial growth factor (VEGF) or steroids), retinal laser treatment, or combination treatment (intravitreal injections plus retinal laser at simultaneous or asynchronous visits).

2.2.6 Statistical analysis

I used the software for statistical computing R (version 4.1.2) for analyses.[99] Age at baseline was divided in categories (20 to 49, 50 to 64, 65 to 79, 80 years of age) to allow for non-linear associations with visual impairment. I conducted a multivariable logistic regression analysis with visual impairment at the last visit as the primary outcome of interest controlling for age, sex, type of diabetes, baseline DR grade, ethnicity, and IMD; CVI was used as a secondary outcome. Linear trend tests were performed for age and IMD.

The reference category for age categories was the 20-to-49-year category, for ethnicity was the white group, for IMD, the most deprived quintile (1st). Odds ratios per year increase in age and IMD category were also examined given graded associations. As part of sensitivity analyses, I calculated the CVI rate in patients with at least 1 year of follow-up, and in the working age population (defined as patients between 16 to 64 years of age).[100]

2.3 Sociodemographic determinants of attendance to diabetic eye screening

2.3.1 The North East London Diabetic Eye Screening Programme Data

Setting

The North East of London is an ethnically diverse region with higher than national average levels of deprivation and mortality.[101] The NELDESP serves the boroughs of Newham, Redbridge, Tower Hamlets, and Waltham Forest, classified as the most ethnically diverse in London;[102] the boroughs of Hackney, Havering, and the borough of Barking and Dagenham, which has a substantial multi-ethnic population. All people with diabetes aged 12 years are identified through the electronic "General Practice to diabetic retinopathy Screening" coding system, which automatically notifies DESPs about new diabetes diagnoses. All new eligible people are invited for screening within 3 months of notification. Software is used to generate invitations to attend for screening appointments. Over the course of one year, every person eligible for DES is offered multiple opportunities to attend.[103] The Homerton Healthcare carries out appointment call/recall, screening, image grading, referral tasks, and is responsible for providing clinical leadership and programme management, including failsafe procedures and internal quality assurance.[101]

A NELDESP screening visit entails history taking by specialist staff, VA assessment, and capture under pupil dilation of two 45° digital retinal images, centred on the fovea and optic nerve for each eye, respectively. Trained graders assess the images for presence and severity of diabetic retinopathy following a multilevel internally and externally quality-assured process[104] using the UK National Screening Committee classification (NSC-UK) system for DR.[14] Diabetic retinopathy grades in order of increasing severity are: no retinopathy (R0), mild non-proliferative diabetic retinopathy (R1), diabetic maculopathy (M1), severe non-proliferative diabetic retinopathy (R2), and proliferative diabetic retinopathy (R3).[14] Sight-

threatening DR comprises DR grades greater than or equal to M1 and, for these, referral to hospital eye services for assessment/treatment is made.

2.3.2 Design

This was a 12-month retrospective cohort study between 01/04/2017 to 31/03/2018. Which included data from people with diabetes living in 6 Clinical Commissioning Group (CCG) areas with inner city multi-ethnic populations, residing in London boroughs of Newham, Redbridge, Tower Hamlets and Waltham Forest, Barking & Dagenham, and Hackney. The main outcome measure was attendance to DES.

2.3.3 Attendance definition

Any person attending any of the offered appointments over the course of one whole year was defined as 'Attended'. Only those who failed to attend all appointments offered in the period were classified as 'Did not attend'.

2.3.4 Variables

Potential determinants of attendance included age, sex, self-defined ethnicity, sociodemographic deprivation, type of diabetes, duration of diabetes, VA, years of registration in NELDESP, distance to screening centre, and Public Transport Accessibility.

Ethnicity

Self-reported ethnicity data was collected from patients at the time of screening, or from the routinely recorded ethnicity data provided by their GP surgery. Ethnicity was recorded in the nationally mandated screening software in accordance with the Office for National Statistics (ONS) census groups.[105]

Index of Multiple Deprivation

The IMD is calculated as specified in Section 2.2.5. Patient postcodes were linked to their IMD scores before data extraction. Rank scores of the IMD were split into quintiles following ONS (1st quintile was the most deprived and the 5th quintile the least deprived).[16]

Visual acuity, distance and Public Transport Accessibility Level (PTAL)

I recorded the most recent VA measure within a 1-year time window in Snellen notation for the analysis. The better-seeing eye visual acuity score was assigned to each person. I calculated distance to screening centre (in kilometres) as a straight line from the patient's postcode to the screening site. For patients who attended, the postcode used was that known to the NELDESP on the day of attendance. For patients who failed to attend at any point within the study period, the postcode used was that known to the NELDESP on the date of the last offered appointment. The PTAL is a metric tool from Transport for London which rates locations by distance to the public transport network, thus reflecting the accessibility to public transport within Greater London. The PTAL grade takes into account walk access time, average waiting time, service availability, and service reliability. The grading has 9 levels from 0 (with the poorest access) to 6b (excellent access).[106] Using Transport for London's Web-based Connectivity Assessment Toolkit (WebCAT),[107] I extracted the PTALs for each patient's home postcode.

2.3.5 Statistical analysis

I used R version 4.0.0 for statistical analysis.[99] Multivariable logistic regression analysis of attendance at screening visit (binary outcome coded "1" if patient attended and "0" if they did not attend) was implemented. A test for linear trend was performed if the odds ratios showed a reasonably linear pattern across categorical variables. Attendance was defined as a participant completing the diabetic eye screening process. Independent variables considered were age, sex,

ethnicity, IMD, type and duration of diabetes, VA, years of registration into the NELDESP, distance to screening centre, and PTAL.

Continuous variables were categorised for the analysis to allow for non-linear patterns in attendance. The PTAL was divided into tertiles, with the 1st tertile having the worst PTAL (0, 1a, 1b) and 3rd tertile the best (5, 6a, 6b). Ethnicity was categorised as white (white British, Irish, any other white background), mixed (white and black Caribbean, white and black African, white Asian, any other mixed background), black (African, Caribbean, any other black background), South Asian (Indian, Pakistani, Bangladeshi), Chinese, any other Asian background, and any other ethnic group. Missing data points were categorised as "Unknown" group within each independent variable.

The reference category for ethnicity was the white ethnic group, for IMD the most deprived quintile (1st), and for PTAL the best tertile (3rd). For the rest of the independent variables, the group with the highest number of observations was considered the reference.

2.4 Ethnic disparities in progression rates of sight-threatening diabetic retinopathy in diabetic eye screening

2.4.1 Design

The data source is described in 2.3.1. Ethical approval details for this and Section 2.5 is described in detail in Section 2.1.

2.4.2 Data extraction

This data source is described in Section 0.1.1. The data set comprises all people with diabetes registered in the NELDESP who were offered screening appointments from 03/01/2012 to 31/12/2021. The NELDESP data manager identified the cohort, and conducted a pseudonymised data extraction into two comma separated

values (csv) files. A data base was created and stored in a trusted research environment (TRE) for analysis.

2.4.3 Trusted Research Environment

A designated Trusted Research Environment (TRE) was specified and set up within the secure network of Homerton Healthcare to host the hardware and software necessary for data storage and analysis. The required approvals for TRE creation, in accordance with the Data Sharing Framework in North East London, were obtained. A Data Protection Impact Assessment (DPIA) form was submitted and approved by the NHS North East London Information Governance Steering Group (IGSG) and the Data Access Group.[108] Access to the TRE is restricted to approved researchers with Homerton Healthcare contracts. Data transfers to and from the TRE is restricted to the data manager (Ryan Chambers), with all transfers requiring approval from the data guardian (Dr John Anderson).

2.4.4 Exclusion criteria

For the purpose of this analysis, I included data from people with non-STDR at baseline,* and with at least two complete screening visits (Figure 2.2).

2.4.5 Variables

Routinely collected data from NELDESP appointments included age at baseline (categorised as <45, 45 to <55, 55 to <65, and 65 years and older), sex, self-defined ethnicity (coded as per ONS standards as: white, black, south Asian, Chinese, any other Asian, mixed, other, and unknown categories for the purpose of these analyses),[109] type of diabetes (Type 2, Type 1, other, and unknown), self-defined duration of diabetes, baseline DR severity (coded as per Klein et al.[110]; DR absent in both eyes [R0M0], non-STDR [R1M0] in one eye only, and non-STDR [R1M0] in both eyes), and IMD. Index of Multiple Deprivation scores were split

*Baseline was defined as the first recorded screen during the study period

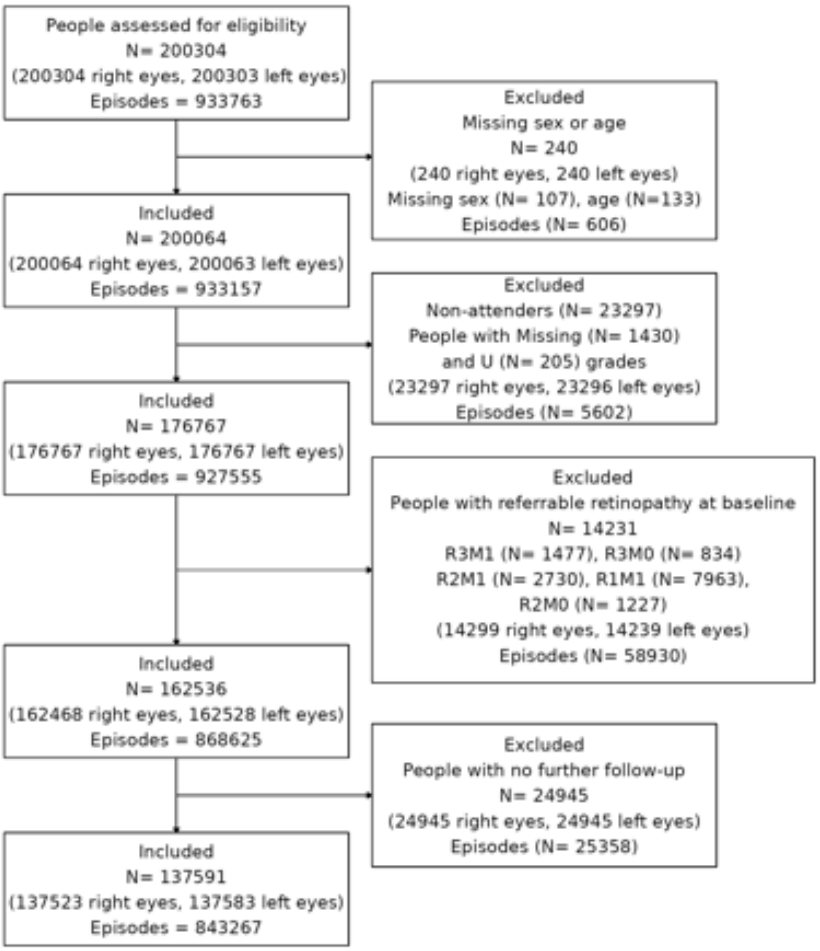

Figure 2.2: Diagram of exclusions.

into quintiles (where 1st and 5th are the most and least deprived, respectively. See section 2.2.5).[16]

2.4.6 Statistical analysis

All analyses were undertaken with R (version 4.2.2).[99] The survival[111] and icenReg[112] packages were used for survival analyses. The primary health outcome was progression to STDR (NSC-UK grades R2, R3, and/or M1). I calculated incidence rates (IRs) for any DR and STDR. The NELDESP data is an example of panel data where, due to the intervals of the screening episodes, the date of diagnosis does not necessarily correspond to the date of change in retinopathy status. However, given

a median (IQR) of 1.0 (0.9-1.1) years between appointments in the NELDESP, and since differences between models for interval and right censored data are expected to be small in studies where individuals attend at regular intervals,[111] I undertook analyses using Cox proportional hazards (PH) model for right censored data to describe hazard ratios (HR) for STDR adjusting for age, sex, baseline DR, ethnicity, duration and type of diabetes, and IMD. Results from survival analysis for interval censored data are available as supplements in the appendix. The proportionality assumption was assessed by graphical inspection of Schoenfeld residuals. As secondary analysis, I explored the associations for development of any DR in people with no DR at baseline with Cox regression.

Fully parametric accelerated failure time PH, and proportional odds models with different baseline distributions (Weibull, log-logistic, exponential, log-normal, and gamma) for interval censored data were fitted to obtain survival probabilities for STDR for people with different baseline characteristics. Parametric assumptions were tested graphically. The model with best fit defined by Akaike Information Criterion (AIC) was the proportional odds model with baseline Weibull distribution. This model was used to create an online calculator to provide 10-year survival probabilities of individuals with different combinations of baseline characteristics (Click here to access).

As part of sensitivity analyses, I allowed for possible cumulative differences in duration of diabetes for people with baseline visits on the first two calendar years of our cohort by calculating IRs of STDR in the 2014-2021 cohort.

Since the implications of implementing biennial diabetic eye screening in populations with sociodemographic diversity remain unknown. I explored the potential impact of extending annual screening intervals to every 2 years, by modelling the follow-up of people with two consecutive R0M0 (no DR) outcome grade visits in a virtual biennial screening system using observed data. Fourteen-month time breaks were used to mirror the annual cycle uptake observed in this cohort. The number of STDR occurring between biennial screening intervals was quantified. People who developed grades R1M0 were right censored.

2.5 Prediction of diabetes complications at point of diabetic eye screening, a streamlined approach to individualised preventive care

2.5.1 Design

This was a retrospective cohort study which used NELDESP data from 01/01/2012 to 31/12/2021. I conducted this work with the detailed approvals in 2.1. The main outcome measures were prediction of:

i) STDR and

ii) all-cause mortality.

2.5.2 Electronic Health Record linkage to NELDESP data

There were a total of 176,767 people with diabetes and DR grades in the NELDESP data cohort (Section 2.4.4). Data from primary and secondary care were extracted for the cohort by the NHS Discovery Data Service, linking by NHS number. The linked data included GP prescription (SNOMED CT) and hospital episode statistics data (diagnoses, ICD-10; operations, OPCS-4), as well as GP diagnostic and investigations records for a curated subset of SNOMED CT codes in order to comply with General Data Protection Regulations (GDPR). For the the curated code list dataset, SNOMED CT codes that map to ICD-10 and OPCS-4, codes that form code lists published on the HDR UK Human Phenotype Library website (`https://phenotypes.healthdatagateway.org`, accessed 7th April 2023), Quality and Outcomes Framework codes (`https://digital.nhs.uk` accessed 7th April 2023), and a further set of manually curated diabetes-related codes were included. Mapping tables from SNOMED CT to ICD-10 and OPCS-4 were obtained from the SNOMED CT UK Monolith Edition, RF2: Snapshot Release 35.4.0, available from the NHS Technology Reference Data Update Distribution (TRUD) website (`https://isd.digital.nhs.uk/trud`). Read 2 and Read 3 codelists from the HDR UK Human Phenotype Library were mapped to SNOMED CT using mapping

tables from the NHS Data Migration Release 29.0.0, also available from the NHS TRUD website.

2.5.3 Baseline definition and characterisation

The baseline corresponded to the first completed recorded visit during the study period. In conjunction with a colleague (Alasdair Warwick), we manually curated codelists to identify diabetes-related comorbidities, physical, and biochemical measurements.

I identified a set of candidate predictor variables from known risk factors with senior supervision from Profs Rudnicka, Owen, Tufail, Egan, and Dr Anderson (Supplementary Tables E.1 and E.2). Comorbidities, smoking, and medication history were defined by the presence of any codes from their corresponding codelists in primary or secondary care records, with the earliest record date taken as the date of diagnosis or treatment initiation. Individuals were therefore deemed to have these comorbidities or medication types at baseline if the EHR-derived diagnosis or treatment commencement date was earlier than or equal to the date of their baseline (first) NELDESP screening episode.

I defined implausible outlier values and removed them from physical and biochemical measurements using range values observed in the UK Biobank datafields for body mass index (BMI),[113] glycated haemoglobin (HbA1c),[114] systolic blood pressure,[115] diastolic blood pressure,[116] cholesterol,[117] low density lipoprotein cholesterol (LDL-C),[118] high-density lipoprotein cholesterol (HDL-C),[119] and triglycerides.[120] Only the HbA1c upper limit differed and was set to 240 mmol/mol (24.1%) as values this high are rare in the NELDESP cohort (discussion with consultant physician, and NELDESP lead, Dr John Anderson). Measurements taken nearest to the initial NELDESP screening episode were utilised for analyses. Given HbA1c reflects average glycaemia over approximately three months,[121] when no HbA1c measurement was available prior to baseline, values up to 29 days after baseline were used. The closest body mass index (BMI), systolic and diastolic blood pressure, total cholesterol, triglycerides, HDL-C, and LDL-C values to baseline were included

under the same assumption (all recorded between -365 to +29 days from baseline). If values were recorded within the defined window both, before and after baseline date, the value before baseline was always used.

2.5.4 Missing data

Continuous variables with missing values greater than the missing rate of HbA1c were imputed to the mean values.[122]

2.5.5 Inclusion criteria

People identified from the NELDESP with available DR grades were identified (See Chapter 5, Figure 2.2) and people with linked EHR were included for all-cause mortality model development. People included in Chapter 5 with non-STDR at baseline (Figure 2.2) with linked EHR were included for STDR model development.

2.5.6 Statistical Analysis

Five-year risk prediction models for all-cause mortality and STDR were developed using Cox proportional hazards regression. To identify the most relevant predictors from the candidate variables, a backward elimination strategy was employed. For continuous variables that exhibited a non-linear relationship with all-cause mortality and STDR, we used multivariable fractional polynomials to ensure the model could flexibly capture these complex associations.

Performance and clinical utility assessment

Model performance was evaluated by assessing discrimination (how well the model separates predictions between those with and without the outcome of interest, in this case all-cause mortality and STDR), calibration (how well predicted risks agree with observed outcome frequencies), and clinical utility.[123]

A prediction model assessed in the same data set ("apparent validation") is usually optimistic, that is, it performs better than it would on new data. This phenomenon is known as optimism.[123] To obtain a more realistic estimate of model

performance in a real-world setting, I conducted an internal validation using bootstrapping with 150 replications. This technique allows us to quantify the degree of optimism and calculate optimism-adjusted performance metrics.[124]

Discrimination refers to the model's ability to correctly distinguish between individuals who will experience the event (e.g., mortality) and those who will not. We quantified discrimination using Harrell's C-statistic.[123,124] A C-statistic of 0.5 indicates the model is no better than chance, while a value of 1.0 signifies perfect discrimination. We report the optimism-adjusted C-statistic as our primary measure of discriminative ability.[123,124]

Calibration measures the agreement between the risks predicted by the model and the actual observed risks.[123,124] A well-calibrated model provides accurate risk estimates. We assessed calibration in two ways: i) The calibration slope, where a ratio (observed vs expected) close to 1 with a narrow confidence interval would suggest good calibration. In this context, when the calibration slope is less than 1, the low predicted risks are too low and high predicted risks are too high, whereas a slope larger than 1 indicates that low predicted risks are too high and high predicted risks are too low.[123] We report the optimism-adjusted (see above) calibration slope to provide a less biased assessment. And, ii) graphical calibration plots, which visually compare the predicted probabilities against the observed proportion of events at 5 years.

Overall model performance was further assessed using the Nagelkerke R^2 statistic to quantify the proportion of variation in the outcome explained by the model (an R^2 of 1 indicates the model explains all variability in the data, whereas an R^2 of 0 indicates that the model does not explain any of the variability). We also generated Kaplan-Meier plots stratified by quintiles of predicted risk and calculated the relative risk between the highest and lowest quintiles to illustrate the models ability to stratify individuals.[123–127]

Discrimination and calibration are statistical measures that are insufficient to decide if a model is actually useful in a clinical setting. That is, if using it to guide decisions (such as by targeting high-risk individuals for additional interventions)

would do more good than harm. This is known as clinical utility or clinical usefulness. We evaluated this using Decision Curve Analysis (DCA). DCA helps to determine the range of clinically meaningful risk thresholds (defined as the minimum probability of disease at which further intervention would be warranted) at which the model would be beneficial. It plots the "net benefit" of using the model to make clinical decisions against a range of these thresholds. Net benefit is a simple type of decision analysis, with benefits and harms put on the same scale so that they can be compared directly. This is expressed as, net benefit = sensitivity x prevalence - (1-specificity) x (1-prevalence) x w where w is the odds at the threshold probability (also known as risk preference). Net benefit differs from discrimination and calibration in that it incorporates the consequences of the decisions made on the basis of a model. A model demonstrates clinical utility if its net benefit is higher than the strategies of treating all patients or treating no patients across a range of clinically reasonable thresholds in DCA.[123,126,127]

I conducted statistical analyses using R (version.4.3.2).[99] The CodeMiner package was used for the curation of clinical code lists (Warwick et al. unpublished work), the survival,[111] rms,[128] and mfp[129] packages were used for survival analyses, and the dcurves package for decision curve analysis.[130] I followed Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines[131] and recommendations from the STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative for assessing performance and clinical usefulness in prediction models with survival outcomes.[123] As a sensitivity analysis, the internal validation process was repeated, restricting the dataset to the working-age population.

All-cause mortality

The cohort survival status was assessed by the NELDESP data manager (Ryan Chambers) from the ONS on 31/12/2023. People were censored: i) at their date

of death, ii) the date of their emigration from the UK, iii) or on 31/12/2023. Five-year Cox proportional hazard models for all-cause mortality were developed by sex due to physiological differences.[132]

We included 26 covariates selected on the basis of known or postulated relationships with the management of diabetes or incidence of diabetes complications. Interaction terms between age and duration were included along with interaction between duration and HbA1c values to represent long term load of HbA1c. The significance threshold for interaction terms was set to p-values <0.01.

Supplementary Table E.1 shows candidate predictors and the modelling strategies followed for the analysis. A base model using age and ethnicity was created and compared with models of increasing complexity using routinely collected DESP variables, as well as EHR-derived covariates.

Sight-threatening diabetic retinopathy

I followed the STDR definition from methods Section 2.3.1. I developed models for males and females combined. Supplementary Table E.2 shows the modelling strategies followed for STDR prediction.

Part III

Results

3

Visual impairment in patients with diabetes and diabetic retinopathy at hospital eye services

Contents

3.1 Abstract

Aims: To estimate the prevalence of visual impairment, compare it to certification of visual impairment (CVI), and examine sociodemographic associations with visual impairment in patients with diabetic retinopathy (DR).

Methods: Retrospective cohort study, which included 8,007 patients with DR

referred from the English diabetic eye screening programme (DESP) to a tertiary referral eye hospital. Main outcome measure was visual impairment, defined as vision in the best eye < 6/24. I conducted a multivariable logistic regression for visual impairment as primary outcome of interest, controlling for age, sex, type of diabetes, baseline DR grade, ethnicity, and index of multiple deprivation (IMD).

Results: Mean (SD) age was 64.5 (13.6) years, 61% of patients were men, and 31% of south Asian ethnicity. There were 68 patients with CVI during the study period, and 84% (272/325) of patients with visual impairment were not certified with visual impairment after a mean (SD) follow-up of 1.87 (±0.86) years. Older age, showed a positive association with visual impairment (OR per decade rise 1.88, 95% CI 1.70-2.08; p 1.8x10-34). Males had lower odds of visual impairment (OR 0.62, 95% CI 0.50-0.79, p 6.0x10-5), and less deprivation showed a graded inverse association with visual impairment (OR per index of multiple deprivation category increase 0.83, 95% CI 0.74-0.93, p for linear trend 0.002).

Conclusion: The majority of people with visual impairment are not registered at the point-of-care which could translate to underestimation of diabetes-related visual impairment, and all-cause visual impairment at a national level if replicated at other centres. Further work is needed to explore rates of visual impairment and uptake of registration.

3.2 Introduction

The number of blind people in the United Kingdom has been documented since 1851 (Figure 3.1).[133,134] Reports on causes of low vision in England and Wales began in 1950.[133–135] From the 1930's, the BD8 designated forms signed by an ophthalmologist were required to certify someone as blind or visually impaired.[29,136] The certification is voluntary and there is no statutory requirement for it to be offered. In November 2003, the BD8 form was replaced by the certificate of vision impairment (CVI).[95] In 2013, an eye health indicator was incorporated into the Public Health Outcomes Framework in England.[137] This resulted in annual reports

derived from CVIs, which are gathered and collated at The Certifications Office based at Moorfields Eye Hospital. The level of certification depends on the degree of visual impairment: sight impaired (SI – previously called partially sighted) and severe sight impaired (SSI – previously called blind). Certification of visual impairment does provide benefits to the patients including tax and public transport (SSI level) benefits, as well as increased access to low vision support.

Diabetic retinopathy (DR) remains the leading cause of incident sight impairment and blindness in the working age population in many countries.[29,138,139] However, as introduced in Section 1.2.3, DR is no longer considered the leading cause of CVI in England and Wales.[15,29] Patients are referred to hospital eye services (HES) when certain severity level based on retinal features is present on retinal photographs.[140]

The aim of this work was to comprehensively analyse the prevalence of visual impairment by visual acuity (VA) eligibility criteria in patients with DR attending a tertiary referral eye hospital. Secondary aims were to analyse the rate of CVI, and to identify demographic and ocular factors associated with visual impairment.

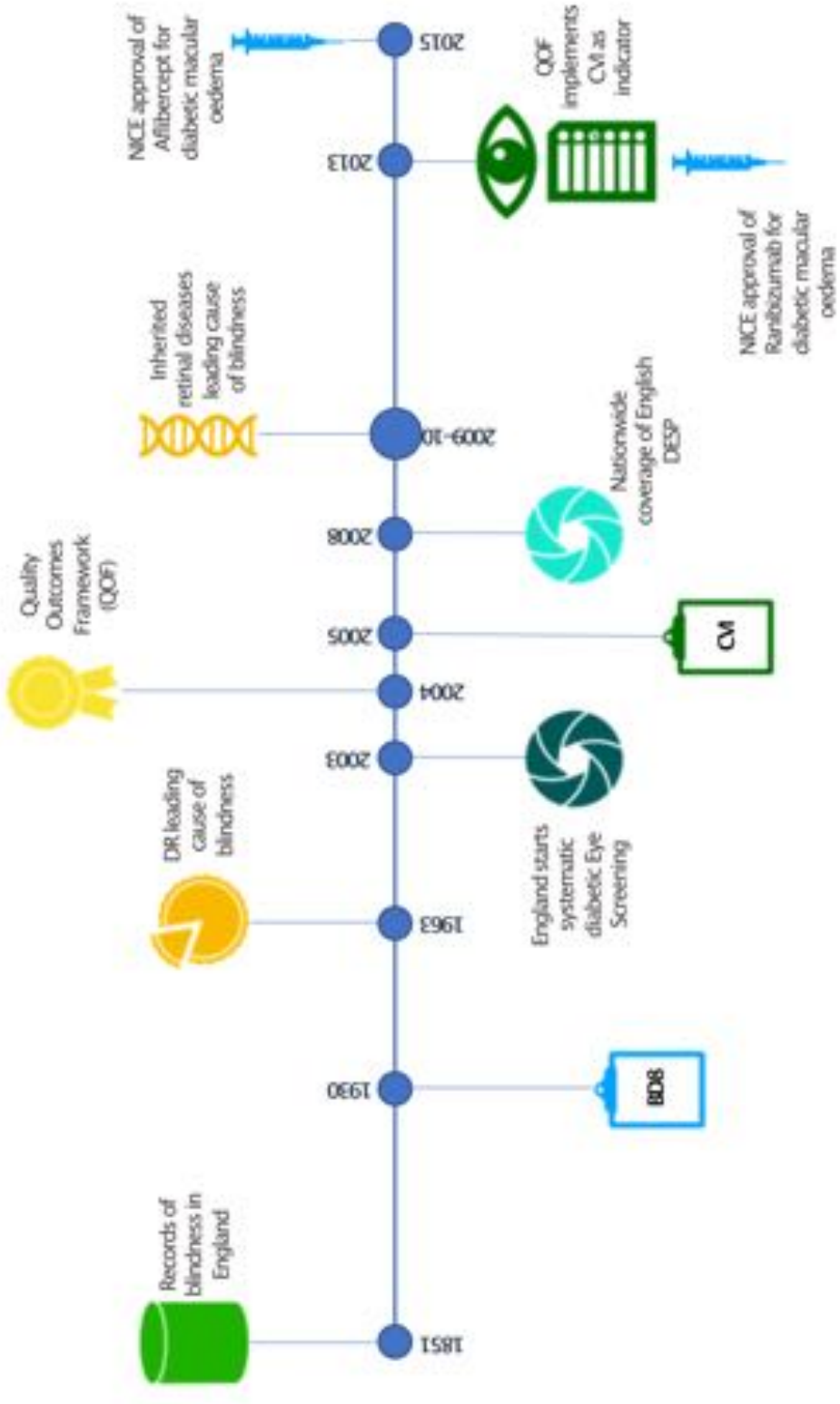

Figure 3.1: Timeline of the record of blindness in the UK and events with implications for diabetic retinopathy.

3.3 Methods

The methods are described in Chapter 2.2, and further details on the data source can be found in Section 0.1.2.

3.4 Results

A total of 8,007 patients (4,859/8,007; 61% male) were included for analysis (Figure 2.1). Table 3.1 shows the patient cohort characteristics. A total of 68 patients were certified visual impairment during the study period (9 CVI per 1000 patients) and 38/68 (49%) had DR recorded as the primary cause of visual impairment (Supplementary Table B.1). Median (interquartile range) final VA in logMAR was 0.00 (0.00 – 0.20) for non-visual-impairment-eligible patients, and 0.80 (0.60 – 1.00) for eligible patients (Snellen equivalent values of 6/6 (6/6 – 6/9.5) and 6/38 (6/24 – 6/60), respectively). Mean follow-up was 1.9 years (SD 0.9, interquartile range 1.1–2.6). There were no statistically significant differences in follow-up of certified patients (years to certification) vs. patients with visual impairment (years followed-up with visual impairment) and no CVI (mean follow-up of 1.6 [95% CI 1.4–1.8] vs 1.7 [95% CI 1.6–1.8], respectively).

Table 3.1: Patients eligible for Certification of Visual Impairment and actual patients certified at baseline and end of follow-up.

	Baseline			Final visit		
Characteristic	**Overall, N = 8,007**	**Not CVI eligibile**	**CVI eligible**	**Overall, N = 8,007**	**Not CVI eligibile**	**CVI eligible**
CVI						
Certified	4 (0.05%)	1 (0.01%)	3 (1.09%)	68 (0.85%)	15 (0.20%)	53 (16.31%)
Not certified	8,003 (99.95%)	7,731 (99.99%)	272 (98.91%)	7,939 (99.15%)	7,667 (99.80%)	272 (83.69%)
Total						
n (%)	8,007 (100.00%)	7,732 (100.00%)	275 (100.00%)	8,007 (100.00%)	7,682 (100.00%)	325 (100.00%)

Count (column %) presented.

Grey cells represent the number of visually impaired patients without certification of visual impairment.

CVI; Certification of visual impairment.

3. Visual impairment in patients with diabetes and diabetic retinopathy at hospital eye services

Excluded patients (Table B.2) were older than those included in the cohort (mean age 65.9 years [95% CI 65.5 – 66.3] vs 64.5 years [95% CI 64.2 – 64.8], respectively) and had worse mean logMAR baseline VA (0.17; 95% CI 0.16 – 0.18) than included patients (0.10; 95% 0.10 – 0.11). From the excluded patients 369/5,350 (6.9%) had visual impairment, 267/5,350 (5.0%) died within the study period, and none of the patients who died were eligible for visual impairment at their baseline HES visit. Among the 5% that died, median (IQR) time to death from the first visit was 1.20 (0.5-1.8) years.

The prevalence of visual impairment at the final visit was 4.3% (325/8,007). Eighty four percent (272/325) of patients with visual impairment were not certified by the last visit (Table 3.1), namely 34 cases with visual impairment not certified per 1000 patients with diabetic retinopathy at HES. A total of 165/8,007 (2.1%) patients had visual impairment at baseline and remained visually impaired by end of follow-up. The incidence rate of visual impairment was 10.9 per 1,000 person-years (160 new visual impairment cases during study period). Figure 3.2 shows groups of patient VA trajectories from baseline to last visit by visual impairment and certification status for the subset of individuals who had visual impairment at any stage during the length of the study (n= 460). A total of 1,260/8,007 (15.7%) patients received any form of DR-related treatment during the study period (Table B.3), however, patients could have received treatment for DR before the study period, and treatment record before the baseline appointment was not available for analysis. In patients with more than 1 year of follow-up (n=6,394, median [IQR] follow-up 2.2 [1.6-2.7] years), 83% (214/258) of patients with visual impairment were not certified by the last visit. In the subset of working age population patients (n=3,952, median [IQR] follow-up 1.8 [1.1-2.5] years), 74% (51/69) of patients with visual impairment were not certified by the last visit.

Table 3.2 shows the results of multivariable logistic regression model with visual impairment as the primary health outcome of interest. Every decade increase in age was associated with 88% greater odds of having visual impairment (p 1.8x10-34). Males showed a 38% reduction in odds of visual impairment when compared

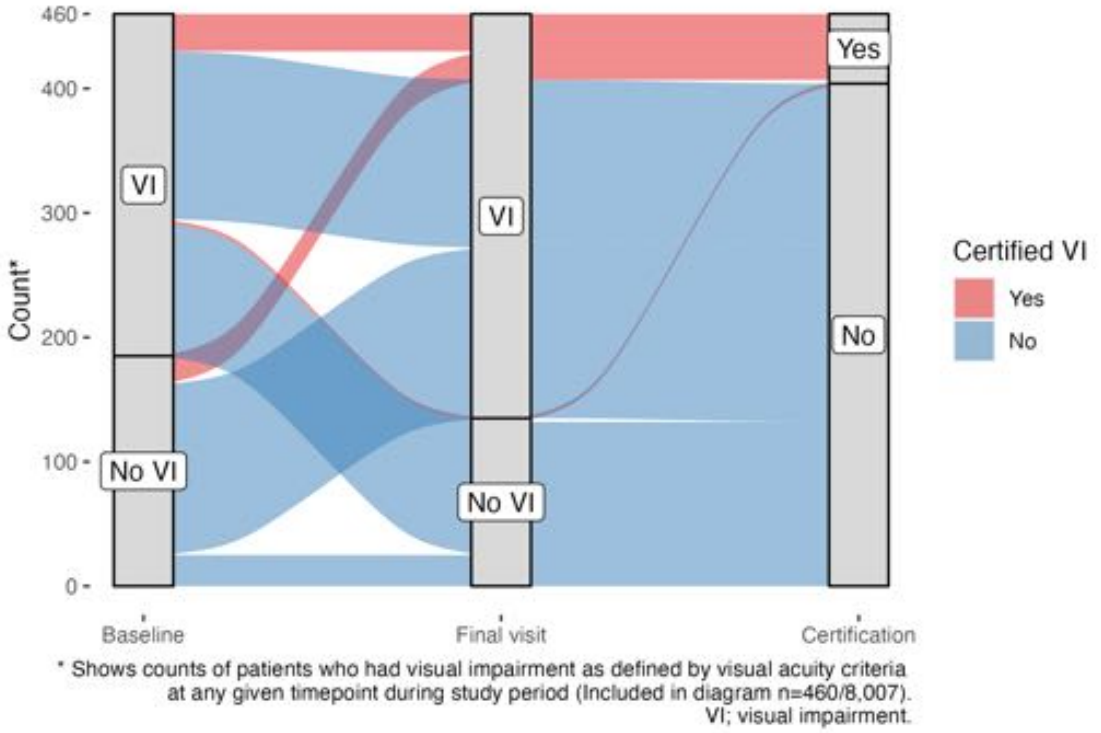

Figure 3.2: Sankey diagram of changes in visual impairment eligibility defined by visual acuity from baseline to final visit of patients who had visual impairment at any given timepoint. The horizontal axis defines two time points (baseline and final visit), and a binary outcome if the patient was certified or not. Vertical columns define visual impairment status.

with females (p 6.0x10-5). The majority of visual impairment and CVI was in older adult patients (Table B.4). In the working age band, males had 59.4% (41/69) and 52.2% (12/23) of visual impairment and CVI, respectively. This was reversed from 65 years and older with females having 57.4% (147/256) and 57.8% (26/45) of visual impairment and CVI, respectively. When compared with patients in the highest quintile of deprivation, the least deprived participants had a 42% reduction in the odds of visual impairment, and every unit increase in IMD category was associated with a 17% reduction in odds of visual impairment (p for linear trend 0.002, Table 3.2). Having STDR at baseline was associated with a 2.20 greater odds of having visual impairment when compared with patients with non-STDR. There were no associations with ethnicity between the main ethnic groups (Black, south Asian) when compared with people self-described as white. The other ethnic group showed

significant associations with visual impairment, however, due to the heterogeneity of this category, meaningful conclusions cannot be drawn. Type of diabetes did not show associations with visual impairment. Formal tests for interaction between sex, age, type of diabetes, baseline DR grade, ethnicity, and IMD were not significant and showed that patterns were consistent across sex. A sub analysis exploring CVI as outcome of interest (n= 69) among patients with visual impairment (n= 325) controlling for the same covariates as our primary logistic regression model showed no significant associations. I additionally assessed whether DR-related visual impairment treatment during the study period impacted on odds of CVI in multivariable logistic regression and found no significant associations (OR and associations with the other covariates remained stable).

Table 3.2: Patient characteristics and adjusted odds ratios for visual impairment.

	Visual impairment			**Multivariable logistic regression**
Characteristic	**Overall, N = 8,007**	**No, N = 7,682**	**Yes, N = 325**	**OR (95% CI); p-value**
Per decade increase in age	64.5 (13.6)	64.1 (13.4)	74.1 (12.7)	1.88 (1.70, 2.08); 1.8e-34
Age categories				
20 to 49	1,025 (13%)	1,013 (13%)	12 (3.7%)	1.00
50 to 64	2,927 (37%)	2,870 (37%)	57 (18%)	1.54 (0.83, 3.10); 0.199
65 to 79	2,873 (36%)	2,749 (36%)	124 (38%)	3.42 (1.89, 6.79); 1.4e-04
>= 80	1,182 (15%)	1,050 (14%)	132 (41%)	9.81 (5.41, 19.5); 2.2e-12
Sex				
Female	3,148 (39%)	2,973 (39%)	175 (54%)	1.00
Male	4,859 (61%)	4,709 (61%)	150 (46%)	0.62 (0.50, 0.79); 6.0e-05
Type of diabetes				

Number and column percentage (%) for categorical variables. Mean (SD) for continuous variables.

Mutually adjusted odds ratios (OR) for all variables shown in table (OR >1 imply greater odds of visual impairment).

DM; diabetes mellitus, DR; diabetic retinopathy, STDR; Sight-threatening diabetic retinopathy,

IMD; index of multiple deprivation.

Table 3.2: Patient characteristics and adjusted odds ratios for visual impairment.

	Visual impairment			**Multivariable logistic regression**
Characteristic	**Overall, N = 8,007**	**No, N = 7,682**	**Yes, N = 325**	**OR (95% CI); p-value**
Type 2 DM	5,821 (73%)	5,565 (72%)	256 (79%)	1.00
Type 1 DM	544 (6.8%)	537 (7.0%)	7 (2.2%)	0.61 (0.25, 1.28); 0.229
Missing	1,642 (21%)	1,580 (21%)	62 (19%)	0.86 (0.64, 1.14); 0.308
Baseline DR grade				
Non-STDR	2,411 (30%)	2,345 (31%)	66 (20%)	1.00
STDR	5,596 (70%)	5,337 (69%)	259 (80%)	2.20 (1.67, 2.93); 4.2e-08
Ethnicity				
White British	1,611 (20%)	1,533 (20%)	78 (24%)	1.00
South Asian	2,472 (31%)	2,362 (31%)	110 (34%)	0.83 (0.61, 1.14); 0.244
Black	1,360 (17%)	1,296 (17%)	64 (20%)	0.78 (0.55, 1.11); 0.170
Other	2,422 (30%)	2,353 (31%)	69 (21%)	0.60 (0.42, 0.84); 0.003
Missing	142 (1.8%)	138 (1.8%)	4 (1.2%)	0.74 (0.22, 1.86); 0.576
IMD				
1 (Most deprived)	1,574 (20%)	1,484 (19%)	90 (28%)	1.00
2	2,886 (36%)	2,779 (36%)	107 (33%)	0.63 (0.47, 0.85); 0.002
3	1,879 (23%)	1,813 (24%)	66 (20%)	0.57 (0.40, 0.79); 9.5e-04
4 (Least deprived)	1,668 (21%)	1,606 (21%)	62 (19%)	0.58 (0.41, 0.82); 0.002
Per IMD unit increase	2.5 (1.0)	2.5 (1.0)	2.3 (1.1)	0.83 (0.74, 0.93); 0.002

Number and column percentage (%) for categorical variables. Mean (SD) for continuous variables.

Mutually adjusted odds ratios (OR) for all variables shown in table (OR >1 imply greater odds of visual impairment).

DM; diabetes mellitus, DR; diabetic retinopathy, STDR; Sight-threatening diabetic retinopathy,

IMD; index of multiple deprivation.

3.5 Discussion

This analysis reports a marked under registration of visually impaired patients with DR at the largest referral centre for ophthalmic diseases in England. Between 2016 and 2019, 84% of the study cohort, and 74% of working age patients with visual impairment who were eligible for certification were not certified visually impaired. For visual impairment, sex differences were present, with males having lower odds than females for visual impairment, however, there were no sex differences in odds of certification. Decreasing levels of deprivation were associated with lower odds of visual impairment. There were no associations with ethnicity between the major ethnic groups. Our findings suggest a remarkable under representation of visual impairment in patients with DR when using the CVI as index of blindness.

3.5.1 Under-registration of visual impairment

Certification of visual impairment data represents a useful epidemiological resource for visual impairment analysis in the UK, but has limitations due to uptake. Since at least 2010, there has been a reduction in CVI due to DR in England and Wales.[29,139] This contrasts with findings from global studies in which the rate of diabetes-related visual impairment has increased, and accounts for a larger proportion of blindness/visual impairment.[135,141] Registration of visual impairment in England is voluntary and must be initiated by a consultant ophthalmologist.[95] In this context, it has been estimated that up to 53% of eligible patients might not be certified blind despite consultation at HES.[142,143] The current findings demonstrate that, at point of care, this difference is even greater, with an 84% under-registration. Derived from this study, we could expect a total of 11 new cases of visual impairment per 1000 patients with DR at HES per year. Attention must be drawn to the fact that Moorfields Eye Hospital medical retina clinics are led by at least one consultant ophthalmologist, and Eye Clinic Liaison Officers are readily available to inform and assist patients who wish to be certified, thus the under-registration might be even greater in other HES settings. There is a

delay from visual impairment onset to certification, and it has been argued that the majority of eligible patients will be certified with longer follow-up or increase in clinic visits.[142,144] I have demonstrated that there were no differences in length of follow-up of unregistered eligible patients vs registered patients in this study cohort (p=0.4). Furthermore, I have shown that after exclusion of cases with less than 1 year of follow-up, in consultant ophthalmologist-led medical retina clinics, the rate of under-registration remained remarkably high at 83%. To our knowledge, there are no formal point of care studies available that assess visual impairment among patients with DR. Considering the increasing population prevalence of diabetes, and the well-established English DESP,[15,74] our results suggest that the visual impairment prevalence among patients with DR is underrepresented in CVI derived analyses, and that further studies are necessary to obtain better visual impairment estimates and to understand factors related to registration uptake.

3.5.2 Sex and age

A recent study assessing the rates of visual impairment impairment in Austria found an overall higher visual impairment incidence in females than in males (32.2 vs 17.7 per 100,000 person-years).[145] In this analysis, 53.8% (175/325) of overall visual impairment was present in females, but males showed greater rates of visual impairment in the working age population (See Table B.4). These findings align with previous reports[142,145] and warrant further investigation. In our multivariable logistic regression models, males showed a 38% decrease in odds of visual impairment (p 6.0x10-5) when compared with females. There were no statistically significant differences in age between males and females (for males, mean 63.5, 95% CI 61.8-65.3; for females, mean 66.1, 95% CI 63.8-68.4).

In this patient cohort with DR, older patients showed greater odds for visual impairment. Recent advances in diabetes treatment, DR treatment, and improvement in therapeutic goals, have allowed people with diabetes to experience increased life expectancies.[146] A phenomenon which translates into longer duration of disease, longer exposure to hyperglycaemia, higher burden for microvascular

disease, higher incidence of non-diabetic ocular comorbidities, and regular contact with health services.[146] Considered the standard of care for diabetic macular oedema (DMO), ranibizumab and aflibercept intravitreal anti-vascular endothelial growth factor (VEGF) injections were approved for use in the UK in 2013 and 2015, respectively.[147,148] Fixed and frequent dosing regimens have shown good VA outcomes with an average of 4.4 to 10.5 ETDRS letter score gain.[149,150] At point of care, fixed treatment regimens are burdensome for patients and clinics, thus as needed (*pro re nata*) or treat and extend protocols are implemented with comparable outcomes. Despite reduction in the number of intravitreal injections with these regimens, a recent multicentre study evidenced that the mean number of clinic visits for DMO patients was 14.2 during the first year, and 13.2 during year 2 of follow-up.[151] A recent qualitative study assessing the CVI process found that consultants found it difficult to ascertain when it is appropriate to certify patients with long-term diseases,[152] stressing the fact that despite repeated visits to eye hospital services, visual impairment remains under-registered. In the context of patients with diabetes and no other age-related ocular comorbidities (such as, cataract or age-related macular degeneration), interactions between the above-mentioned factors with the psychological impact of certifying a disability,[152] along with hope of VA improvement from patient and/or clinician perspectives, and the nature of injection services focused on treatment delivery, rather than counselling and administrative activities like CVI, might explain the associations with visual impairment in older individuals.

3.5.3 Deprivation

Socioeconomic deprivation has been associated with attendance at diabetic eye screening (DES).[153–158] People from more deprived areas are less likely to attend DES appointments,[153,159,160] which is further associated with presentation to DES or HES with late STDR.[15,161] In the context of the universal health coverage provided by the National Health Service in the UK, where access to services are limited by service capacity rather than by the economic circumstances of the

patient, our findings provide further evidence of nuanced health inequalities and their repercussion on VA outcomes.

3.5.4 Strengths and limitations

The strengths of this analysis are as follows. I have analysed point of care data of patients with DR of the largest eye referral centre in the UK. I have included a clear definition of visual impairment based on VA following UK CVI guidance[95] and included cases with at least 6 months of follow-up to account for VA variation and to allow both patients and clinicians time to perform the certification. I have utilised a rich data set that includes both demographic and ocular variables.

The limitations of this study are that despite the large catchment area, the results are from a single centre and might not extrapolate to other settings. I have not verified the causes of visual impairment, often multiple in people with DR, but used the information recorded on the CVI form, which requires the ophthalmologist to specify causes of vision loss. Given the duration of follow-up, I have allowed sufficient time for cataract surgery to have occurred in our cohort and I have further excluded cases with ungradable DR severity. Certification data are not shared between HES, and it is possible that patients could have been registered elsewhere, hence not recorded with the data collection method. Given evidence from larger CVI studies, it is unlikely that this could have an appreciably impact on these findings. Data on systemic risk factors was not available, hence I could not examine any associations between systemic risks markers and risk of visual impairment. Nevertheless, it is expected that the data does represent the presence of visual impairment in people with DR regardless of cause. I did not account for visual field criteria for visual impairment definition, which could have included more visual impairment cases. Further work at a national level in both diabetic eye screening and HES to assess prevalence of visual impairment as well as CVI is needed to confirm these findings. More importantly, people who are sight impaired and not certified may not be receiving the specific advice, support, and recognition required to prevent adverse economic, social, and health outcomes. Alternatively,

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CVI may not be providing the kind of support that sight impaired people need or may be viewed negatively by those who are currently employed or unwilling to access support due to perceptions about independence. Improved understanding of the reasons for low rates of CVI would help address the inequalities identified.

3.5.5 Conclusion

These findings suggest that visual impairment can be underrepresented by over 80% when relying solely on CVI data. This raises critical concerns, including the potential lack of support for unregistered patients and missed opportunities to optimise resource allocation for the leading causes of blindness. The results underscore the urgent need to strengthen secondary prevention measures to delay or prevent STDR and to improve awareness of CVI registration and its benefits among patients and healthcare providers.

"In Aldous Huxley's dystopia, Brave New World, there were five castes. The Alphas and Betas were allowed to develop normally. The Gammas, Deltas, and Epsilons were treated with chemicals to arrest their development intellectually and physically, progressively more affected from Gamma to Epsilon. The result: a neatly stratified society with intellectual function, and physical development, correlated with caste.
This was a satire, wasn't it?…"

— From Sir Michael Marmot's *The health gap: the challenge of an unequal world* (*Lancet*; 2015).

4

Sociodemographic determinants of attendance to diabetic eye screening

Contents

4.1 Abstract

Aims: To determine the association of sociodemographic characteristics and other related factors on attendance at diabetic eye screening (DES) in a large ethnically diverse urban population.

Methods: Retrospective cohort study. Screening visits in the North East London Diabetic Eye Screening Programme (NELDESP). A total of 84,449 people with diabetes aged 12 years or older registered in the NELDESP and scheduled for screening between 1st April 2017 to 31st March 2018. Main outcome measure was attendance at DES appointments.

Results: The mean (standard deviation) age was 60 (14.2) years, 53.4% were male, 41% South Asian, 29% white and 17% Black; 83.4% attended screening. People self-described as Black had similar levels of attendance compared with white individuals. However, South Asian, Chinese and any other Asian background ethnicities showed greater odds of attendance compared with white. When compared with their respective reference group, high levels of deprivation, younger age, longer duration of diabetes, worse visual acuity and longer distance to screening centre, were all associated with non-attendance. There were higher odds of attendance with every increase (improvement) in deprivation quintile (odds ratio [OR], 1.06; 95% CI, 1.03-1.08), with increasing age (OR per decade, 1.17; 95% CI, 1.15-1.19), with better visual acuity (OR per 5 letters 1.12, 95% CI 1.11-1.14) and with longer time of NELDESP registration (OR per year, 1.02; 95% CI 1.01-1.03).

Conclusion: Ethnic differences in DES uptake are evident, but despite preconceptions, a higher likelihood of screening attendance was observed amongst people of asian ethnicities compared with people self-described as white. Poorer socioeconomic profile was associated with higher likelihood of non-attendance for screening. Further work is needed to understand how to target individuals at risk of non-attendance and reduce inequalities.

4.2 Introduction

Non-attendance to annual diabetic eye screening (DES) appointments has been associated with late presentation of sight-threatening diabetic retinopathy (STDR).[161,162] In accordance with the National Health Service (NHS) Diabetic Eye Screening Programme (DESP) standards, screening of 85% of the people living with diabetes is considered achievable. However, uptake data from 2016-2017 showed that this goal was not met in 75% of London's Clinical Commissioning Groups (CCGs) areas.[163,164] Regional differences in screening delivery and uptake may explain regional variation in diabetic eye disease.[6]

Inequalities in health tend to be present in urban areas with contrasting sociodemographic conditions. London, a metropolis where people from the extremes of the deprivation indices live side-by-side, is a remarkable example of how these inequalities can result in different uptake rates across and within boroughs.[165–167] Health inequalities can create significant attendance variation amongst subgroups, and are of concern to any screening programme. Sociodemographic factors such as, age,[153–156,159,168–170] sex,[160,170,171] ethnicity,[153,159,160] transportation,[172] and socioeconomic deprivation[153–160,170] have all been associated with non-attendance.

The North East London population is sociodemographically diverse, with a wide variation in ethnicities and a varied health profile with higher than average level of deprivation and a lower than average life expectancy.[16,101] The North East London DESP (NELDESP) aims to invite 98% of people with diabetes to attend a screening appointment, and expects to achieve an uptake 85%. I have examined attendance at DES to identify sociodemographic determinants of attendance in a large multi-ethnic population with high levels of deprivation (Data source 0.1.1).

4.3 Methods

The methods are described in Chapter 2.3, and further details on the data source can be found in Section 0.1.1.

4.4 Results

A total of 84,449 people were invited for a screening appointment during the study period. Mean age was 60 years (standard deviation 14.2 yrs), 53.4% were male, and 93.7% of those invited for screening had type 2 diabetes. The majority were of South Asian ethnicity (41.2%), followed by white (29%) and Black ethnic groups (17%). A total of 74.7% of the participants lived in areas with the highest levels of deprivation (1st and 2nd index of multiple deprivation (IMD) quintiles). Overall, screening attendance during the study period was 83.4%.

Table 4.1 summarises sociodemographic characteristics of the study cohort. Table 4.2 shows mutually adjusted odds ratios (OR) from our multivariable logistic regression model (Crude ORs are provided in Table C.1, for comparison). I report adjusted ORs from the multivariable model unless otherwise stated.

People aged 12 to 45 years of age showed poorer attendance when compared with the reference 46 to 60-year-old group. In adjusted analyses, participants 18 to 30 years of age were least likely to attend for screening showing a 58% reduction in the odds of attendance, and an absolute uptake difference of 18.8% when compared with the reference. Each decade rise in age increased the odds of attendance by about 17% (OR= 1.17; 95%CI 1.15-1.19, p-value < 0.001).

Table 4.1: Sociodemographic characteristics stratified by attendance to diabetic eye screening.

Characteristic	**Overall, N = 84,449**	**Attended, N = 70,405**	**Did not attend, N = 14,044**
Age	60 (14)	60 (14)	58 (16)
Age categories			
12-17 years	350 (100%)	276 (79%)	74 (21%)

N = number (row %) for categorical variables.

Mean and standard deviation (SD) for continuous variables.

MODY; maturity onset diabetes of the young, PTAL; Public transport accessibility level, IMD; index of multiple deprivation.

†Groups with uptake below the national diabetic eye screening programme goal of 75%.

Table 4.1: Sociodemographic characteristics stratified by attendance to diabetic eye screening.

Characteristic	**Overall, N = 84,449**	**Attended, N = 70,405**	**Did not attend, N = 14,044**
18-30 years†	1,546 (100%)	1,003 (65%)	543 (35%)
31-45 years	10,750 (100%)	8,296 (77%)	2,454 (23%)
46-60 years	30,808 (100%)	25,779 (84%)	5,029 (16%)
61-75 years	28,338 (100%)	24,482 (86%)	3,856 (14%)
76-90 years	12,039 (100%)	10,109 (84%)	1,930 (16%)
>90 years†	618 (100%)	460 (74%)	158 (26%)
Sex			
Male	45,127 (100%)	37,569 (83%)	7,558 (17%)
Female	39,322 (100%)	32,836 (84%)	6,486 (16%)
Type of diabetes			
Type 2	79,116 (100%)	67,265 (85%)	11,851 (15%)
Type 1	2,933 (100%)	2,223 (76%)	710 (24%)
MODY	49 (100%)	40 (82%)	9 (18%)
Not specified†	2,351 (100%)	877 (37%)	1,474 (63%)
Duration of diabetes (years)	9 (7)	9 (7)	9 (8)
Duration of diabetes categories			
0 to < 11 years	53,668 (100%)	44,890 (84%)	8,778 (16%)
11 to <20 years	23,563 (100%)	20,327 (86%)	3,236 (14%)
>20 years	6,034 (100%)	5,057 (84%)	977 (16%)
Missing†	1,184 (100%)	131 (11%)	1,053 (89%)
Visual acuity (ETDRS letters)	82 (9)	82 (8)	81 (11)
Visual acuity			

N = number (row %) for categorical variables.

Mean and standard deviation (SD) for continuous variables.

MODY; maturity onset diabetes of the young, PTAL; Public transport accessibility level, IMD; index of multiple deprivation.

†Groups with uptake below the national diabetic eye screening programme goal of 75%.

Table 4.1: Sociodemographic characteristics stratified by attendance to diabetic eye screening.

Characteristic	**Overall, N = 84,449**	**Attended, N = 70,405**	**Did not attend, N = 14,044**
6/6 to 6/9	58,193 (100%)	52,035 (89%)	6,158 (11%)
Better than 6/6	15,867 (100%)	14,069 (89%)	1,798 (11%)
Worse than 6/9 to 6/18	4,085 (100%)	3,459 (85%)	626 (15%)
Worse than 6/18	871 (100%)	683 (78%)	188 (22%)
Unknown†	5,433 (100%)	159 (2.9%)	5,274 (97%)
Years of registration	6.8 (3.9)	6.9 (3.9)	6.3 (3.9)
Years of registration categories			
0 to <5 years	35,631 (100%)	28,809 (81%)	6,822 (19%)
5 to <10 years	27,051 (100%)	22,948 (85%)	4,103 (15%)
10 to <15 years	21,314 (100%)	18,242 (86%)	3,072 (14%)
15 to 20 years	453 (100%)	406 (90%)	47 (10%)
Distance to screening centre	1.68 (1.61)	1.66 (1.59)	1.76 (1.72)
Distance to screening centre categories			
0 to 2km	66,188 (100%)	55,436 (84%)	10,752 (16%)
<2 to 5km	15,653 (100%)	12,895 (82%)	2,758 (18%)
>5 to 8km	1,298 (100%)	1,044 (80%)	254 (20%)
>8km	251 (100%)	190 (76%)	61 (24%)
Unknown	1,059 (100%)	840 (79%)	219 (21%)
PTAL tertiles			
3rd (Best)	12,628 (100%)	10,589 (84%)	2,039 (16%)
1st (Worst)	27,995 (100%)	23,281 (83%)	4,714 (17%)

N = number (row %) for categorical variables.

Mean and standard deviation (SD) for continuous variables.

MODY; maturity onset diabetes of the young, PTAL; Public transport accessibility level, IMD; index of multiple deprivation.

†Groups with uptake below the national diabetic eye screening programme goal of 75%.

Table 4.1: Sociodemographic characteristics stratified by attendance to diabetic eye screening.

Characteristic	**Overall, N = 84,449**	**Attended, N = 70,405**	**Did not attend, N = 14,044**
2nd	43,826 (100%)	36,535 (83%)	7,291 (17%)
Ethnicity			
White British	24,475 (100%)	20,040 (82%)	4,435 (18%)
Mixed	1,087 (100%)	845 (78%)	242 (22%)
Black	14,323 (100%)	11,869 (83%)	2,454 (17%)
South Asian	34,792 (100%)	29,708 (85%)	5,084 (15%)
Chinese	597 (100%)	536 (90%)	61 (10%)
Any other Asian background	5,323 (100%)	4,683 (88%)	640 (12%)
Any other Ethnic group	2,708 (100%)	2,248 (83%)	460 (17%)
Unknown†	1,144 (100%)	476 (42%)	668 (58%)
IMD quintiles			
1 (most deprived)	24,592 (100%)	20,136 (82%)	4,456 (18%)
2	38,522 (100%)	32,163 (83%)	6,359 (17%)
3	14,399 (100%)	12,196 (85%)	2,203 (15%)
4	5,235 (100%)	4,457 (85%)	778 (15%)
5 (least deprived)	1,701 (100%)	1,453 (85%)	248 (15%)

N = number (row %) for categorical variables.

Mean and standard deviation (SD) for continuous variables.

MODY; maturity onset diabetes of the young, PTAL; Public transport accessibility level, IMD; index of multiple deprivation.

†Groups with uptake below the national diabetic eye screening programme goal of 75%.

Compared with individuals self-described as white, people of mixed or Black

ethnicity did not show any difference in the odds of attendance after adjustment. However, odds of attendance were higher amongst individuals of Asian (South Asian, Chinese and Any other Asian background) ethnicities when compared with white individuals, even after adjustment.

Adjusted analyses showed that individuals living in the least deprived areas (5th IMD quintile) were most likely to attend for their screening appointments. Those in the 5th IMD quintile showed 25% greater odds of attendance compared with people living in the most deprived areas (1st IMD quintile). Each IMD quintile increase (i.e. less deprivation) suggested a 6% rise in the odds of attendance (linear trend test p-value < 0.001).

People with longer duration of diabetes were less likely to attend. The OR per 5-year increase in duration of diabetes was 0.97 (95%CI 0.95-1.00, p-value=0.019). The average distance to screening centre was 1.7 km (IQR 1–2km). Only people who lived 9km from the screening centre (outside the geographical boundaries of the CCGs) were formally more likely not to attend. Odds of attendance decreased by 1% for every km further from the screening centre, suggesting a trend (OR= 0.99; 95%CI 0.97-1.00, p-value=0.031).

Individuals with lower visual acuity (VA), specifically starting from VA worse than 6/9, showed a graded decline in the odds of attending the screening visit. Those with VA worse than 6/18 were least likely to attend and showed a 60% reduction in odds of attendance compared with those with acuity of 6/6 to 6/9. This equates to an absolute difference in attendance of 11 percentage points when compared with the reference group.

Attendance did not appear to differ by sex, type of diabetes, or Public Transport Accessibility Level (PTAL) score. People registered in the screening programme for more than 5 years were more likely to attend than those registered for less than 5 years. People with >15 years of registration showed almost twice the odds of attendance than people with <5 years of registration. The OR per year of registration was 1.02 (95%CI 1.01-1.03, p-value <0.001).

Table 4.2: Adjusted odds ratios (OR) for attendance vs non-attendance.

Characteristic	OR (95% CI)	p-value
Age categories		
46-60 years	1.00	
12-17 years	0.71 (0.52, 0.99)	**0.036**
18-30 years	0.42 (0.36, 0.49)	**1.5e-28**
31-45 years	0.71 (0.66, 0.76)	**2.8e-23**
61-75 years	1.28 (1.21, 1.35)	**4.3e-17**
76-90 years	1.2 (1.11, 1.29)	**3.6e-06**
>90 years	0.92 (0.73, 1.17)	0.487
Sex		
Male	1.00	
Female	0.99 (0.95, 1.04)	0.717
Type of diabetes		
Type 2	1.00	
Type 1	1.09 (0.96, 1.25)	0.190
MODY	0.85 (0.40, 2.07)	0.687
Not specified	0.46 (0.40, 0.53)	**9.4e-27**
Duration of diabetes		
0 to < 11 years	1.00	
11 to <20 years	0.99 (0.92, 1.06)	0.727
>20 years	0.87 (0.78, 0.97)	**0.011**
Missing	0.35 (0.26, 0.47)	**2.1e-12**
Visual acuity		

Mutually adjusted odds ratios (OR) for all variables shown in the table (OR > 1.00 mean greater odds of attendance).

CI; Confidence interval, MODY; maturity onset diabetes of the young, PTAL; public transport accesibility level,

IMD; index of multiple deprivation.

Bold p-values show statistically significant results.

Table 4.2: Adjusted odds ratios (OR) for attendance vs non-attendance.

Characteristic	OR (95% CI)	p-value
6/6 to 6/9	1.00	
Better than 6/6	1.08 (1.02, 1.15)	**0.007**
Worse than 6/9 to 6/18	0.6 (0.55, 0.66)	**5.8e-27**
Worse than 6/18	0.4 (0.34, 0.48)	**5.6e-26**
Years of registration		
0 to <5 years	1.00	
5 to <10 years	1.13 (1.07, 1.20)	**9.7e-06**
10 to <15 years	1.22 (1.12, 1.33)	**2.5e-06**
15 to 20 years	1.94 (1.35, 2.89)	**5.6e-04**
Distance to screening centre		
0 to 2km	1.00	
<2 to 5km	0.97 (0.91, 1.03)	0.301
>5 to 8km	0.9 (0.75, 1.09)	0.268
>8km	0.66 (0.46, 0.97)	**0.027**
Unknown	0.93 (0.77, 1.12)	0.433
PTAL tertiles		
3rd (Best)	1.00	
1st (Worst)	0.95 (0.89, 1.02)	0.189
2nd	0.97 (0.90, 1.03)	0.309
Ethnicity		
White British	1.00	
Mixed	0.9 (0.75, 1.09)	0.264

Mutually adjusted odds ratios (OR) for all variables shown in the table (OR > 1.00 mean greater odds of attendance).

CI; Confidence interval, MODY; maturity onset diabetes of the young, PTAL; public transport accesibility level,

IMD; index of multiple deprivation.

Bold p-values show statistically significant results.

Table 4.2: Adjusted odds ratios (OR) for attendance vs non-attendance.

Characteristic	OR (95% CI)	p-value
Black	1.02 (0.95, 1.09)	0.590
South Asian	1.16 (1.09, 1.23)	**6.4e-07**
Chinese	1.91 (1.39, 2.71)	**1.3e-04**
Any other Asian background	1.3 (1.17, 1.45)	**1.0e-06**
Any other Ethnic group	1.05 (0.92, 1.20)	0.453
Unknown	0.32 (0.27, 0.38)	**4.2e-41**
IMD quintiles		
1 (most deprived)	1.00	
2	1.09 (1.04, 1.15)	**7.3e-04**
3	1.17 (1.10, 1.26)	**5.9e-06**
4	1.15 (1.04, 1.27)	**0.009**
5 (least deprived)	1.25 (1.06, 1.50)	**0.012**

Mutually adjusted odds ratios (OR) for all variables shown in the table (OR > 1.00 mean greater odds of attendance).

CI; Confidence interval, MODY; maturity onset diabetes of the young, PTAL; public transport accesibility level,

IMD; index of multiple deprivation.

Bold p-values show statistically significant results.

4.5 Discussion

People with diabetes self-described as mixed or Black show very similar likelihoods of attendance at DES appointments when compared with white people, but indi-

viduals of Asian ethnic groups were more likely to attend than white people in this large, well organised, sociodemographically diverse urban DESP. This is the most current study with large scale data on ethnicity and diabetic eye screening. In addition, people with poorer VA, younger age and residing in areas with higher levels of deprivation were less likely to attend for DES appointments.

4.5.1 Ethnicity

Non-white ethnic groups have been reported to be more likely to develop diabetic retinopathy, more likely to present with sight-threatening retinopathy,[159,173,174] and less likely to attend for diabetic eye screening than people of white ethnicity.[153,159,160] Attendance rates for non-white ethnic groups in this analysis were all higher than white people, except for the small mixed ethnic group, which had a lower, though non-significant, rate of attendance (4.2% uptake difference). Chinese, South Asian and any other Asian background ethnicities were most likely to attend, more so than any other ethnic group. These findings suggest that the underlying increased rates of retinopathy and STDR reported in non-white ethnic groups[174,175] are not necessarily explained by non-attendance, raising the issue of increased susceptibility or poorer diabetes control. A study by Gulliford et al.[159] analysing sociodemographic inequalities in the South London DESP reported that African, Caribbean and other ethnic groups were more likely to attend for DES than white individuals. Notably, there was a higher proportion of missing ethnicity data in their data when compared with the current NELDESP cohort (~39% vs 1.4%, respectively).

4.5.2 Deprivation

Socioeconomic deprivation has consistently been associated with attendance, where those from more deprived areas are less likely to attend for DES appointments.[153–158] Although the overall average difference in attendance of 3.5% between most and least deprived areas found in this study is less than the 9.3% reported in earlier studies,[157] this is still greater than the 2% uptake difference found in a population from South London in 2010.[159] Results from this work provide further evidence

of the ingrained health inequalities present in a multi-ethnic study population with high levels of deprivation.

4.5.3 Duration of disease and visual acuity

Longer duration of diabetes and worsening VA showed an association with non-attendance compared with individuals with shorter disease duration and better VA. Previous reports have shown an association of longer duration of diabetes with non-attendance.[154,159] Given that duration of diabetes is one of the three major risk factors for DR,[6,30] and considering that >60% of people with type 2 diabetes and almost all people with type 1 diabetes will have diabetic retinopathy after 20 years duration of the disease,[30,31,56] the reduced odds of attendance observed in this group places them at increased risk of visual complications. There was no evidence available in the literature about the association of VA with attendance to DES at the time this chapter was written.

4.5.4 Distance to screening centre and public transport accessibility

In other areas of the UK, increased distance from screening clinic has been associated with an increased risk of non-attendance.[155,173] I have found that only individuals living 9 km from a screening centre were formally less likely to attend, but there was evidence of a trend in non-attendance with increasing distance. It is noteworthy that an 8 km radius from one of the NELDESP screening centre covers all of the geographic areas of the 6 CCGs, and it is possible that people living beyond 8km may have moved outside the CCG areas and not updated their GP. Interestingly, I found that the association of distance to screening centre with non-attendance is independent from PTALs in this inner-city population. This may be due to London having a well-developed public transport network and good transport-related access. These findings may not apply elsewhere, particularly to non-urban populations less served by public transport.

4.5.5 Age

In accordance with previous evidence,[153–156,159,162,176,177] young individuals from 12 to 45 years of age had lower odds of attendance compared with people age 46-60 years. Possible underpinning factors are over confidence about their health or demanding work schedules.[155,172] Nonetheless, within the context of diabetes chronicity and the need for regular contact with health care services, these individuals are at increased risk of complications through longer duration of disease and possible suboptimal metabolic control.[178,179]

4.5.6 Strengths and limitations

This study has several strengths. First, a large sample size with considerable proportions of individuals from different ethnic groups representing a diverse population group all living within the DESP area, with one of the most complete data sets on ethnicity reported to date. Second, the use of PTALs in addition to distance to screening centre to evidence the associations of accessibility and transport with attendance. And third, the fact that three quarters of the participants were distributed between two of the most deprived quintiles of IMD, allowing the comparative association between deprivation and ethnicity with attendance to be examined. This analysis has several limitations. First, major systemic risk factors for DR/STDR, namely blood pressure and glycaemic control, were not available to include in the analysis. Second, I did not analyse the association of the sociodemographic variables with the presence of DR, which although desirable, would have been difficult to ascertain for repeated non-attenders. Further work to unravel the interplay between ethnicity, deprivation, and disease severity is needed to inform strategies to improve attendance, particularly in high risk under privileged groups.

4.5.7 Conclusion

Smaller previous studies have reported an association between non-white ethnicities and poor attendance at DES appointments, however, in this large diverse urban population, South Asian, Chinese, and individuals of any other Asian background were more likely to attend DES appointments when compared with white people. Public health strategies have in the past focused on ethnic differences as a possible cause of variance in DES uptake. The data from this large cohort shows that there are other more influential factors. I have shown that worse VA, higher levels of deprivation, younger age, and longer duration of diabetes are associated with non-attendance. The evidence suggests that strategies to improve uptake should be directed at these groups, in order to reduce inequalities in DES and improve outcomes in diabetes care.

5

Ethnic disparities in progression rates of sight-threatening diabetic retinopathy in diabetic eye screening

Contents

5. Ethnic disparities in progression rates of sight-threatening diabetic retinopathy in diabetic eye screening

5.1 Abstract

Aims: To examine incidence and associations of sight-threatening diabetic retinopathy (STDR), and potential impact of biennial rather than annual screening on STDR detection.

Methods: North-East London diabetic eye screening programme (NELDESP) cohort data (Jan/2012-Dec/2021) with 137,591 people with diabetes and no diabetic retinopathy (DR), or non-STDR at baseline in one/both eyes, was used to calculate STDR incidence rates by sociodemographic factors, diabetes type and duration. Cox models examined associations with STDR. I estimated the number of missed STDR events in biennial screening intervals among people with diabetes without DR.

Results: There were 16,388 incident STDR cases over a median of 5.4 years (IQR 2.8-8.2; STDR rate 22.14, 95% CI 22.14-22.15 per 1000 person-years). Compared with people with no retinopathy at baseline, people with non-STDR in one eye, and people with non-STDR in both eyes had a 3.03 (95% CI 2.91-3.15, $p<0.001$) and 7.88 (95% CI 7.59-8.18, $p<0.001$) HR for STDR, respectively. Compared with white people, black (HR 1.57, 95% CI 1.50-1.64) and South Asian (HR 1.36, 95% CI 1.31-1.42) people showed greater STDR hazards. Every 5-year increase in age at inclusion was associated with an 8% reduction in STDR hazards ($p<0.001$). Sixty-six percent (58/88) of proliferative DR cases would have had a 1-year delay in diagnosis with biennial screening.

Conclusion: While DR at baseline was a strong determinant of STDR development, biennial screening would have delayed detection of some proliferative DR, and other STDR instances by one year in a large predominantly urban multiethnic population.

5.2 Introduction

Demographic characteristics and social determinants of health are associated with any degree of diabetic retinopathy (DR) and with sight-threatening DR (STDR),[173–175,180] however, there is little data from large scale studies of sociodemographically diverse populations with standardised DR grading in the UK.

Biennial diabetic eye screening (DES) has been recommended in people with diabetes and no DR by several clinical guidelines, with personalised-risk interval screening being proposed in the literature.[25,77] Less frequent intervals for DES in people with low-risk of progression could reduce the number of appointments, workload, and was shown to be cost-effective in a comprehensive analysis finalised before the National Institute for Health and Care Excellence (NICE) approval of anti-vascular endothelial growth factor (VEGF) for the treatment of diabetic macular oedema.[25] However, the potential consequences of missing STDR between longer intervals has not yet been examined in large multi-ethnic cohorts.

I report incidence rates (IR) of any DR, STDR, and examine sociodemographic associations of STDR, including ethnicity, age, sex, and deprivation in a large representative multi-ethnic population from the NELDESP. I also examine the potential changes in the detection of STDR with biennial screening as opposed to annual screening in this large well-characterised cohort.

5.3 Methods

The methodology for this analysis and further information about the data source are found in Section 2.4, and Section 0.1.1, respectively.

5.4 Results

A total of 137,591 people (73,840/137,591, 53.7% male) with a mean (standard deviation) age of 56.8 (14.8) years were included (Figure 2.2). There were a total of 16,388 incident STDR cases (82.9% M1, 13.2% R2, and 3.8% R3). Table

5. Ethnic disparities in progression rates of sight-threatening diabetic retinopathy in diabetic eye screening

5.1 summarises this cohort baseline characteristics. Median (interquartile range) follow-up time was 5.4 (2.8-8.2) years. Ethnicity codes were usable for 98.5% of the population (135,487/137,591); 37% were white (50,907/137,591), and 42.3% (58,195/137,591) of the sample lived in areas with the two index of multiple deprivation (IMD) quintiles of highest deprivation (1 and 2).

Table 5.1: Baseline population characteristics among people with non-sight-threatening diabetic retinopathy at baseline.

Characteristic	Overall, N = 137,591	No retinopathy, N = 107,701†	Retinopathy in one eye, N = 17,570†	Retinopathy in both eyes, N = 12,320†
Follow-up (years)	5.4 (2.8)	5.5 (2.8)	5.4 (2.9)	4.4 (2.9)
Age at baseline	56.8 (14.8)	56.5 (14.8)	58.0 (14.6)	57.1 (15.1)
Age categories				
<45yr	28,173 (20%)	22,552 (21%)	3,124 (18%)	2,497 (20%)
45 to <55yr	32,982 (24%)	26,038 (24%)	4,115 (23%)	2,829 (23%)
55 to <65yr	33,798 (25%)	26,373 (24%)	4,425 (25%)	3,000 (24%)
65yr and over	42,638 (31%)	32,738 (30%)	5,906 (34%)	3,994 (32%)
Sex				
Female	63,751 (46%)	51,233 (48%)	7,615 (43%)	4,903 (40%)
Male	73,840 (54%)	56,468 (52%)	9,955 (57%)	7,417 (60%)
Type of diabetes				
Type 2	128,270 (93%)	101,363 (94%)	16,301 (93%)	10,606 (86%)
Type 1	5,130 (3.7%)	3,141 (2.9%)	736 (4.2%)	1,253 (10%)

Mean (standard deviation) for continuous variables.

Count (column %) for categorical variables.

†No retinopathy (R0M0); retinopathy in one eye (R1M1 in one eye); retinopathy in both eyes (R1M0 in both eyes).

Table 5.1: Baseline population characteristics among people with non-sight-threatening diabetic retinopathy at baseline.

Characteristic	**Overall, N = 137,591**	**No retinopathy, N = 107,701**[†]	**Retinopathy in one eye, N = 17,570**[†]	**Retinopathy in both eyes, N = 12,320**[†]
Other	251 (0.2%)	219 (0.2%)	15 (<0.1%)	17 (0.1%)
Missing	3,940 (2.9%)	2,978 (2.8%)	518 (2.9%)	444 (3.6%)
Ethnicity				
White	50,907 (37%)	39,663 (37%)	6,423 (37%)	4,821 (39%)
South Asian	47,994 (35%)	37,951 (35%)	5,992 (34%)	4,051 (33%)
Black	22,095 (16%)	17,303 (16%)	2,907 (17%)	1,885 (15%)
Any other Asian	7,741 (5.6%)	6,013 (5.6%)	1,039 (5.9%)	689 (5.6%)
Other	4,051 (2.9%)	3,097 (2.9%)	594 (3.4%)	360 (2.9%)
Mixed	1,744 (1.3%)	1,373 (1.3%)	206 (1.2%)	165 (1.3%)
Chinese	955 (0.7%)	745 (0.7%)	119 (0.7%)	91 (0.7%)
Unknown	2,104 (1.5%)	1,556 (1.4%)	290 (1.7%)	258 (2.1%)
Duration of diabetes	4.7 (6.4)	3.9 (5.4)	6.2 (7.2)	10.1 (9.2)
Index of Multiple Deprivation				

Mean (standard deviation) for continuous variables.

Count (column %) for categorical variables.

[†]No retinopathy (R0M0); retinopathy in one eye (R1M1 in one eye); retinopathy in both eyes (R1M0 in both eyes).

Table 5.1: Baseline population characteristics among people with non-sight-threatening diabetic retinopathy at baseline.

Characteristic	**Overall, N = 137,591**	**No retinopathy, N = 107,701**[†]	**Retinopathy in one eye, N = 17,570**[†]	**Retinopathy in both eyes, N = 12,320**[†]
1	14,598 (11%)	11,537 (11%)	1,792 (10%)	1,269 (10%)
2	43,597 (32%)	34,155 (32%)	5,527 (31%)	3,915 (32%)
3	39,756 (29%)	31,167 (29%)	5,064 (29%)	3,525 (29%)
4	25,906 (19%)	20,114 (19%)	3,408 (19%)	2,384 (19%)
5	13,541 (9.8%)	10,600 (9.8%)	1,746 (9.9%)	1,195 (9.7%)
Missing	193 (0.1%)	128 (0.1%)	33 (0.2%)	32 (0.3%)

Mean (standard deviation) for continuous variables.

Count (column %) for categorical variables.

[†]No retinopathy (R0M0); retinopathy in one eye (R1M1 in one eye); retinopathy in both eyes (R1M0 in both eyes).

5.4.1 Prevalence and incidence of diabetic retinopathy and sight threatening diabetic retinopathy

At study baseline, the point prevalence of any DR and STDR was 27.5% (48,628/176,767), and 8.1% (14,231/176,767), respectively. Overall IR (95% CI) of STDR was 2.21 (2.21–2.21) per 100 person-years. Table 5.2 shows cumulative IRs of STDR per 100 person-years by follow-up. Baseline DR severity showed a strong relationship with STDR rates. Progression to STDR with advancing yearly intervals showed an overall monotonic increase in rates, which was more pronounced in younger age groups when compared with the consistently lower rates in older age groups (Supplementary Table D.1). Sensitivity analyses excluding the earliest 2 years of the study period did not materially alter STDR IR (Supplementary Table D.2).

The raw incidence of any DR and of STDR for participants with no retinopathy at baseline was 35.4% (38,169/107,701) and 6.6% (7,139/107,701), respectively. The overall IR (95% CI) of any retinopathy was 1.48 (1.48 - 1.48) per 100 person-years. The highest IR for any DR and STDR were observed in people of black ethnicity (1.98 [1.98–1.98], and 2.68 [2.68–2.68] per 100 person-years, respectively). People of Chinese ethnicity had the lowest IR for any DR and STDR (0.08 [0.08-0.09], and 1.65 [1.63-1.67] per 100 person-years, respectively [Supplementary Table D.3]). Cumulative IR of any retinopathy per 100 person-years by follow-up is shown in Supplementary Table D.4.

Table 5.2: Cumulative incidence rates of sight-threatening diabetic retinopathy per 100 person-years by length of follow-up with 95% confidence intervals.

Characteristic	Year 1	Year 2	Year 3	Year 4	Year 5	Year 10
Overall	0.86 (0.82 - 0.90)	1.48 (1.43 - 1.54)	1.66 (1.61 - 1.72)	1.78 (1.73 - 1.84)	1.89 (1.83 - 1.95)	2.21 (2.15 - 2.28)
Age groups						
Less than 45 years	0.90 (0.81 - 0.99)	1.59 (1.47 - 1.72)	1.82 (1.69 - 1.95)	2.02 (1.88 - 2.15)	2.20 (2.05 - 2.34)	2.84 (2.68 - 3.01)
45 to <55 years	0.86 (0.78 - 0.95)	1.54 (1.43 - 1.66)	1.76 (1.64 - 1.88)	1.86 (1.73 - 1.98)	2.01 (1.88 - 2.13)	2.42 (2.28 - 2.55)
55 to <65 years	0.85 (0.77 - 0.93)	1.42 (1.31 - 1.52)	1.57 (1.46 - 1.69)	1.68 (1.56 - 1.79)	1.73 (1.61 - 1.84)	1.96 (1.84 - 2.09)
65 years and over	0.84 (0.77 - 0.91)	1.41 (1.32 - 1.51)	1.55 (1.46 - 1.65)	1.66 (1.56 - 1.76)	1.72 (1.62 - 1.83)	1.87 (1.76 - 1.98)
Sex						
Female	0.78 (0.72 - 0.84)	1.36 (1.28 - 1.43)	1.55 (1.47 - 1.63)	1.68 (1.59 - 1.76)	1.77 (1.68 - 1.85)	2.08 (1.98 - 2.17)
Male	0.93 (0.87 - 0.99)	1.59 (1.51 - 1.67)	1.76 (1.68 - 1.84)	1.88 (1.80 - 1.96)	1.99 (1.91 - 2.08)	2.34 (2.25 - 2.43)
Ethnicity						
White	0.76 (0.69 - 0.82)	1.25 (1.17 - 1.33)	1.40 (1.31 - 1.49)	1.50 (1.42 - 1.59)	1.56 (1.47 - 1.65)	1.77 (1.68 - 1.87)
South Asian	0.85 (0.78 - 0.92)	1.53 (1.44 - 1.62)	1.71 (1.61 - 1.80)	1.85 (1.75 - 1.95)	1.99 (1.88 - 2.09)	2.44 (2.32 - 2.55)
Black	1.08 (0.97 - 1.19)	1.87 (1.72 - 2.02)	2.09 (1.93 - 2.25)	2.19 (2.03 - 2.36)	2.32 (2.15 - 2.49)	2.68 (2.50 - 2.86)
Any other Asian	0.84 (0.67 - 1.01)	1.52 (1.29 - 1.75)	1.68 (1.44 - 1.92)	1.86 (1.61 - 2.12)	2.02 (1.76 - 2.28)	2.24 (1.97 - 2.52)
Other	1.07 (0.80 - 1.34)	1.42 (1.11 - 1.72)	1.70 (1.37 - 2.04)	1.79 (1.45 - 2.14)	1.90 (1.55 - 2.26)	2.33 (1.94 - 2.71)
Mixed	0.75 (0.41 - 1.09)	1.33 (0.88 - 1.78)	1.70 (1.19 - 2.21)	1.94 (1.40 - 2.49)	2.14 (1.57 - 2.71)	2.41 (1.81 - 3.02)

Table 5.2: Cumulative incidence rates of sight-threatening diabetic retinopathy per 100 person-years by length of follow-up with 95% confidence intervals.

Characteristic	Year 1	Year 2	Year 3	Year 4	Year 5	Year 10
Chinese	1.16 (0.59 - 1.73)	1.62 (0.95 - 2.29)	1.81 (1.10 - 2.52)	1.73 (1.04 - 2.43)	1.69 (1.00 - 2.38)	1.65 (0.97 - 2.33)
Unknown	0.91 (0.57 - 1.26)	2.09 (1.57 - 2.60)	2.51 (1.95 - 3.07)	2.59 (2.02 - 3.16)	2.64 (2.07 - 3.22)	2.61 (2.03 - 3.18)
Baseline DR grade						
No retinopathy	0.21 (0.19 - 0.23)	0.44 (0.41 - 0.48)	0.56 (0.52 - 0.59)	0.66 (0.62 - 0.70)	0.79 (0.75 - 0.84)	1.20 (1.15 - 1.26)
Retinopathy in one eye	1.23 (1.10 - 1.37)	2.37 (2.18 - 2.56)	2.78 (2.58 - 2.99)	3.16 (2.94 - 3.37)	3.33 (3.11 - 3.55)	3.80 (3.56 - 4.03)
Retinopathy in both eyes	6.04 (5.69 - 6.39)	9.81 (9.37 - 10.26)	10.61 (10.15 - 11.06)	10.78 (10.32 - 11.24)	10.77 (10.31 - 11.23)	10.43 (9.98 - 10.88)

5.4.2 Survival probabilities and sociodemographic associations with sight-threatening-diabetic-retinopathy

Survival probabilities for STDR development stratified by DR severity at baseline and age groups were consistently lower in younger people with non-STDR in both eyes (Figure 5.1). Survival curves stratified by retinopathy severity at baseline and the three major ethnic groups consistently showed lower survival probabilities for non-white ethnicities (Figure 5.2). A survival curve plot for interval censored data showed comparable findings (Supplementary Figure D.1).

5.4.3 Sight-threatening diabetic retinopathy associations

Table 5.3 summarises HRs from our multivariable Cox model. Age categories showed a strong graded inverse association with hazards of STDR (p for linear trend <0.0001). Males showed a 4% greater STDR hazards when compared with females (p 0.011). When compared with people with no retinopathy at baseline, people with non-STDR in one eye had a 3-fold greater STDR hazard, whereas people with non-STDR in both eyes at baseline showed an 8-fold greater STDR hazard.

When compared with the white ethnic group, non-white ethnic groups showed greater STDR hazard. The biggest effect sizes were observed in people of black (HR 1.57; 95% CI 1.50-1.64), mixed (HR 1.39; 95% CI 1.20-1.60), and south Asian (HR 1.36; 95% CI 1.31-1.42) ethnicity. The Chinese ethnic group did not show differences for STDR when compared with white people. The unknown ethnic group was composed of an undetermined mixture of people who chose not to disclose their ethnicity and missing data (proportions not available for analysis) and was associated with a 71% greater STDR hazards when compared with white ethnicity ($p < 0.0001$).

Every 5-year increase in duration of diabetes conferred a 14% increase in STDR hazard. When compared with the highest quintile of deprivation, only the least deprived IMD quintile showed a 7% reduction in hazards of STDR (p=0.041). However, IMD was the only variable in Cox regression that was no longer significant

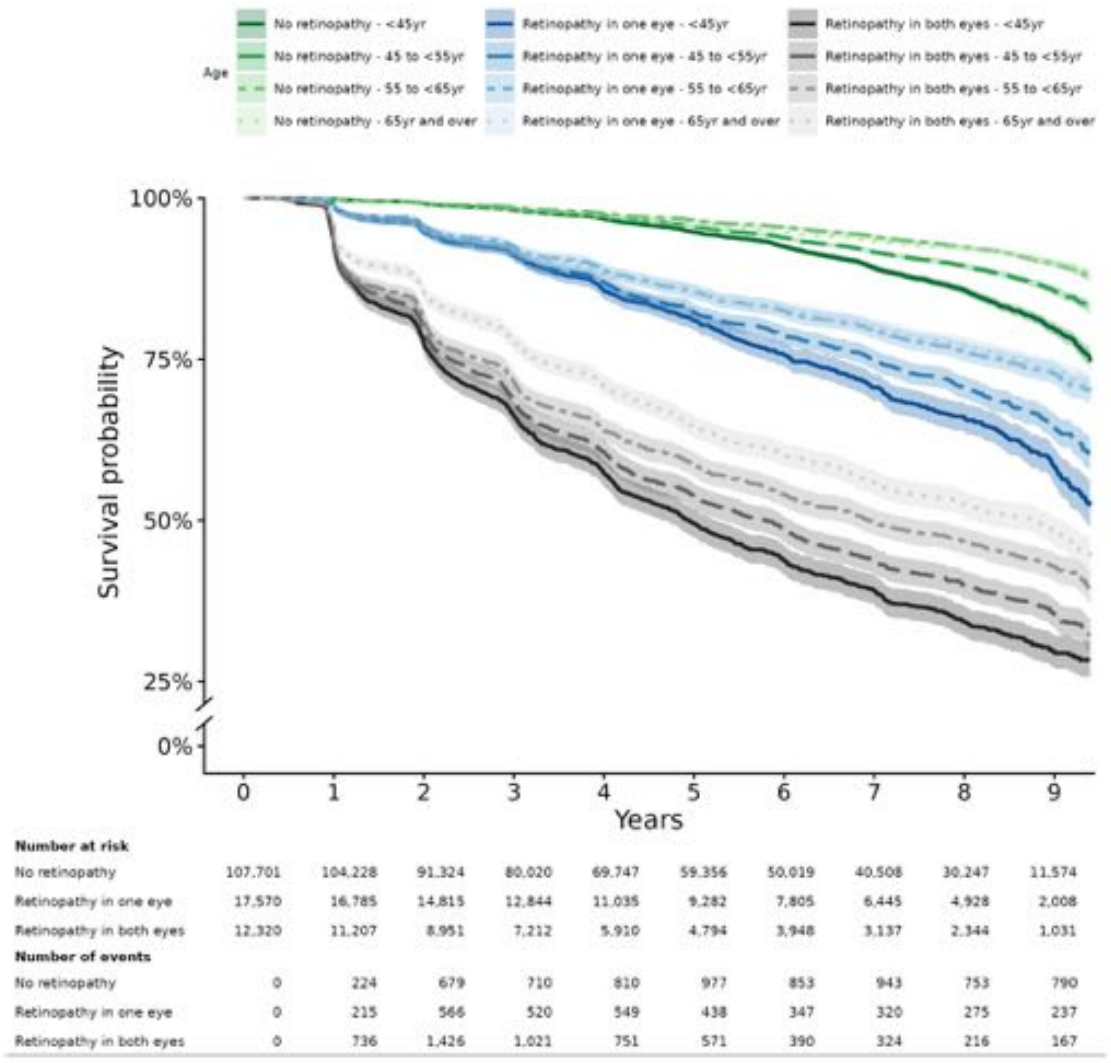
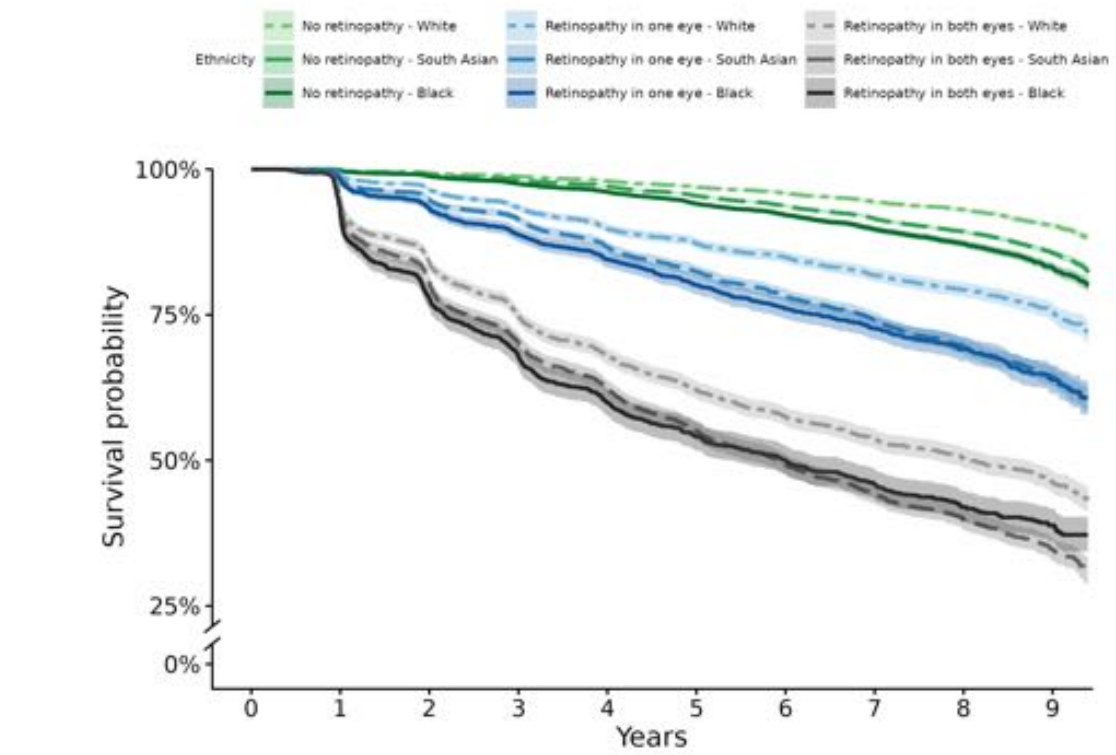


Figure 5.1: Survival plots for development of sight-threatening diabetic retinopathy (STDR) stratified by non-STDR at baseline (No retinopathy, non-STDR in one eye, non-STDR in both eyes) and age.

with interval censoring (Table 5.3 and Supplementary Table D.5). Type of diabetes was not associated with STDR.

5.4.4 Diabetic retinopathy associations

Associations for development of any DR in people with no retinopathy at baseline (R0M0, n=107,701) are shown in Supplementary Table D.6. When compared with type 2 diabetes, people with type 1 diabetes showed a strong association with the larger effect size for any DR (HR 1.36, 95% CI 1.28–1.44), and every 5-year rise in



Number at risk										
No retinopathy	107,701	104,228	91,324	80,020	69,747	59,356	50,019	40,508	30,247	11,574
Retinopathy in one eye	17,570	16,785	14,815	12,844	11,035	9,282	7,805	6,445	4,928	2,008
Retinopathy in both eyes	12,320	11,207	8,951	7,212	5,910	4,794	3,948	3,137	2,344	1,031
Number of events										
No retinopathy	0	224	679	710	810	977	853	943	753	790
Retinopathy in one eye	0	215	566	520	549	438	347	320	275	237
Retinopathy in both eyes	0	736	1,426	1,021	751	571	390	324	216	167

Figure 5.2: Survival plots for development of sight-threatening diabetic retinopathy (STDR) stratified by non-STDR at baseline (No retinopathy, non-STDR in one eye, non-STDR in both eyes) and three major ethnic groups.

duration of diabetes was associated with 18% increase in DR hazard. Every 5-year increase in age conferred a 1% decrease in DR hazard, males had a 6% greater in DR hazard when compared with females, and ethnic differences were considerably less pronounced and only statistically significantly different from people of self-described white ethnicities for south Asian (HR 1.03, 95% CI 1.00–1.06), other (HR 1.09, 95% CI 1.02–1.16), and unknown (HR 1.36, 95% CI 1.21–1.54) ethnic groups. No associations were observed for IMD.

Table 5.3: Hazard ratios (HR) for sight-threatening diabetic retinopathy mutually adjusted for all factors shown in table (HR greater than 1 imply greater hazards for sight-threatening diabetic retinopathy).

Characteristic	HR (95% CI)	p-value
Age (per 5-year increase)	0.92 (0.92, 0.93)	**1.0e-133**
Age categories		
<45yr	1.00	
45 to <55yr	0.79 (0.75, 0.82)	**1.5e-26**
55 to <65yr	0.60 (0.58, 0.63)	**1.1e-96**
65yr and over	0.57 (0.54, 0.59)	**1.4e-115**
Sex		
Female	1.00	
Male	1.04 (1.01, 1.07)	**0.011**
Baseline DR grade[†]		
No retinopathy	1.00	
Retinopathy in one eye	3.03 (2.91, 3.15)	**4.6e-626**
Retinopathy in both eyes	7.88 (7.59, 8.18)	**2.5e-2521**
Ethnicity		
White	1.00	
South Asian	1.36 (1.31, 1.42)	**1.0e-52**
Black	1.57 (1.50, 1.64)	**2.6e-81**
Any other Asian	1.25 (1.16, 1.34)	**4.0e-10**
Other	1.29 (1.18, 1.42)	**4.7e-08**
Mixed	1.39 (1.20, 1.60)	**5.7e-06**
Chinese	0.98 (0.79, 1.21)	0.831
Unknown	1.71 (1.41, 2.07)	**4.8e-08**
Duration of diabetes (per 5-year increase)	1.14 (1.13, 1.15)	**8.3e-138**
Type of diabetes		
Type 2	1.00	

HR; hazard ratio, CI; confidence interval, IMD; index of multiple deprivation.

[†]No retinopathy; R0M0 (both eyes), retinopathy in one eye; R1M1 in one eye, retinopathy in both eyes; R1M0 in both eyes.

Table 5.3: Hazard ratios (HR) for sight-threatening diabetic retinopathy mutually adjusted for all factors shown in table (HR greater than 1 imply greater hazards for sight-threatening diabetic retinopathy).

Characteristic	HR (95% CI)	p-value
Type 1	1.03 (0.97, 1.11)	0.337
Other	0.73 (0.44, 1.22)	0.231
Missing	1.34 (1.20, 1.51)	**6.3e-07**
Deprivation (IMD quintiles)		
1	1.00	
2	1.04 (0.99, 1.10)	0.141
3	1.03 (0.98, 1.09)	0.281
4	0.98 (0.93, 1.04)	0.592
5	0.93 (0.87, 1.00)	**0.041**
Missing	1.68 (0.75, 3.75)	0.208

HR; hazard ratio, CI; confidence interval, IMD; index of multiple deprivation.

[†]No retinopathy; R0M0 (both eyes), retinopathy in one eye; R1M1 in one eye, retinopathy in both eyes; R1M0 in both eyes.

5.4.5 Incidence of sight-threatening-diabetic-retinopathy on biennial screening intervals

Biennial screening intervals for people without retinopathy in two consecutive visits, could have led to, at least, a 1-year delay in the diagnosis of 43.6% (45/103) and 56.3% (1,007/1,788) of the R3 and STDR cases during the study period, respectively (Figure 5.3). Relative to number of people at risk by ethnicity, the proportion of cases with delayed diagnosis would be consistently higher for people of south Asian and black ethnicities when compared with white.

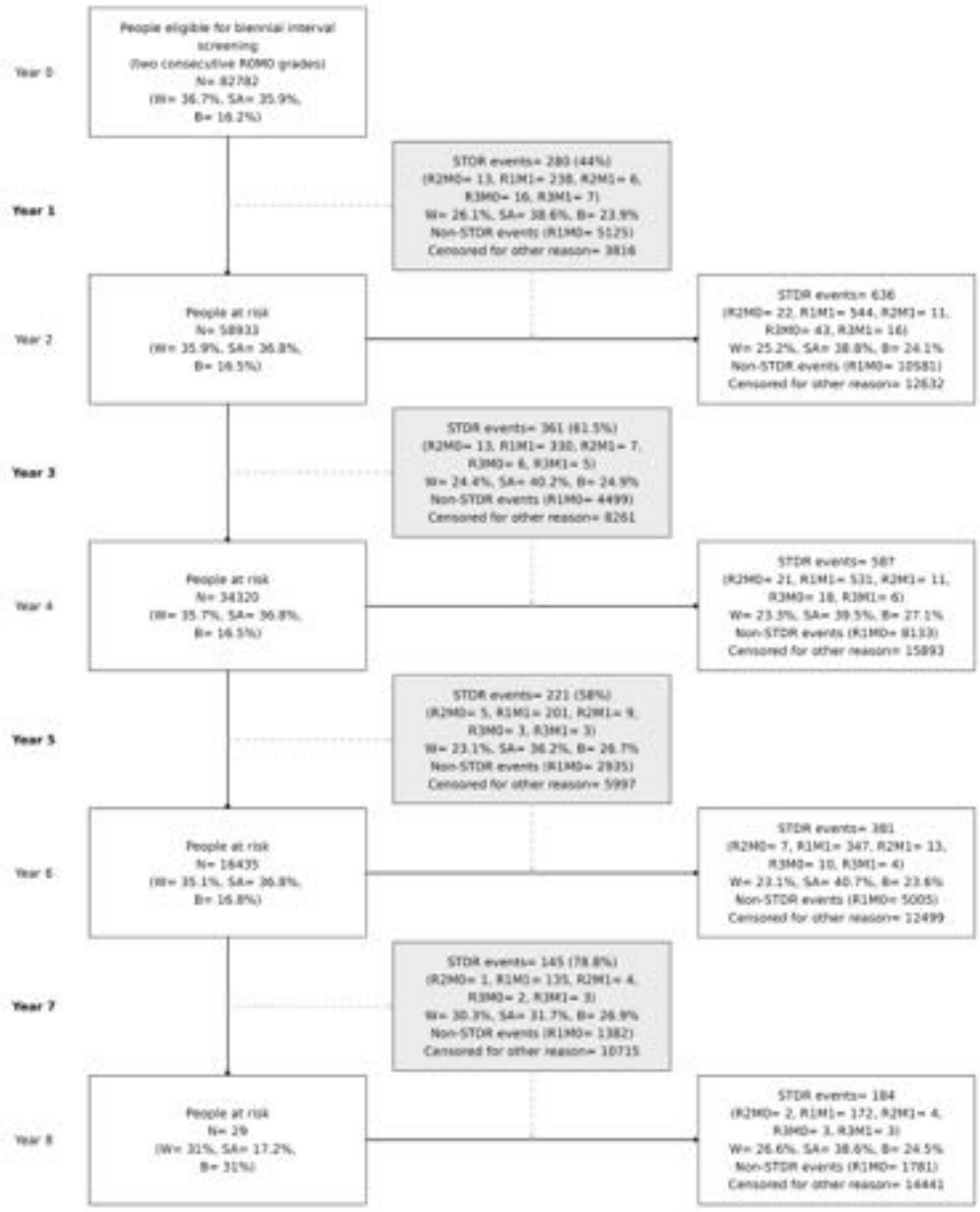


Figure 5.3: Model of biennial screening in the North East London Diabetic Eye Screening cohort. Grey boxes in column 2 show the number of sight-threatening diabetic retinopathy (STDR) events that would have been diagnosed and referred in routine screening during the biennial interval but diagnosed at least one year later in two-yearly interval screening. A breakdown by 3 major ethnic groups is presented in each box. Percentages in grey boxes relative to the total STDR events from a 2-year interval. W: white, SA: south Asian, B: black

5.5 Discussion

This study provides definitive IRs for STDR by demographic characteristics routinely collected in DES. There is a strong relationship in cumulative IR increases with retinopathy severity at baseline, and a monotonic increase in rates with advancing yearly intervals, more pronounced in younger people (Table 5.2 and Supplementary Table D.1). I have defined and calculated sociodemographic associations with STDR, and provide a web calculator (click here to go to the website, or just, copy and paste in your browser: `https://bit.ly/desp-stdr-web-calculator`) to estimate disease trajectories of individuals with different sociodemographic profiles. Young, male, non-white ethnic groups with longer duration of diabetes show higher STDR hazards when compared with older, female, whites with shorter duration of diabetes. Using observed, rather than modelled DES data, I have shown that we could expect at least a 1-year delay in the diagnosis of 43.6% of the proliferative DR cases in biennial screening.

5.5.1 Associations with sight-threatening diabetic retinopathy

Diabetic retinopathy status at baseline was the most important predictor for development of STDR. When compared to people with no DR at baseline, the 3- and almost 8-fold greater hazards of STDR for non-STDR in one eye and non-STDR in both eyes, respectively, is consistent with the reported HRs in the literature.[25,77] The absence of DR and the degree of non-STDR (non-STDR in one or both eyes) provides valuable information for simple risk stratification in groups of people that were previously considered of low homogeneous risk.[77,110]

Younger age groups have been reported to have higher incidence of STDR.[6,181–183] Derived from this analysis, I provide evidence of increased risk of STDR in younger people (HR per 5-year rise in age 0.92, $p<0.001$). From the evidenced associations, I hypothesise the causes are likely multiple, and can result from a complex interplay of different factors that could be partially explained by higher levels of

non-attendance to DES,[103,104] and by sub optimal control of major modifiable risk factors in young people.[179,184] Individuals younger than 45 years of age are at a critical stage of their work, or career development, and the lifetime burden and health costs of sight-threatening complications on this population is of considerable public health importance.

Males are at higher risk for STDR development than women. Similar effect sizes to what is reported in this study are available.[103,182] An electronic health record (EHR)-based study analysing the development of STDR in people with diabetes in the UK, found a HR of 1.22 (95% CI 1.01–1.47) and 1.15 (95% CI 1.06–1.26) for males newly diagnosed, and males with known diagnosis of diabetes when compared with females, respectively.[182] Similarly, Mathur et al.[6] reported a greater relative risk of DR (HR 1.08, 95%CI 1.05-1.09), and severe DR (HR 1.25, 95%CI 1.12-1.39), in males when compared with females. Lawrenson et al.[103] found 23% greater odds (95% CI 1.15–1.35) of STDR in males when compared with females in a 15-month-limited follow-up DES study. Non-attendance to diabetic eye screening,[103] and hormonal differences[185] are possible underpinning factors for which the evidence remains contradictory.

South Asian and black ethnic groups have been reported to have higher prevalence of diabetes,[6,180,186] be more likely to develop both STDR[180] and visual impairment[174] than white people. Sivaprasad et al.[180] reported, in a predominantly white (66%) population, an 82% (HR 1.82, 95%CI 1.61–2.06) and 99% (HR 1.99, 95%CI 1.81–2.18) greater risk of STDR in South Asian and black ethnic groups when compared with white people, respectively. Mathur et al.[6] showed a 25% (HR 1.25, 95% CI 1.00–1.56) greater risk of severe retinopathy (defined as advanced, proliferative, or laser treated DR) in South Asian patients when compared with white patients, however, a third of the ethnicity data were missing. Scanlon et al.[25] showed a 55%, 58%, and 24% greater hazards of STDR in African, Caribbean, and other ethnic groups when compared with white people in a small (n=1223) data set from South London. More recently, an EMR-based study with over 98% usability of ethnicity coding, identified greater risk of STDR in African (HR 1.36, 95% CI

1.02-1.83), Indian (HR 1.38, 95% CI 1.17-1.63), Pakistani (HR 1.28, 95% CI 1.04-1.55), Bangladeshi (HR 1.36, 95% CI 1.19-1.54), Caribbean (HR 1.22, 95% CI 1.03-1.43), and other (HR 1.25, 95% CI 1.06-1.47) ethnicities with a new diagnosis of diabetes when compared with white individuals.[182] These results stress the need to address health inequalities across ethnic groups to improve secondary prevention of sight-threatening complications.

5.5.2 Biennial diabetic eye screening intervals for people with low risk of sight-threatening complications

Personalised biennial screening in people with no DR has been proposed as a safe cost-effective strategy for diabetic eye screening.[25,77] By empirically examining a biennial screening with observed data in people with no retinopathy, we report a 1-year delay in referral of 52% of the STDR events, but more importantly, a 1-year delay of 43.6% of the R3 diagnoses that would have waited an additional year compared with annual screening during an 8-year follow-up. We have shown that South Asian, and black ethnic groups could further be at disadvantage compared to with people in this setting (higher rate of STDR events with delayed detection in biennial screening relative to the proportion of people at risk [Figure 5.3]). These rates assume an uptake equivalent to annual screening. Possible belief of good health in people with no DR invited to biennial screening could lead to repeated non-attendance, forestalling STDR detection,[161] and possibly limiting the benefits of timely treatment.[74]

5.5.3 Strengths and limitations

This study has several strengths. First, a large sample size allowing for sufficient power to detect associations with STDR stratified by age, sex, ethnicity, DR severity at baseline, and deprivation, otherwise unfeasible in smaller studies. Second, IR provided by our results are of importance to drive future power calculations for clinical trials. Third, there is high quality in ethnicity recording with usability of 98.5%. Fourth, the prevalence of any DR falls in line with previous reports

(27.5% prevalence overall. 49.1% and 26.4% in people with type 1 and type 2 diabetes, respectively).[6,25,187] Fifth, retinopathy classification was performed by trained assessors following a multilevel internally and externally quality-assured grading protocol that meets national recommendations.

The limitations of this study are as follows. First, HbA1c, blood pressure, blood lipids, medication history, or body mass index were not available at the time of this analysis. However, estimates of the Cox model are in alignment with reports from a previous EHR-based study which controlled for the above mentioned variables.[182] Second, I cannot exclude human errors in grading of retinal fundus images despite the well-established grading protocol, but it is expected that, based on HES outcomes, findings of the study would not substantially differ.

5.5.4 Conclusion

I present a contemporary analysis of STDR incidence and associations at unprecedented scale in a multi-ethnic sociodemographically diverse population undergoing DES. Incidence rates provided in this analysis are valuable for future research. These survival analysis revealed significant associations based on simple sociodemographic variables available in routine DES which provide significant information for simple risk stratification of people with diabetes. The biennial screening empirical analysis shows a 1-year delay in diagnosis of 43.6% of R3 cases, which warrants further research to support such a screening strategy in ethnically diverse populations. Approaches that maintain yearly appointments with potential use of automated retinal image analysis could be further considered. Understanding IR, associations of STDR, and potential implications of biennial screening in cohorts such as this, helps to guide further research, improve service planning and delivery of eye care. Further work is necessary to develop accurate prediction models and test if inclusion of additional clinical, imaging, and imaging-derived data allow for a more accurate risk stratification than current models.

6

Prediction of diabetes complications at point of diabetic eye screening, a streamlined approach to individualised preventive care

Contents

6.1 Abstract

Aims: To develop prediction models for sight-threatening diabetic retinopathy (STDR) and all-cause mortality in people living with diabetes (PLD).

Methods: North-East London diabetic eye screening programme (NELDESP) cohort data (01/01/2012-31/12/2021) of 176,751 PLD with linked primary and secondary care electronic health records (EHR).
Mutually adjusted 5-year Cox proportional hazard models were developed for the primary outcomes of interest (i.e. STDR, and all-cause mortality). Candidate predictors were progressively added to 5 different models compared with a base model to quantify the contribution of additional variables to predictive performance.

Results: A total of 176,751 PLD with DR grading, and 137,590 PLD with no DR or non-STDR at baseline contributed data for all-cause mortality and STDR model development, respectively. There were 28,987 deaths over a median 7.9 years (IQR 4.5-10.2; all-cause mortality rate 164, 95% CI 162.55-165.45 per 1000 person-years). There were 16,388 incident STDR cases over a median of 5.4 years (IQR 2.8-8.2; STDR rate 22.14, 95% CI 22.14-22.15 per 1000 person-years). Models for all-cause mortality show reasonably high performance metrics with C-statistics ranging from 0.817 to 0.841 in females, and from 0.806 to 0.831 in males. Optimism-adjusted calibration slope ranged from 0.994 to 1.001 in females and from 0.995 to 1.000 in males. Net benefit at 10% threshold probability ranged from 31 to 35 per 1000 people-at-risk in females and from 39.5 to 44.5 per 1000 people-at-risk in males. Sensitivity analyses for all-cause mortality in people of working age showed a significant decline in clinical utility with net benefits at 10% threshold probability ranging from in females and from in males.

Models for STDR show reasonably high performance metrics which were not materially altered in sensitivity analyses. A parsimonious model including age, sex, ethnicity, type and duration of diabetes, index of multiple deprivation, and HbA1c (DESP + HbA1c model) showed good performance when compared with models of increasing complexity, showing an optimism-adjusted C-statistic of 0.804 (95% CI 0.801-0.806), optimism-adjusted calibration slope of 0.993 (95% CI 0.962-1.000), and net benefit at 10% threshold probability of 43 per 1000 people-at-risk.

Conclusion: Prediction models with routinely collected variables at the point of diabetic eye screening (DES) may be useful tools to assist decision-making at the point of DES to enhance STDR secondary prevention in PLD. The strategies followed for development of all-cause mortality prediction models are useful for future work. Age is the most important predictive factor. Work on mortality exemplifies the importance of a comprehensive performance assessment to identify the contribution of examined variables.

6.2 Introduction

Not all people living with diabetes (PLD) will develop sight-threatening diabetic retinopathy (STDR), nor are all deaths in PLD attributable to diabetes. An estimate of 4.2 to 6.2% of PLD have STDR.[188] With a mortality rate in PLD greater than the background population,[3,84,85] an estimate of 6.7 million deaths were attributed to diabetes in 2021 (a third of which occurred in working age adults).[7] Additionally, time to development of diabetes complications varies widely among PLD. Currently, no clinical decision tools exist to identify people at high risk of adverse outcomes.

I developed 5-year Cox proportional hazard models to predict STDR and all-cause mortality in a large representative multi-ethnic population from the North East London Diabetic Eye Screening Programme (NELDESP).

6.3 Methods

The methodology for this analysis and further information about the data source are found in Sections 2.4.2 and 2.5, respectively.

6.4 Results

6.4.1 All-cause mortality

A total of 176,751/176,767 (99.9%) people with diabetic retinopathy (DR) grading (Chapter 5, Figure 2.2) were linked to electronic health records (EHR) and contributed data for model development. There were 28,987 deaths (14,131 within 5 years; 6,029 female) and 1,268,227 person-years of data over a median (IQR) follow-up of 7.9 (4.5-10.2) years. Table 6.1 summarises patient level baseline characteristics from routinely collected diabetic eye screening programme (DESP) data.

A total of 163,622/176,751 (92.6%) participants had a valid HbA1c record at baseline. Table 6.2 summarises EHR variable baseline characteristics. A breakdown of continuous variables with missing values is shown in supplementary Table E.21.

Table 6.1: Baseline population characteristics.

Characteristic	**Overall**	**Female**	**Male**
	N=176,751	**N=80,711**	**N=96,040**
Follow-up (years)	7.91 (4.47, 10.19)	8.05 (4.50, 10.22)	7.80 (4.43, 10.17)
Age at baseline	56 (46, 67)	58 (47, 69)	55 (46, 66)
DR severity at inclusion			
R0M0	128,132 (72%)	60,608 (75%)	67,524 (70%)
R1M0	34,390 (19%)	14,331 (18%)	20,059 (21%)
R1M1	7,962 (4.5%)	3,499 (4.3%)	4,463 (4.6%)
R2M0	1,227 (0.7%)	456 (0.6%)	771 (0.8%)
R2M1	2,729 (1.5%)	930 (1.2%)	1,799 (1.9%)
R3M0	834 (0.5%)	357 (0.4%)	477 (0.5%)
R3M1	1,477 (0.8%)	530 (0.7%)	947 (1.0%)

DR, diabetic retinopathy.

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

Table 6.1: Baseline population characteristics.

Characteristic	**Overall**	**Female**	**Male**
	N=176,751	**N=80,711**	**N=96,040**
Severity in contralateral eye			
Equal	147,113 (83%)	68,126 (84%)	78,987 (82%)
Better	29,638 (17%)	12,585 (16%)	17,053 (18%)
Ethnicity			
White	63,964 (36%)	27,924 (35%)	36,040 (38%)
South Asian	60,633 (34%)	27,703 (34%)	32,930 (34%)
Black	28,616 (16%)	14,565 (18%)	14,051 (15%)
Any other Asian	9,748 (5.5%)	4,342 (5.4%)	5,406 (5.6%)
Other	5,366 (3.0%)	2,320 (2.9%)	3,046 (3.2%)
Mixed	2,384 (1.3%)	1,186 (1.5%)	1,198 (1.2%)
Chinese	1,172 (0.7%)	579 (0.7%)	593 (0.6%)
Unknown	4,868 (2.8%)	2,092 (2.6%)	2,776 (2.9%)
Duration of diabetes at inclusion	2.1 (0.3, 7.5)	2.2 (0.3, 7.9)	2.0 (0.3, 7.1)
Type of diabetes			
Type 2	161,127 (91%)	73,682 (91%)	87,445 (91%)
Type 1	7,937 (4.5%)	3,520 (4.4%)	4,417 (4.6%)
Other	414 (0.2%)	231 (0.3%)	183 (0.2%)
Missing	7,273 (4.1%)	3,278 (4.1%)	3,995 (4.2%)
Index of multiple deprivation			
1	18,280 (10%)	8,716 (11%)	9,564 (10.0%)
2	54,133 (31%)	25,550 (32%)	28,583 (30%)

DR, diabetic retinopathy.

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

Table 6.1: Baseline population characteristics.

Characteristic	**Overall**	**Female**	**Male**
	N=176,751	**N=80,711**	**N=96,040**
3	49,343 (28%)	22,506 (28%)	26,837 (28%)
4	32,082 (18%)	14,249 (18%)	17,833 (19%)
5	16,751 (9.5%)	7,182 (8.9%)	9,569 (10.0%)
Missing	6,162 (3.5%)	2,508 (3.1%)	3,654 (3.8%)

DR, diabetic retinopathy.

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

Table 6.2: Baseline Electronic Health Record characteristics.

Characteristic	**Overall**	**Female**	**Male**
	N=176,751	**N=80,711**	**N=96,040**
Hypertension†	91,314 (52%)	43,982 (54%)	47,332 (49%)
Chronic Kidney Disease	24,214 (14%)	11,700 (14%)	12,514 (13%)
Myocardial infarction	8,931 (5.1%)	2,240 (2.8%)	6,691 (7.0%)
Stroke	8,639 (4.9%)	3,809 (4.7%)	4,830 (5.0%)
Systolic blood pressure	130 (120, 139)	130 (120, 139)	130 (120, 139)
Diastolic blood pressure	78 (70, 81)	77 (70, 80)	78 (71, 82)
Mean arterial pressure†	95 (89, 100)	94 (88, 99)	95 (89, 100)

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

†N missing values for HbA1c = 13,129; systolic blood pressure = 10,496; diastolic blood pressure = 10,493; mean arterial pressure = 10,506; triglycerides = 44,679; total cholesterol = 15,602; HDL-cholesterol = 26,638; LDL-cholesterol = 48,712.

Table 6.2: Baseline Electronic Health Record characteristics.

Characteristic	**Overall**	**Female**	**Male**
	N=176,751	**N=80,711**	**N=96,040**
HbA1c†	7.00 (6.50, 8.10)	6.90 (6.50, 7.90)	7.00 (6.50, 8.20)
Triglycerides†	1.76 (1.18, 1.82)	1.76 (1.16, 1.76)	1.76 (1.19, 1.90)
Total cholesterol†	4.40 (3.70, 5.00)	4.41 (3.80, 5.10)	4.30 (3.60, 4.90)
HDL-Cholesterol†	1.21 (1.00, 1.32)	1.21 (1.10, 1.44)	1.14 (0.95, 1.22)
LDL-Cholesterol†	2.45 (2.00, 2.70)	2.45 (2.05, 2.80)	2.45 (1.90, 2.70)
LDL/HDL ratio	2.02 (1.60, 2.50)	2.02 (1.51, 2.36)	2.02 (1.69, 2.64)
Insulin use	27,476 (16%)	13,643 (17%)	13,833 (14%)
Non-insulin hypoglycaemic use	131,682 (75%)	60,045 (74%)	71,637 (75%)
Lipid lowering use	108,334 (61%)	48,618 (60%)	59,716 (62%)
Calcium channel blocker use	27,847 (16%)	14,045 (17%)	13,802 (14%)
Beta blocker use	46,776 (26%)	21,786 (27%)	24,990 (26%)
Alpha blocker use	15,120 (8.6%)	6,948 (8.6%)	8,172 (8.5%)
Renin angiotensin blocker use	94,549 (53%)	42,429 (53%)	52,120 (54%)
Diuretic use	58,030 (33%)	31,304 (39%)	26,726 (28%)

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

†N missing values for HbA1c = 13,129; systolic blood pressure = 10,496; diastolic blood pressure = 10,493; mean arterial pressure = 10,506; triglycerides = 44,679; total cholesterol = 15,602; HDL-cholesterol = 26,638; LDL-cholesterol = 48,712.

Section 2.5.6 describes in detail the assessment of model performance. Table 6.3 shows optimism-adjusted performance metrics for the six all-cause mortality

models developed. Performance is reported with C-statistic (where values around 0.5 indicate no better performance than chance, hence values closer to 1 correspond to better discrimination), calibration (values closer to 1 indicate better agreement of predictions with observed risk), and R-squared (where a value of 1 indicates the model explains all variability in the data). Diabetic retinopathy grading alone (DR grade model), and routinely collected DESP data (DESP model) were identified as statistically significant predictors of mortality both in males and females. The addition of clinical history, clinical measures, and medication history significantly improved model performance. A diagnosis of hypertension at baseline significantly contributed to the medical history model in males only, to the clinical measure model in both males and females (model adjusting for mean arterial pressure), and it was not significant both in males and females when medication use was introduced in the modelling strategy. Renin angiotensin blockers significantly modified the risk of all-cause mortality in males only (Supplementary Table E.1). For reproducibility, all multivariable fractional polynomial model regression coefficients and corresponding standard errors for males and females are shown in supplementary Tables E.3 to E.8, and E.9 to E.14, respectively.

Calibration and discrimination

Apparent validation, model baseline survival probability and variable transformations are shown in Supplementary Tables E.24 and E.25. In males and females, optimism-adjusted calibration slope (0.993-0.999), concordance (0.812-0.840) and R^2 (0.219-0.241) statistics were reasonably high (Table 6.3, see Supplementary Table E.1 for a visualisation of variables tested and included in final models). Graphical inspection of all models revealed good calibration in males and females (Figures 6.1 and 6.2, respectively).

Table 6.3: Optimism adjusted model performance (95% CI) for prediction of all-cause mortality.

Model	Male	Female
Medication use model (Events/Sample size)	6588/82577	4675/69725
C-statistic	0.831 (0.828-0.834)	0.841 (0.840-0.843)
Slope	0.996 (0.993-0.999)	0.994 (0.989-1.000)
R-squared	0.241 (0.237-0.244)	0.237 (0.231-0.242)
Clinical measures model (Events/Sample size)	6588/82577	4675/69725
C-statistic	0.826 (0.824-0.830)	0.838 (0.836-0.840)
Slope	0.995 (0.984-0.999)	0.994 (0.989-1.000)
R-squared	0.235 (0.231-0.237)	0.232 (0.227-0.237)
Medical history model (Events/Sample size)	8102/96040	6029/80711
C-statistic	0.822 (0.821-0.824)	0.832 (0.829-0.836)
Slope	0.998 (0.995-0.999)	0.998 (0.996-1.002)
R-squared	0.234 (0.232-0.236)	0.234 (0.230-0.239)
Diabetic eye screening model (Events/Sample size)	8102/96040	6029/80711
C-statistic	0.815 (0.813-0.817)	0.827 (0.824-0.830)
Slope	0.998 (0.995-1.001)	0.998 (0.996-1.003)
R-squared	0.224 (0.222-0.226)	0.226 (0.222-0.231)
Diabetic retinopathy grades model (Events/Sample size)	8102/96040	6029/80711
C-statistic	0.812 (0.811-0.814)	0.824 (0.821-0.828)
Slope	0.999 (0.996-1.001)	0.999 (0.996-1.004)
R-squared	0.220 (0.218-0.222)	0.222 (0.217-0.227)
Base model (Events/Sample size)	8102/96040	6029/80711
C-statistic	0.806 (0.804-0.807)	0.817 (0.814-0.820)
Slope	1.000 (0.997-1.003)	1.001 (0.997-1.006)

All estimates calculated with bootstraping (B=150) for each model.

Table 6.3: Optimism adjusted model performance (95% CI) for prediction of all-cause mortality.

Model	Male	Female
R-squared	0.213 (0.211-0.215)	0.213 (0.209-0.218)

All estimates calculated with bootstraping (B=150) for each model.

Risk groups (using quintiles of predicted risk to illustrate the models ability to stratify risk among individuals) showed a clear separation in event distribution in both, males and females (Figure 6.3, 6.4). Models captured between 64.6% to 72.9% of all-cause mortality cases in the top quintile of risk distribution (Table 6.4).

Table 6.4: Risk between highest vs lowest predicted risk quintile for all-cause mortality defined by 95% CIs. Number (percent) of events captured in the highest risk quintile shown in last column.

Model	Relative Risk	Risk Difference	Events in highest risk quintile
Male			
Medication use	55.33 (46.26-69.69)	28.93 (29.53-28.33)	4600/6588 (69.8%)
Clinical measures	50.72 (42.75-63.07)	28.61 (29.20-28.01)	4543/6588 (69.0%)
Medical history	41.95 (36.40-49.89)	29.68 (30.22-29.13)	5524/8102 (68.2%)
DESP data	39.58 (34.43-46.90)	29.13 (29.66-28.59)	5451/8102 (67.3%)
Diabetic retinopathy grades	40.25 (35.01-47.73)	29.05 (29.59-28.50)	5344/8102 (66.0%)
Base model (Age and Ethnicity)	32.03 (28.36-37.04)	28.27 (28.79-27.74)	5233/8102 (64.6%)
Female			
Medication use	75.64 (59.36-106.63)	25.61 (26.25-24.96)	3407/4675 (72.9%)
Clinical measures	68.58 (54.43-94.67)	25.40 (26.03-24.75)	3379/4675 (72.3%)
Medical history	52.44 (43.81-66.15)	27.91 (28.51-27.31)	4324/6029 (71.7%)
DESP data	46.76 (39.44-58.13)	27.33 (27.91-26.74)	4265/6029 (70.7%)

DESP, diabetic eye screening programme.

Table 6.4: Risk between highest vs lowest predicted risk quintile for all-cause mortality defined by 95% CIs. Number (percent) of events captured in the highest risk quintile shown in last column.

Model	Relative Risk	Risk Difference	Events in highest risk quintile
Diabetic retinopathy grades	45.30 (38.38-55.93)	27.40 (27.99-26.80)	4168/6029 (69.1%)
Base model (Age and Ethnicity)	39.24 (33.62-47.62)	26.55 (27.12-25.97)	4127/6029 (68.5%)

DESP, diabetic eye screening programme.

Clinical usefulness

Given the reduction in risk of micro and macrovascular diabetes complications with lasting benefits persisting even after intensive measures to control glucose are stopped,[66,189–192] my decision curve analysis explored operating threshold probabilities between 5-30%. Treatment would imply a more intensive control of glucose and blood pressure in individuals at high risk detected by the models. In the context of decision curve analysis, thinking of threshold probabilities in terms of odds is useful to understand the operating risk threshold. A threshold of 10% would be equal to an odds of 1:9 and could be interpreted as saying that "missing an individual who will die is 9 times worse than implementing an unnecessary intensive treatment strategy". For completeness, the corresponding odds for the operating thresholds explored are 1:19 for 5%, 1:9 for 10%, 1:5.7 for 15%, 1:4 for 20%, 1:3 for 25%, and 1:2.33 for 30%. Results showed clinical utility over the entire threshold range (Figure 6.5) with net benefits ranging from 31-44 per 1000 people with diabetes (Table 6.5). If we were to extrapolate these clinical utility metrics translated to a cohort of 170,000 people with diabetes, a net benefit (i.e. true positives without incurring in any other type of harm from false positives) ranging from 5,270 to 7,480 would be expected.

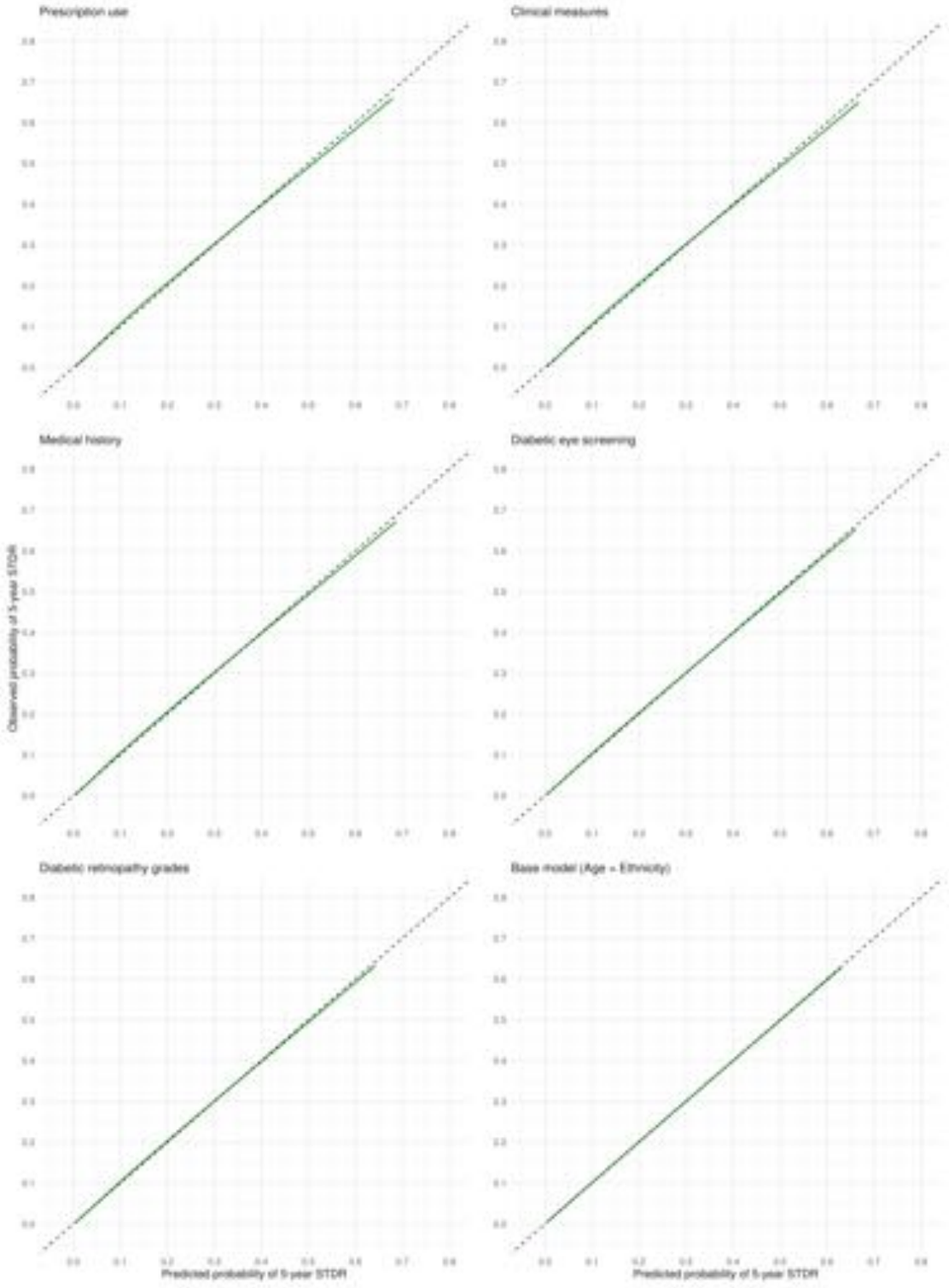


Figure 6.1: Male. Graphical prediction performance for predicting all-cause mortality within 5-years.

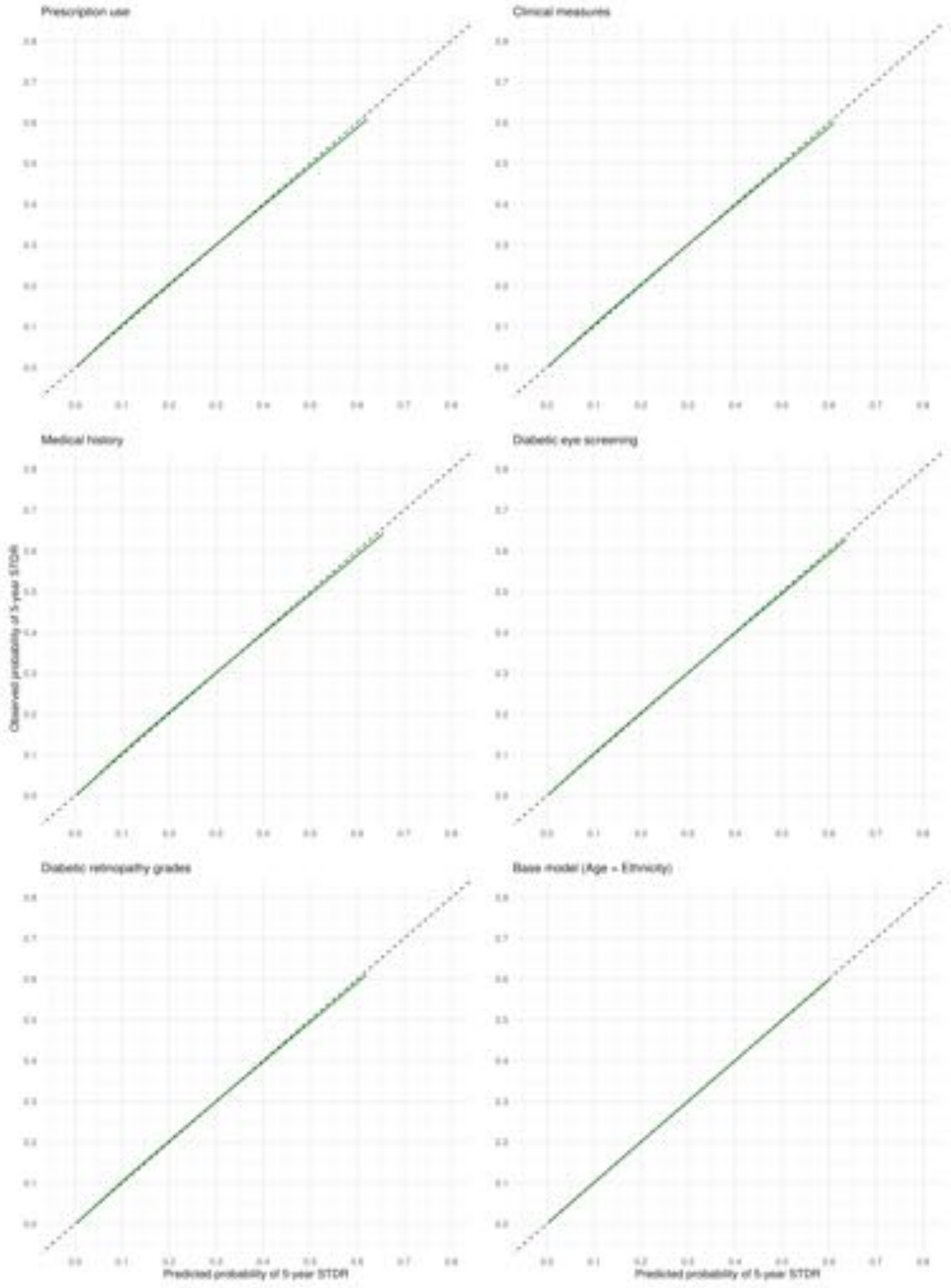


Figure 6.2: Female. Graphical prediction performance for predicting all-cause mortality within 5-years.

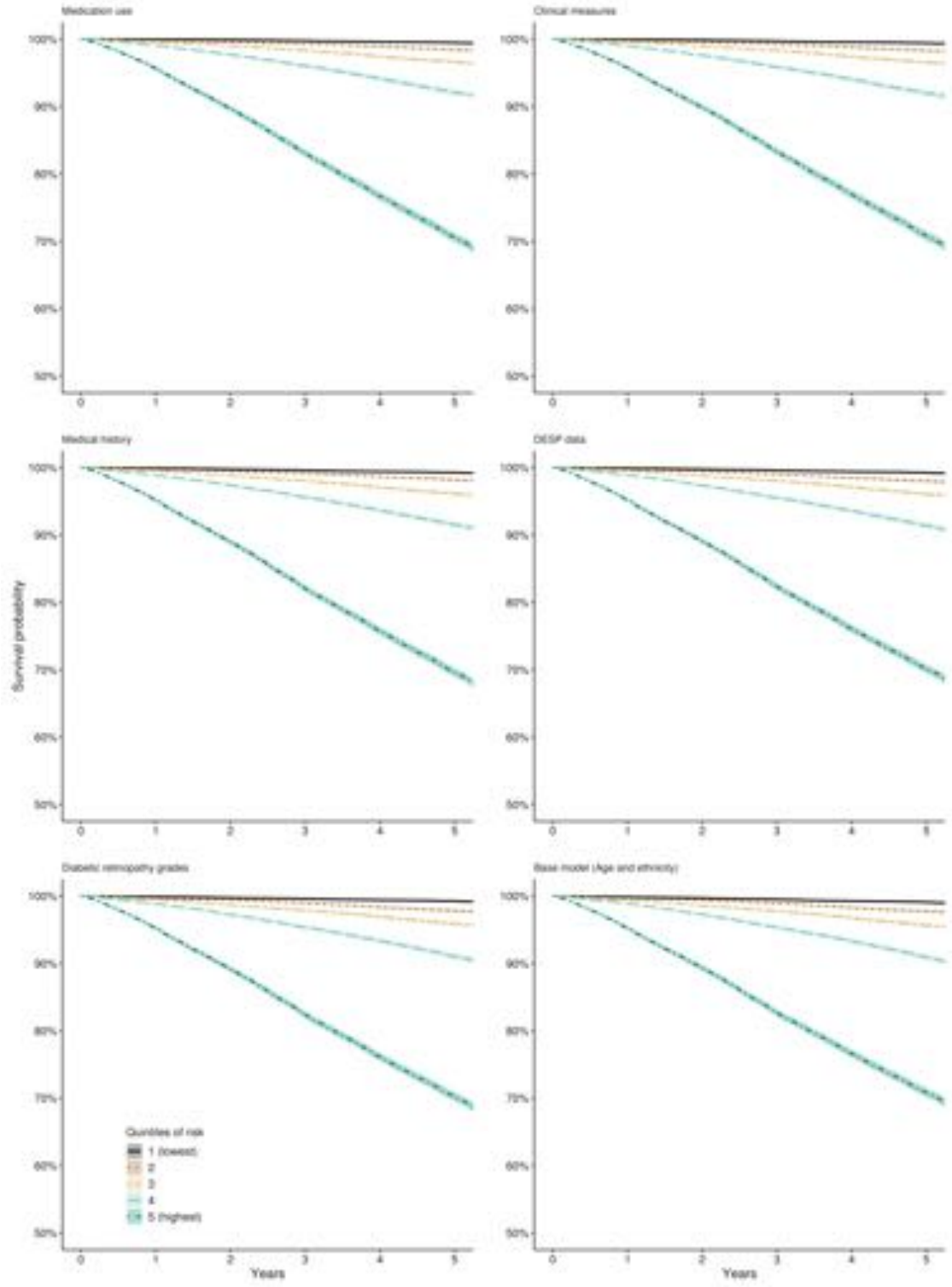


Figure 6.3: Males. Quintiles of predicted risk for all-cause mortality within 5-years.

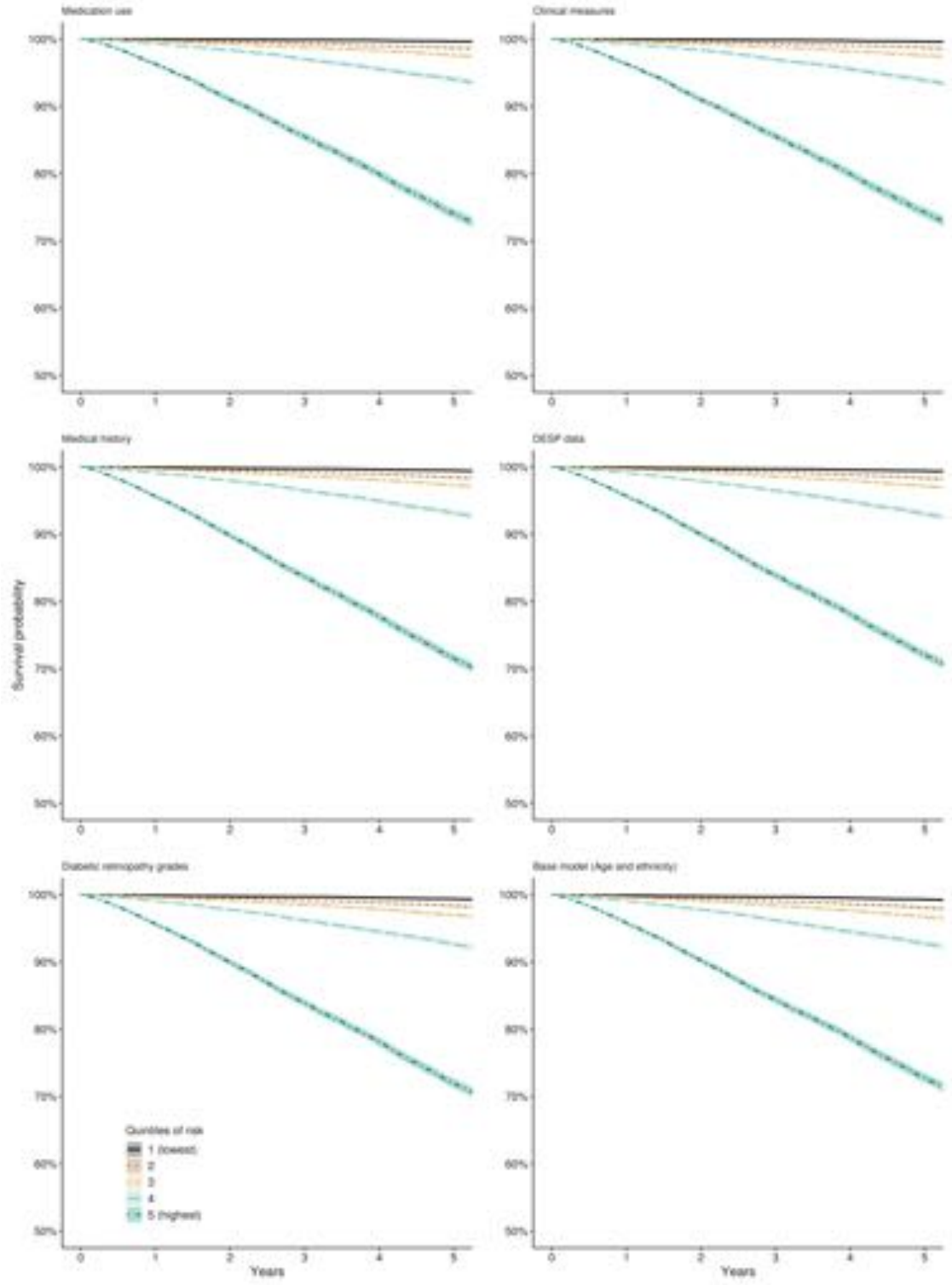


Figure 6.4: Females. Quintiles of predicted risk for all-cause mortality within 5-years.

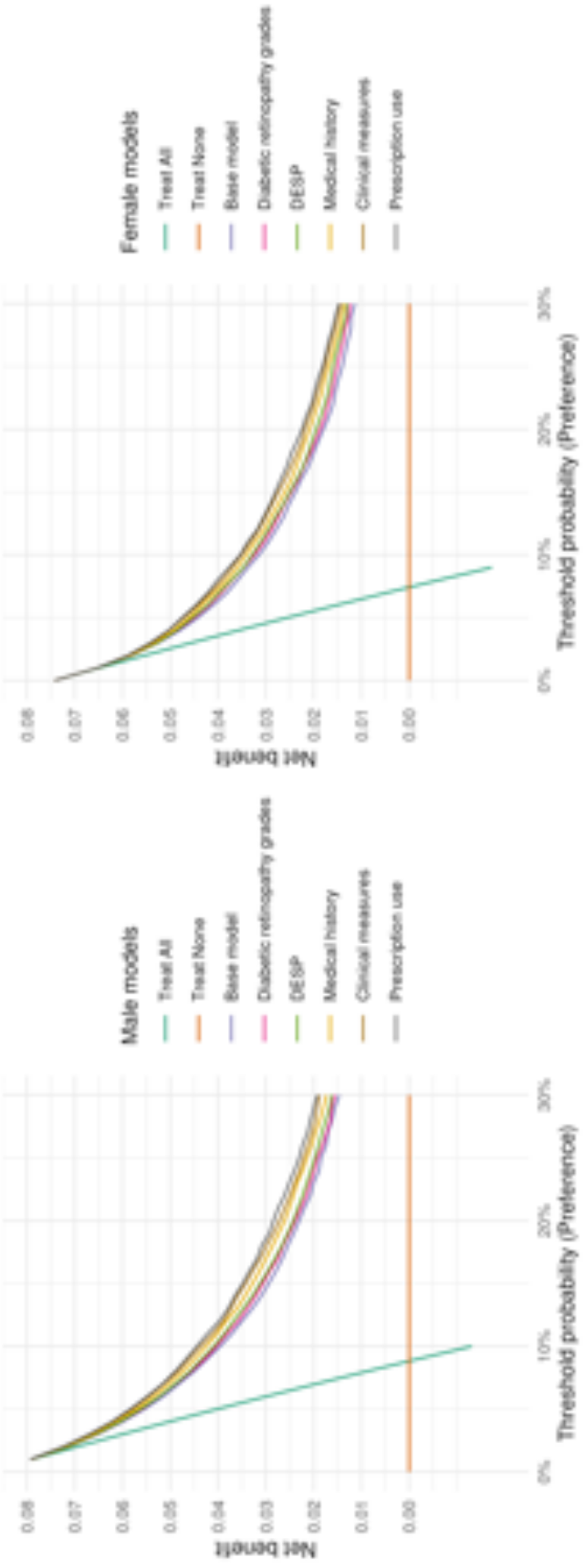


Figure 6.5: Decision curve analysis for all-cause mortality models.

Table 6.5: Net benefit for all-cause mortality per 1000 people with diabetes by threshold probability.

Model	5%	10%	20%	30%
Male				
Base model	55.4	39.5	23.0	14.6
Diabetic retinopathy grades	56.0	40.3	23.8	15.5
DESP	56.2	40.8	24.2	16.2
Medical history	57.0	42.4	26.0	17.3
Clinical measures	57.9	43.6	27.1	18.8
Prescription use	58.4	44.5	28.4	19.3
Female				
Base model	44.2	31.4	17.9	11.3
Diabetic retinopathy grades	45.0	32.4	18.6	12.4
DESP	45.4	32.8	19.4	13.0
Medical history	46.0	34.1	20.8	13.5
Clinical measures	47.1	35.1	21.8	14.2
Prescription use	47.5	35.3	22.4	14.7

Sensitivity analysis

Restricting model performance measures to people of working age resulted in a drop in C-statistic and R^2 (Supplementary Table 6.6). A descriptive assessment of baseline population characteristics by predicted risk quintiles for all models revealed age was a possible driver of predictive performance. Assessment of clinical usefulness revealed a significant drop in net benefits across the tested threshold probability (female > males) which would be difficult to justify for use given the outcome (Figure 6.6, and Table 6.6).

Table 6.6: Net benefit for all-cause mortality per 1000 people with diabetes by threshold probability in the working age population.

Model	5%	10%	20%	30%
Male				
Base model	5.8	1.9	0.7	0.0
Diabetic retinopathy grades	6.9	2.5	0.7	0.2
DESP	7.3	3.1	0.8	0.2
Medical history	8.3	3.8	1.2	0.5
Clinical measures	9.5	4.6	1.5	0.6
Prescription use	10.2	5.4	1.8	0.8
Female				
Base model	2.0	1.3	0.1	0.0
Diabetic retinopathy grades	3.3	1.5	0.3	0.0
DESP	3.8	1.6	0.5	0.1
Medical history	4.4	2.1	0.5	0.2
Clinical measures	5.2	2.6	0.8	0.3
Prescription use	5.6	2.8	1.0	0.3

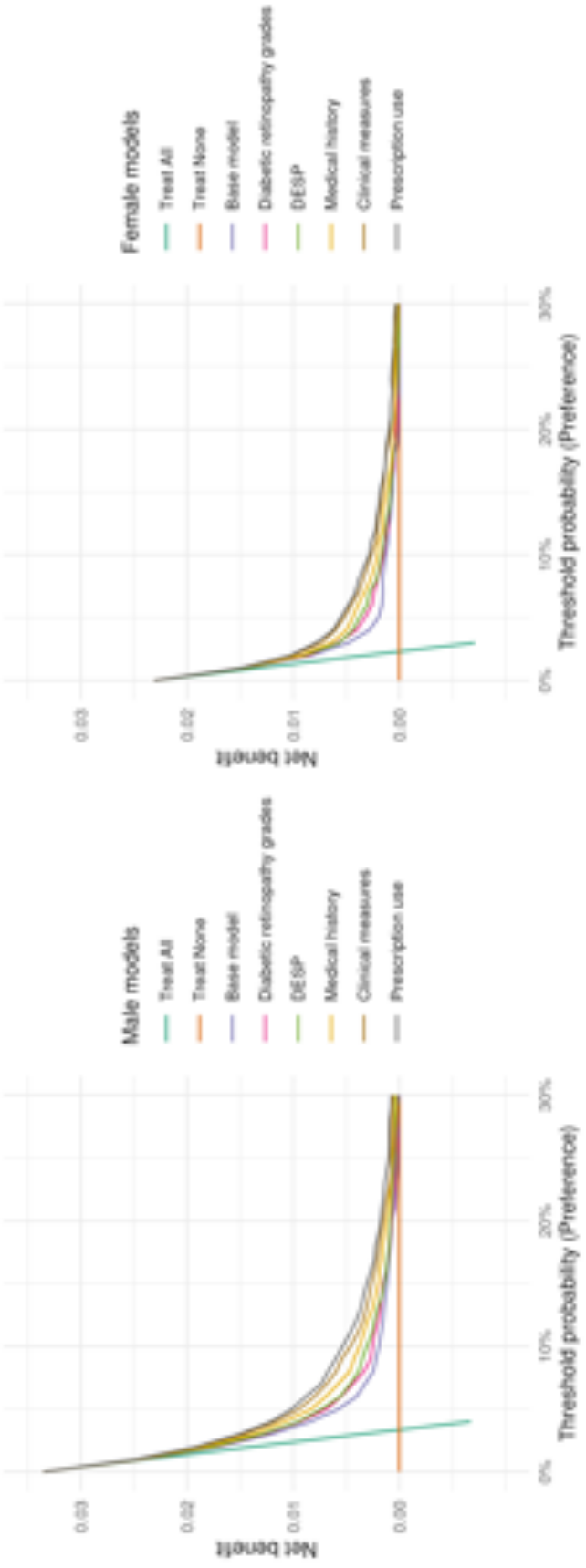


Figure 6.6: Decision curve analysis for all-cause mortality models in working age population.

6.4.2 Sight-threatening diabetic retinopathy

A total of 137,590/137,591 (99.9%) people with non-STDR or no DR at baseline contributed data with linked EHR (See Figure 2.2). There were 16,388 incident STDR cases (10,193 within 5 years) and 740,067 person-years of data with a median (IQR) follow-up of 5.4 (2.4-8.2) years. Table 6.7 summarises patient level baseline characteristics from DESP. A total of 128,219/137,590 (93.2%) participants had a valid HbA1c record at baseline. Table 6.8 summarises EHR variable baseline characteristics. Supplementary Table E.22 shows variables with missing values.

Table 6.7: Baseline population characteristics among people with non-sight-threatening diabetic retinopathy at baseline.

Characteristic	**Overall**	**Female**	**Male**
	N=137,590	**N=63,751**	**N=73,839**
Events - STDR	16,388 (12%)	7,228 (11%)	9,160 (12%)
Age at baseline	57 (47, 67)	58 (47, 69)	56 (46, 66)
DR severity at inclusion			
No retinopathy	107,701 (78%)	51,233 (80%)	56,468 (76%)
Retinopathy in one eye	17,569 (13%)	7,615 (12%)	9,954 (13%)
Retinopathy in both eyes	12,320 (9.0%)	4,903 (7.7%)	7,417 (10%)
Ethnicity			
White	50,907 (37%)	22,404 (35%)	28,503 (39%)
South Asian	47,994 (35%)	22,320 (35%)	25,674 (35%)
Black	22,094 (16%)	11,386 (18%)	10,708 (15%)
Any other Asian	7,741 (5.6%)	3,574 (5.6%)	4,167 (5.6%)
Other	4,051 (2.9%)	1,788 (2.8%)	2,263 (3.1%)
Mixed	1,744 (1.3%)	879 (1.4%)	865 (1.2%)

STDR, sight-threatening diabetic retinopathy; DR, diabetic retinopathy.

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

Table 6.7: Baseline population characteristics among people with non-sight-threatening diabetic retinopathy at baseline.

Characteristic	**Overall**	**Female**	**Male**
	N=137,590	**N=63,751**	**N=73,839**
Chinese	955 (0.7%)	472 (0.7%)	483 (0.7%)
Unknown	2,104 (1.5%)	928 (1.5%)	1,176 (1.6%)
Duration of diabetes at inclusion	2.1 (0.3, 7.0)	2.3 (0.3, 7.4)	2.0 (0.3, 6.6)
Type of diabetes			
Type 2	128,269 (93%)	59,453 (93%)	68,816 (93%)
Type 1	5,130 (3.7%)	2,350 (3.7%)	2,780 (3.8%)
Other	251 (0.2%)	146 (0.2%)	105 (0.1%)
Missing	3,940 (2.9%)	1,802 (2.8%)	2,138 (2.9%)
Index of multiple deprivation			
1	14,598 (11%)	7,042 (11%)	7,556 (10%)
2	43,596 (32%)	20,765 (33%)	22,831 (31%)
3	39,756 (29%)	18,378 (29%)	21,378 (29%)
4	25,906 (19%)	11,585 (18%)	14,321 (19%)
5	13,541 (9.8%)	5,898 (9.3%)	7,643 (10%)
Missing	193 (0.1%)	83 (0.1%)	110 (0.1%)

STDR, sight-threatening diabetic retinopathy; DR, diabetic retinopathy.

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

Table 6.8: Baseline Electronic Health Record characteristics among people with non-sight-threatening diabetic retinopathy at baseline.

Characteristic	**Overall**	**Female**	**Male**
	N=137,590	**N=63,751**	**N=73,839**
Body mass index†	29.2 (25.9, 33.5)	30.2 (26.5, 34.9)	28.4 (25.5, 32.2)
Hypertension	72,004 (52%)	35,086 (55%)	36,918 (50%)
Chronic Kidney Disease	16,736 (12%)	8,220 (13%)	8,516 (12%)
Myocardial infarction	6,653 (4.8%)	1,589 (2.5%)	5,064 (6.9%)
Stroke	6,280 (4.6%)	2,777 (4.4%)	3,503 (4.7%)
Systolic blood pressure	130 (120, 139)	130 (120, 139)	130 (120, 139)
Diastolic blood pressure†	78 (70, 81)	77 (70, 80)	78 (71, 82)
Mean arterial pressure†	94 (89, 100)	94 (88, 99)	95 (89, 100)
HbA1c†	6.90 (6.50, 7.90)	6.90 (6.40, 7.80)	7.00 (6.50, 8.00)
Triglycerides†	1.74 (1.16, 1.83)	1.74 (1.15, 1.76)	1.74 (1.18, 1.90)
Total cholesterol†	4.39 (3.70, 5.00)	4.39 (3.80, 5.00)	4.30 (3.50, 4.80)
HDL-Cholesterol†	1.21 (1.00, 1.33)	1.21 (1.10, 1.45)	1.13 (0.95, 1.22)
LDL-Cholesterol†	2.44 (1.98, 2.70)	2.44 (2.00, 2.80)	2.44 (1.90, 2.70)
Insulin use	17,519 (13%)	9,070 (14%)	8,449 (11%)
Non-insulin hypoglycaemic use	103,170 (75%)	47,761 (75%)	55,409 (75%)
Lipid lowering use	86,817 (63%)	39,517 (62%)	47,300 (64%)
Calcium channel blocker use	21,307 (15%)	10,867 (17%)	10,440 (14%)
Beta blocker use	36,707 (27%)	17,255 (27%)	19,452 (26%)
Alpha blocker use	11,334 (8.2%)	5,237 (8.2%)	6,097 (8.3%)

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

†N missing values for body mass index = 8,780; HbA1c = 9,371; Systolic blood pressure = 6,853; diastolic arterial pressure = 6,852; mean arterial pressure = 6,862; triglycerides = 33,122; total cholesterol = 10,746; HDL-cholesterol = 21,188; LDL-cholesterol = 36,125.

Table 6.8: Baseline Electronic Health Record characteristics among people with non-sight-threatening diabetic retinopathy at baseline.

Characteristic	**Overall**	**Female**	**Male**
	N=137,590	**N=63,751**	**N=73,839**
Renin angiotensin blocker use	73,898 (54%)	33,571 (53%)	40,327 (55%)
Diuretic use	45,991 (33%)	25,148 (39%)	20,843 (28%)

Median (Interquartile range) for continuous variables.

Count (column %) for categorical variables.

[†]N missing values for body mass index = 8,780; HbA1c = 9,371; Systolic blood pressure = 6,853; diastolic arterial pressure = 6,852; mean arterial pressure = 6,862; triglycerides = 33,122; total cholesterol = 10,746; HDL-cholesterol = 21,188; LDL-cholesterol = 36,125.

Compared with the base model (age, sex, and ethnicity, Supplementary Table E.2), the addition of all routinely collected DESP variables significantly added information to the models, leading to improvements in model performance with further addition of covariates (Table 6.9). Supplementary Tables E.15 to E.20 show multivariable fractional polynomial model regression coefficients and corresponding standard errors.

Calibration and discrimination

Apparent validation, model baseline survival probability and variable transformations are shown in Supplementary Table E.23. Optimism-adjusted calibration slope (0.988-0.998), concordance (0.560-0.807) and R^2 (0.008-0.150) statistics were reasonable in all but the base model (Table 6.9, see Supplementary Table E.2 for a visualisation of variables tested and included in final models). Graphical inspection of all models revealed good calibration (Figure 6.7.

Table 6.9: Optimism adjusted model performance (95% CI) for prediction of sight-threatening diabetic retinopathy.

Model	Metric
Medication use model	8785/120732
C-statistic	0.807 (0.803-0.810)
Slope	0.993 (0.960-1.000)
R-squared	0.150 (0.146-0.162)
Clinical measures model	8785/120732
C-statistic	0.805 (0.801-0.808)
Slope	0.998 (0.996-1.000)
R-squared	0.147 (0.144-0.150)
Medical history model	8785/120732
C-statistic	0.804 (0.801-0.806)
Slope	0.998 (0.996-0.999)
R-squared	0.147 (0.144-0.151)
Diabetic eye screening + HbA1c model	9314/128219
C-statistic	0.804 (0.801-0.806)
Slope	0.993 (0.962-1.000)
R-squared	0.149 (0.144-0.162)
Diabetic eye screening model	10193/137590
C-statistic	0.774 (0.771-0.777)
Slope	0.999 (0.995-1.002)
R-squared	0.116 (0.113-0.119)
Base model	10193/137590
C-statistic	0.560 (0.556-0.563)
Slope	0.988 (0.968-1.007)
R-squared	0.008 (0.008-0.008)

All estimates calculated with bootstraping (B=150) for each model.

Models adjust for the following variables. Base model: age, sex, and ethinicity; DESP model: age, ethinicity, diabetic retinopathy severity, type of diabetes, duration of diabetes, index of multiple deprivation; DESP + HbA1c model: as DESP model plus HbA1c; Medical history model: as DESP + HbA1c model plus sex, chronic kidney disease, stroke, and smoking history; Clinical measures model: as DESP + HbA1c model plus sex, chronic kidney disease, myocardial infarction, stroke, smoking history, body mass index, mean arterial pressure, total cholesterol, and LDL-C/HDL-C; Medication use model: as DESP + HbA1c model plus sex, chronic kidney disease, smoking history, body mass index, mean arterial pressure, total cholesterol, insulin use, non-insulin hypoglycaemics use, alpha blocker use, and diuretics use.

Risk groups showed a clear separation in event distribution when DESP variables were included (Figure 6.8). Models captured between 23.5% to 68.4% of incident STDR cases in the top risk quintile distribution (Table 6.10).

Table 6.10: Risk between highest vs lowest predicted risk quintile for sight-threatening diabetic retinopathy defined by 95% CIs. Number (percent) of events captured in the highest risk quintile shown in last column.

Model	Relative Risk	Risk Difference	Events in highest risk quintile
Medication use	17.88 (16.32-19.87)	27.83 (28.27-27.39)	6011/8785 (68.4%)
Clinical measures	17.42 (15.92-19.31)	27.55 (27.98-27.11)	5957/8785 (67.8%)
Medical history	17.13 (15.72-18.90)	27.49 (27.91-27.06)	6309/9314 (67.7%)
DESP + HbA1c	17.27 (15.84-19.08)	27.49 (27.92-27.07)	6306/9314 (67.7%)
DESP data	12.57 (11.71-13.61)	26.18 (26.55-25.80)	6606/10193 (64.8%)
Base model (Age and Ethnicity)	1.86 (1.83-1.88)	5.57 (5.70-5.44)	2395/10193 (23.5%)

DESP, diabetic eye screening programme.

Clinical usefulness

Decision curve analysis focusing on an operating threshold between 5-30% for intensive glucose, blood pressure, and metabolic control, showed clinical utility over the entire threshold range (Figure 6.9) with net benefits ranging from 14-56 per 1000

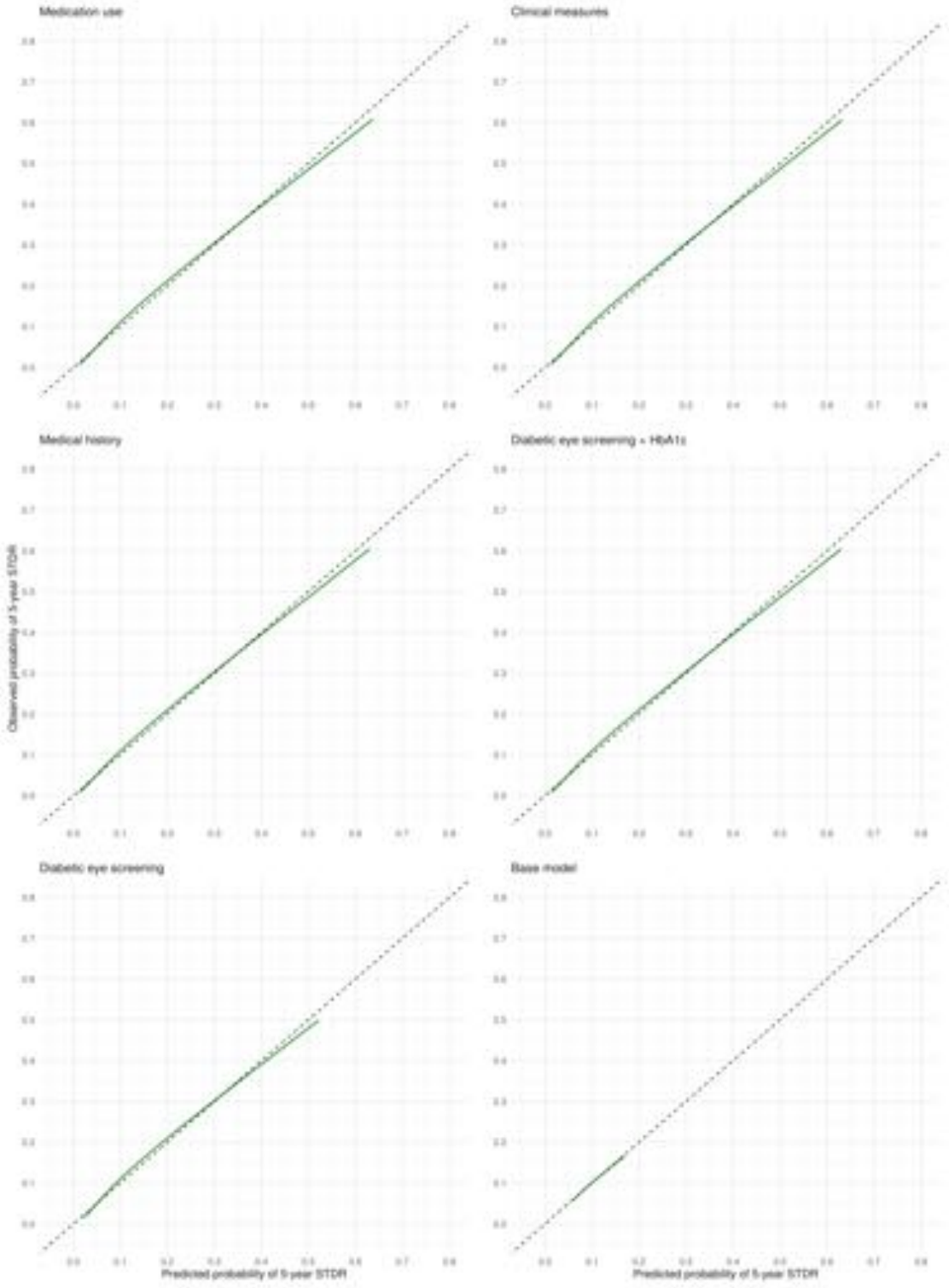


Figure 6.7: Graphical performance for predicting sight-threatening diabetic retinopathy (STDR) within 5-years.

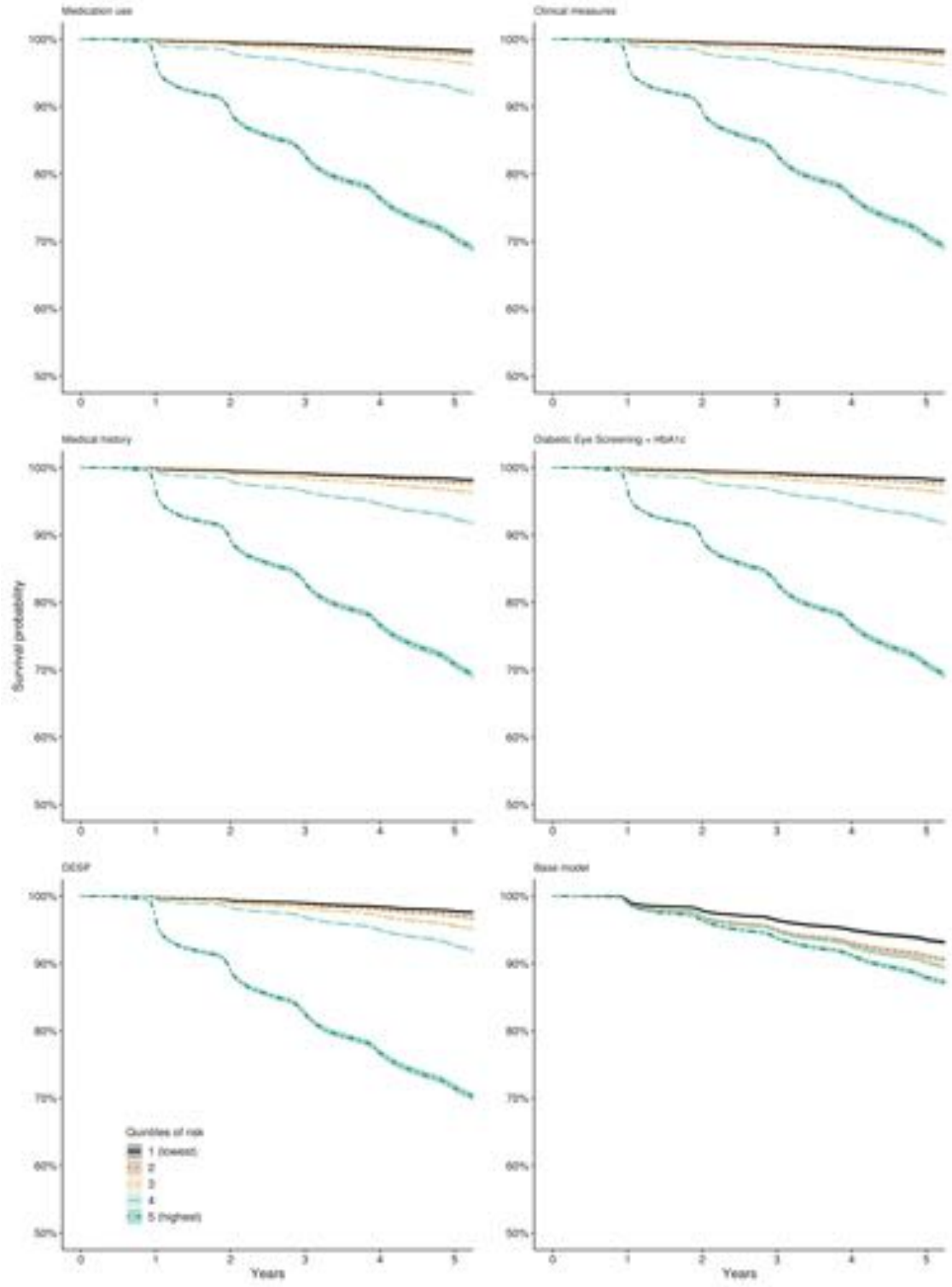


Figure 6.8: Quintiles of predicted risk for sight-threatening diabetic retinopathy (STDR) within 5-years.

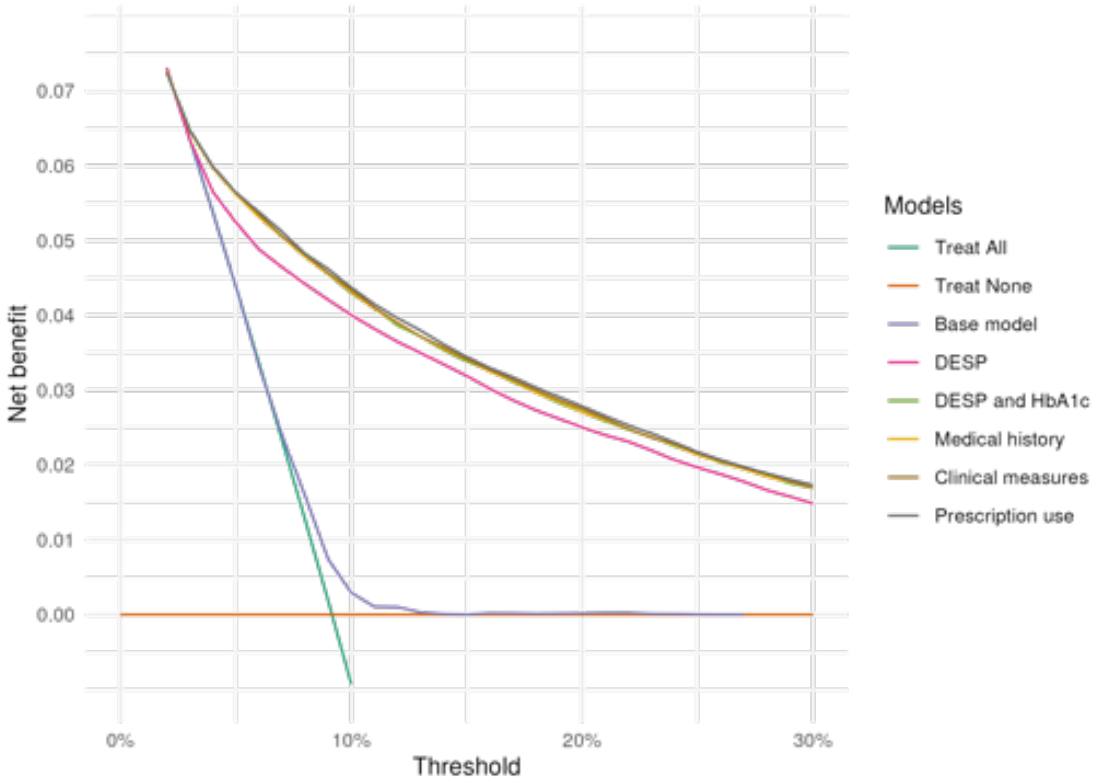


Figure 6.9: Decision curve analysis for STDR models.

people with diabetes (excluding the base model, see Table 6.11). At a 10% threshold probability the benefit between the model with greater complexity (medication history model) vs the pragmatic DESP + HbA1c model was of only one additional true positive (0.7) per 1000 people with diabetes. If we were to extrapolate the DESP + HbA1c model net benefits using a preference (risk threshold) ranging from 5 to 10% to a cohort of 130,000 people with diabetes, a net benefit (i.e. true positives without incurring in any other type of harm from false positives) ranging from 5,590 to 7,306 would be expected.

Table 6.11: Net benefit per 1000 people with diabetes by threshold probability.

Model	**5%**	**10%**	**20%**	**30%**
Prescription use	56.4	43.7	27.8	17.3
Clinical measures	56.4	43.4	27.5	16.9
Medical history	56.2	43.1	27.1	16.9
DESP and HbA1c	56.2	43.0	27.1	16.9

Table 6.11: Net benefit per 1000 people with diabetes by threshold probability.

Model	5%	10%	20%	30%
DESP	52.4	40.0	25.0	14.8
Base model	43.8	2.9	0.2	0.0

Sensitivity analysis

Restricting internal validation to people <65 years of age did not materially alter the model performance (Supplementary Table E.27, Supplementary Figure E.2).

6.5 Discussion

I have developed, and rigorously assessed, principled prediction models using 1,268,227 and 740,067 patient-years of observational data for prediction of all-cause mortality and STDR, respectively. I have assessed the predictive contribution of routinely collected DESP, primary, and secondary care-derived variables to model performance. Risk models for all-cause mortality and STDR showed that DR grades, and variables from routinely collected DESP data, medical history, clinical measures, and medication history significantly contributed to risk prediction. Predictions of both outcomes using variables from all available data sources (i.e. routinely collected DESP data, targeted medical history, targeted clinical measures, and targeted medication use history) yielded the highest performance in terms of C-statistic, R^2 (Tables 6.3, 6.9), and largest net benefits (Figure 6.5, 6.9). The followed modelling strategy suggest promising pathways for identification of people at risk of STDR with good discrimination, calibration, and clinical utility when using a parsimonious model with routinely collected DESP data and HbA1c measures. For all-cause mortality, comprehensive model assessment and sensitivity analyses, evidenced a strong effect of age. Despite high performance metrics (calibration, discrimination) and clinical utility overall, net benefits observed on the working-age population (<65 years) showed a significant decline which would not justify clinical

utility for the population that would benefit the most from early interventions (Supplementary Figure E.1, Supplementary Table E.26).

All-cause mortality prediction

Optimism-adjusted discrimination (C-statistic) ranged from 0.806 to 0.831 in males, and 0.817 to 0.841 in females (Table 6.3). Models to predict all-cause mortality exist in the literature and include the ENFORCE model, the RECODe model, and a model by Chang et al[193–195]. These models include covariates which are mainly demographic, blood pressure, blood lipid-related, or renal variables. In external validation, they have showed acceptable to good discrimination with C-statistics, comparable to my study, of 0.75–0.82 (ENFORCE), 0.71–0.81 (RECODe), and 0.69 (Chang et al).[193–197] Of note, only the study by Chang and colleagues[195] reported optimism-corrected performance metrics. Compared with a UK Biobank study of 22,579 people with diabetes in which traditional (Cox) and machine learning models for all-cause mortality were developed,[198] the achieved C-statistics were higher in my work with strong internal validation (Table 6.3). The best performing model developed by Zhang et al.[198] (DeepHit) achieved a C-statistic of 0.92 (training) and 0.73 (validation). Cox PH models achieved 0.72 and 0.71 C-statistics in training and validation datasets, respectively, suggesting overfitting from machine learning models.

A recent scoping review of prediction models for diabetes complications identified 40 models for all-cause mortality prediction out of which 39 studied people with type 2 diabetes and none studied only people with type 1 diabetes.[199] The cohort used for development of these models includes a large proportion of people with diabetes type 1 (n=7,937 for all-cause mortality analysis, and n=5,130 for the STDR analysis).

I have shown that the addition of DR severity at baseline significantly contributes to all-cause mortality prediction in all modelling strategies (Supplementary Table E.1). Associative studies have found inconsistent DR associations with all-cause mortality which are no longer significant after adjusting for established risk

factors, comorbidities, or after using all steps from DR classification systems.[200–202] In the context of DES, information captured by DR severity or by fundus images poses advantages for risk stratification and for exploration of artificial intelligence feature extraction for prediction of adverse patient outcomes.[132,203,204]

6.5.1 Sight-threatening diabetic retinopathy prediction

A parsimonious model for STDR including routinely collected DESP data and HbA1c at baseline showed a good discrimination, calibration, and clinical utility (Tables 6.9, 6.11)). A recent literature review identified a total of 20 models predicting the risk of retinopathy (n=19/20) and blindness (n=1/20) up to 2022. Of the models that reported performance, models were well calibrated in internal and external validation, however, few showed good discrimination in internal (n=5/12) and external validation (n=2/6) with C-statistics ranging from 0.630 to 0.918.[199] My approach showed that good calibration and discrimination in all models with justifiable net benefits which can be considered for health economic analyses and clinical implementation. A gradual increase in performance with the introduction of additional covariates was seen, and can be a reflection of the statistical power available in this dataset, and of the complexity of diabetes. When compared with the parsimonious DESP + HbA1c model, the better performing model (medication history model, Tables E.2, 6.9) showed a 0.003 unit gain in C-statistic, and almost an extra net benefit unit (0.7 at the 10% probability threshold, Table 6.11). The predictive performance of adding HbA1c to routinely collected and readily available variables from diabetic eye screening (age, sex, ethnicity, type and duration of diabetes, and index of multiple deprivation) is relevant for patient-risk stratification at the point of care and should be stressed given data availability.

6.5.2 Implications for patient care

While the risk of micro and macrovascular adverse events in people with diabetes is higher than in the general population, the risk and time to event differs from person to person. Evidence from landmark diabetes trials has shown that both improved

glucose and blood pressure control reduce the risk of all-cause mortality[66,191,205,206] and STDR.[50,51] There is a well described legacy protective effect associated with intensive glucose control long after the cessation of interventions in patients with type 1 and type 2 diabetes.[190,191] In the UKPDS, a 1% reduction in HbA1c conferred a 31% reduction in risk of retinopathy and a 10mmHg reduction in systolic blood pressure conferred an 11% reduction in risk of photocoagulation or vitreous haemorrhage.[207] A 17% (p=0.01) and 13% (p=0.007) relative reductions in risk for diabetes-related death and all-cause mortality have been reported to persist after interventions for over 10-years in the UKPDS study, respectively.[191] And intensive multifactorial interventions (renin-angiotensin blockers, aspirin, lipid-lowering agents, and behavioural modifications) have shown reductions in all-cause mortality in people with diabetes type 2 (HR 0.54, 95%CI 0.32-0.89).[205] In this context, the first contact of people with diabetes in diabetic eye screening represents a crucial moment in diabetes care. By efficiently identifying people at high risk of complications individualised secondary preventive measures can be enhanced to improve quality of life and optimise healthcare resources. "Time is outcomes" and the earlier we achieve effective risk stratification, the wider the window of opportunity to benefit individuals. Further work will be necessary to externally validate current models, and to conduct health economic analyses for targeted intervention of people at high-risk.

6.5.3 Strengths and limitations

This study has several strengths. First and notably, I have leveraged a large contemporary sociodemographically diverse cohort of people with diabetes including groups not routinely included in prediction model development (e.g. South Asian, Black ethnic groups, and people with both type 1 and type 2 diabetes). Second, the availability of quality-assured multilevel DR severity grading with a 7-step classification system is unique on diabetes research at this scale. Third, primary and secondary care record linkage allowed for inclusion of major risk factors to be included in the prediction models. Lastly, predictions from these models can

inform, early in the course of diabetes, about the need for personalised intensive approaches for control of modifiable risk factors.

My study limitations follow. First, causes of death and STDR outcomes after referral to eye hospital services were not assessed, and warrant exploration in future work. Second, diabetes-related complications such as peripheral neuropathy and ulceration, which can impact patient outcomes, were not included in model development. Nevertheless, the pragmatic approach followed, grounded in domain knowledge and the inclusion of major risk factors with robust internal validation, provides reliable model performance estimates. Third, external validation can be informative for confirming generalisability. Although larger cohorts can provide greater statistical power, the cohort's diversity and rich clinical characterisation make it a valuable resource for prognostic research in people with diabetes. Lastly, the English universal healthcare system setting may limit comparisons with populations where access to care, treatment availability, and diabetic eye screening practices differ.

6.5.4 Conclusion

With more than 170 thousand people with a varied sociodemographic profile, structured multilevel DR severity grading, and linkage of risk factors, I have shown prediction modelling strategies which may be useful tools for integration in clinical pathways. A parsimonious model using routinely collected DESP data plus HbA1c measures showed promise to improve patient outcomes. Through comprehensive performance assessment, I have identified developed prediction models for all-cause mortality not clinically useful given the population in the young age groups would be the ones who could benefit from intensive control of modifiable risk factors. Further work reviewed in Chapter 7 is needed to introduce additional diabetes complications (e.g. diabetic neuropathy, diabetic foot/ulceration) and retinal fundus imaging-derived metrics in the model development pipeline, to demonstrate model generalisability, and to assess cost-effectiveness of intensive glucose and blood pressure monitoring in people at high-risk.

Part IV

Summary and future research

7 Summary and future research

The work in this thesis leveraged routinely collected diabetic eye screening (DES) and electronic health record (EHR) data to provide insights in the life course of diabetes from diagnosis to development of complications, posing potential utility to address the rising burden of diabetes complications. While the primary focus was on sight-threatening diabetic retinopathy (STDR) and all-cause mortality, the curated dataset and methodology resulting from this work offer a resource of paramount importance for future research.

This section summarises results from Chapters 3 to 6, emphasising their implications for diabetes care and broader application beyond visual outcomes. I finalise by briefly outlining avenues for future research, expanding on the groundwork established in this thesis.

7.1 Summary of main findings

7.1.1 Visual impairment in patients with diabetes and diabetic retinopathy at hospital eye services

A seminal paper from Liew and colleagues[29] reported that, according to CVI data, diabetic retinopathy (DR) was no longer the leading cause of blindness in the UK from at least 2010 onwards. In Chapter 3 I explored the certification of

visual impairment (CVI) rate in patients with DR and visual impairment reviewed at Hospital Eye Services (HES). I have shown that relying on CVI data alone significantly underestimates visual impairment in people with DR. A total of 84% of CVI elegible patients were not registered over the duration of follow-up. This is of significant importance for patient counseling, public health, and resource allocation.

These results emphasise that visual impairment in patients with DR remains a major public health issue, underscoring the need for improved epidemiological surveillance and rigorous methods to guide public policy and resource allocation in diabetes-related blindness prevention. Findings from this work were disseminated locally at Moorfields Eye Hospital in a departmental meeting, published in a peer review journal,[208] and presented in the Royal College of Ophthalmologists annual meeting in 2024 as part of a dedicated CVI session.

7.1.2 Sociodemographic determinants of attendance to diabetic eye screening

In Chapter 4 I conducted a contemporary analysis of over 84 thousand people invited for DES to explore determinants of attendance. Despite preconceptions that people of non-white ethnic groups are more likely to miss their DES appointments,[153,159,160] I have shown that people of mixed and black ethnic groups have similar attendance rates. Chinese, south Asian and any other Asian ethnic groups were more likely to attend when compared with white people. Importantly, I showed how younger people show higher odds of missing their annual DES appointments.

This work shows how, in an established well run DES programme (DESP), uptake of people with diabetes is not negatively impacted by ethnic background. How age is a relevant factor to take into consideration in this group of people, and how deprivation, measured with the Index of Multiple Deprivation (IMD), can capture ingrained inequalities, even in a universal healthcare setting as the National Health Service (NHS). My work resulted in a peer reviewed publication.[209]

7.1.3 Ethnic disparities in progression rates of sight-threatening diabetic retinopathy in diabetic eye screening

Given a need of contemporary information on STDR progression rates in subgroups of the population which are not adequately represented in diabetes research in the UK (non white ethnic groups, people with type 1 diabetes, people with high deprivation), I leveraged a large sociodemographically diverse cohort of over 130 thousand people with type 1 and type 2 diabetes to provide STDR transition probabilities (Chapter 5). Diabetic retinopathy severity at baseline, ethnicity, and age were strongly associated with clinical outcomes (Section 5.4.3, Table 5.3). People with non-STDR in both eyes, younger age groups, and non-white ethnicities showed greater STDR incidence rates. These findings showed a clear risk stratification with variables routinely collected and available at a single DES visit (Figures 5.1, 5.2). A web-based tool to inform on simple risk stratification following the methods of this manuscript was developed and can be accessed here. This piece of work provided incidence rates for the development of STDR which update transition probabilities previously provided from landmark trials where the baseline DR severity was much worse that what health professionals would most frequently face in DESPs or clinics. Moreover, the transition probabilities are useful for future sample size calculation for clinical trials and inform health economic models. These findings were disseminated in a peer reviewed publication.[210]

From October 2023, the UK National Screening Committee recommended biennial screening among people living with diabetes (PLD) with no DR on two consecutive screening visits, as the risk of progression to referable was considered low (~0.7% per year) and cases would still be treatable if delayed.[76] In Section 5.4.5 I have shown that the evidenced sociodemographic disparities evidenced in the general population lead to different rates of STDR progression in people who would be eligible for biennial DES. Simulating biennial screening using observed, rather than modelled data, I report a possible delay of at least 1 year in the diagnosis of 56% of STDR and 43% of proliferative DR cases. This manuscript was published in a peer reviewed journal,[211] with a commentary,[212] and received media coverage.

7.1.4 Prediction of diabetes complications at point of diabetic eye screening, a streamlined approach to individualised preventive care

Between 2000 and 2020, a total of 26/78 studies reported 51/260 risk prediction models for all-cause mortality and STDR/blindness in people with diabetes.[92] Nevertheless, studies have primarily included older people with type 2 diabetes of white ethnic background.[92,200] In Chapter 6 I have leveraged a large diverse cohort of people with diabetes to develop prediction models for all-cause mortality and STDR. This is one of the largest data sources of unprecedented scale which has allowed for model development and robust assessment of performance.

Calibration, discrimination, and clinical utility showed improvements (Table 6.3, 6.9) with incremental addition of available variables (Supplementary Tables E.1, E.2). Given the sociodemographic differences in STDR progression rates shown in Chapter 5, and the robust evidence in reduction of death, and micro and macrovascular complications of diabetes with multifactorial interventions including glucose, blood pressure control[63,66,190–192,206] and behavioural modifications,[205] I developed risk prediction models which adequately represent people of diverse ethnic backgrounds, and diverse levels of deprivation of both, type 1 and type 2 diabetes.

For STDR, a model which includes routinely collected DESP + HbA1c data (age, sex, ethnicity, type and duration of diabetes, index of multiple deprivation, and HbA1c) showed similar performance and clinical utility when compared with the most complex model which included targeted medical history, other clinical and laboratory measures, and medication history (Table 6.9, 6.11). For all-cause mortality, all models showed high performance metrics and clinical utility, however, testing the developed models in people younger than 65 reduced the clinical utility of the current modelling strategies. By doing this, I have shown the strong effect of age on prediction of all-cause mortality, and evidence on the modelling strategies for this outcome emphasise on the importance of comprehensive performance assessment with clinical utility and sensitivity analyses.

7.2 Future research

I am co-leading efforts to enrich the created data base with ophthalmic EHR linkage. People with STDR referred to hospital eye services (namely Moorfields Eye Hospital and Whipps Cross Eye Unit) will contribute data to the existing dataset. Moreover, as a result of collaborative efforts causes of death are being extracted. Ophthalmic EHR linkage will enhance prediction models by improving STDR outcome definitions (including diabetes-related interventions such as pan-retinal photocoagulation, macular laser, and/or intravitreal anti-VEGF injections). Causes of death will similarly allow for development of significant disabling and life-threatening diabetes complications such as myocardial infarction and stroke.

Further diabetes complications will be identified using SNOMED and ICD-10 codes to improve model development. I will use retinal fundus images will be used as part of machine learning algorithms (end-to-end and feature extraction approaches) to assess their contribution to prediction of diabetes complications. In the short term, all-cause mortality model development will be restricted to people of working age population to improve identification of people at risk of death who would benefit from targeted interventions modifying risk factors. Considering the major contributions to medical research derived from the UK Biobank (over 500,000 participants enrolled and an estimated 7% prevalence of diabetes),[213] the size, characteristics, phenotyping, and potential for genotyping of the contemporary curated dataset from the North East London DESP presented here offer a focused, powerful resource for diabetes research.

I aim to implement prediction tools to assist clinical decision making which allow the delivery of personalised medicine in people with diabetes to improve patient outcomes.

7.3 Conclusion

I have demonstrated how visual impairment remains being highly prevalent in people with DR.[208] This work provides crucial insights into diabetes care, from

identification of factors associated to DES non-attendance,[209] sociodemographic disparities in STDR progression rates,[214] the potential inequalities in the delivery of a "one-size fits all" measure of biennial DES,[211] and presents a parsimonious model for prediction of STDR with good performance and clinical utility. The large dataset with adequate representation of subgroups of the population with detailed characterisation which has being used for this thesis represents a resource of unprecedented power for diabetes research and has the potential to improve patient outcomes through secondary prevention.

Supplementary materials

Appendices

A

University College London Doctoral School Research Images as Art Competition 2021/2022

Figure A.1: The doors of perception. Cataracts are a clouding of the naturally transparent lens of the eye and are amongst the leading causes of blindness worldwide. Cataract surgery is one of the most common performed surgeries in the world. During surgery, patients may experience unique visual phenomena which may be perceived as pleasant or distressing. Few actual visual representations of these experiences are available in the literature. The image shows 45 digitised drawings donated by 38 patients who experienced visual perceptions during their cataract surgery. The result is a unique piece of artwork which represents a resource of importance for pre and postoperative patient counselling in ophthalmology.

B

Visual impairment in patients with diabetes and diabetic retinopathy at hospital eye services

B.1 Supplementary tables

Table B.1: Causes of Certification of Visual Impairment (CVI).

Characteristic	Left eye cause, N = 68	Right eye cause, N = 68
Primary cause for CVI		
Retina - diabetic retinopathy	30 (44%)	29 (43%)
Neurological - cerebrovascular disease	8 (12%)	7 (10%)
Glaucoma - primary open angle	5 (7.4%)	9 (13%)
Lens - cataract (excludes congenital)	5 (7.4%)	5 (7.4%)
Glaucoma - secondary	6 (8.8%)	3 (4.4%)
Retina - age-related macular degeneration - atrophic / geographic macular atrophy	4 (5.9%)	4 (5.9%)
Cornea - corneal scars and opacities	3 (4.4%)	3 (4.4%)
Missing	1 (1.5%)	3 (4.4%)
Neurological - optic atrophy	2 (2.9%)	2 (2.9%)
Retina - retinal vascular occlusions	2 (2.9%)	2 (2.9%)
Retina - hereditary retinal dystrophy	1 (1.5%)	1 (1.5%)
Retina - age-related macular degeneration - subretinal neovascularisation	1 (1.5%)	0 (0%)

Count and column percentages (%).

Table B.2: Characteristics of patients excluded.

Characteristic	Overall, N = 5,350	No visual impairment, N = 4,981	Visual impairment, N = 369
Age	66, (16)	65, (16)	76, (15)
Sex			
Female	2,355 (44%)	2,140 (43%)	215 (58%)
Male	2,995 (56%)	2,841 (57%)	154 (42%)
Ethnicity			
White	656 (12%)	610 (12%)	46 (12%)
South Asian	998 (19%)	907 (18%)	91 (25%)
Black	475 (8.9%)	423 (8.5%)	52 (14%)
Other	1,219 (23%)	1,127 (23%)	92 (25%)
Missing	2,002 (37%)	1,914 (38%)	88 (24%)
Type of diabetes			
Type 2 DM	3,430 (64%)	3,177 (64%)	253 (69%)
Type 1 DM	334 (6.2%)	324 (6.5%)	10 (2.7%)
Missing	1,586 (30%)	1,480 (30%)	106 (29%)
Baseline DR grade			
Missing	1,426 (27%)	1,307 (26%)	119 (32%)
Non-STDR	1,148 (21%)	1,086 (22%)	62 (17%)
R0M0	908 (17%)	810 (16%)	98 (27%)
STDR	1,868 (35%)	1,778 (36%)	90 (24%)
Died during study period	267 (5.0%)	267 (5.4%)	0 (0%)

Mean (SD) for age and number (column %) for categorical variables.

In addition to these, there were 7 extra cases with missing age and sex (not shown in this table).

DM; diabetes mellitus, DR; Diabetic retinopathy, STDR; sight-treathening diabetic retinopathy

Table B.3: Treatment among cohort during study period.

		Visual impairment		Certification of visual impairment	
Characteristic	**Overall, N = 8,007**	**No, N=7,682**	**Yes, N=325**	**No, N=7,939**	**Yes, N=68**
Treatment					
Combination treatment	225 (2.8%)	210 (2.7%)	15 (4.6%)	220 (2.8%)	5 (7.4%)
Intravitreal injections	864 (11%)	805 (10%)	59 (18%)	848 (11%)	16 (24%)
Laser	171 (2.1%)	160 (2.1%)	11 (3.4%)	167 (2.1%)	4 (5.9%)
No DR treatment	6,747 (84%)	6,507 (85%)	240 (74%)	6,704 (84%)	43 (63%)

Count (column %).

Table B.4: Visual impairment and certification of blindess by sex and working age bands.

	Visual impairment			Certification of visual impairment		
Characteristic	**Overall, N = 325**	**Female, N = 175**	**Male, N = 150**	**Overall, N = 68**	**Female, N = 37**	**Male, N = 31**
Age band						
20 to 64	69 (21%)	28 (16%)	41 (27%)	23 (34%)	11 (30%)	12 (39%)
>= 65	256 (79%)	147 (84%)	109 (73%)	45 (66%)	26 (70%)	19 (61%)

Count (column %).

C

Sociodemographic determinants of attendance to diabetic eye screening

C.1 Supplementary tables

Table C.1: Crude odds ratios defined by 95% confidence interval for attendance vs non-attendance to diabetic eye screening.

Characteristic	OR (95% CI)	p-value
Age categories		
46-60 years	1.00	
12-17 years	0.73 (0.57, 0.95)	**0.016**
18-30 years	0.36 (0.32, 0.40)	**1.2e-75**
31-45 years	0.66 (0.62, 0.70)	**3.8e-51**
61-75 years	1.24 (1.18, 1.30)	**2.8e-20**
76-90 years	1.02 (0.97, 1.08)	0.461
>90 years	0.57 (0.47, 0.68)	**1.4e-09**
Sex		
Male	1.00	
Female	1.02 (0.98, 1.06)	0.323
Type of diabetes		
Type 2	1.00	
Type 1	0.55 (0.51, 0.60)	**3.3e-41**
MODY	0.78 (0.40, 1.72)	0.508
Not specified	0.1 (0.10, 0.11)	**<1.0e-200**
Duration of diabetes		
0 to < 11 years	1.00	
11 to <20 years	1.23 (1.18, 1.28)	**2.3e-20**
>20 years	1.01 (0.94, 1.09)	0.743
Missing	0.02 (0.02, 0.03)	**<1.0e-200**
Visual acuity		
6/6 to 6/9	1.00	

Crude odds ratios (OR) for all variables shown in the table (OR > 1.00 mean greater odds of attendance).

CI; Confidence interval, MODY; maturity onset diabetes of the young, PTAL; public transport accesibility level, IMD; index of multiple deprivation.

Bold p-values show statistically significant results.

Table C.1: Crude odds ratios defined by 95% confidence interval for attendance vs non-attendance to diabetic eye screening.

Characteristic	OR (95% CI)	p-value
Better than 6/6	0.93 (0.88, 0.98)	**0.007**
Worse than 6/9 to 6/18	0.65 (0.60, 0.72)	**9.6e-21**
Worse than 6/18	0.43 (0.37, 0.51)	**4.8e-24**
Years of registration		
0 to <5 years	1.00	
5 to <10 years	1.32 (1.27, 1.38)	**1.6e-38**
10 to <15 years	1.41 (1.34, 1.47)	**6.6e-47**
15 to 20 years	2.05 (1.53, 2.81)	**3.7e-06**
Distance to screening centre		
0 to 2km	1.00	
<2 to 5km	0.91 (0.87, 0.95)	**3.1e-05**
>5 to 8km	0.8 (0.70, 0.92)	**0.001**
>8km	0.6 (0.46, 0.81)	**6.4e-04**
Unknown	0.74 (0.64, 0.87)	**1.1e-04**
PTAL tertiles		
3rd (Best)	1.00	
1st (Worst)	0.95 (0.90, 1.01)	0.083
2nd	0.96 (0.91, 1.02)	0.192
Ethnicity		
White British	1.00	
Mixed	0.77 (0.67, 0.90)	**5.7e-04**
Black	1.07 (1.01, 1.13)	**0.014**
South Asian	1.29 (1.24, 1.35)	**2.9e-30**

Crude odds ratios (OR) for all variables shown in the table (OR > 1.00 mean greater odds of attendance).

CI; Confidence interval, MODY; maturity onset diabetes of the young, PTAL; public transport accesibility level, IMD; index of multiple deprivation.

Bold p-values show statistically significant results.

Table C.1: Crude odds ratios defined by 95% confidence interval for attendance vs non-attendance to diabetic eye screening.

Characteristic	OR (95% CI)	p-value
Chinese	1.94 (1.50, 2.56)	**1.0e-06**
Any other Asian background	1.62 (1.48, 1.77)	**1.9e-26**
Any other Ethnic group	1.08 (0.97, 1.20)	0.145
Unknown	0.16 (0.14, 0.18)	**1.4e-193**
IMD quintiles		
1 (most deprived)	1.00	
2	1.12 (1.07, 1.17)	**1.6e-07**
3	1.23 (1.16, 1.30)	**9.8e-13**
4	1.27 (1.17, 1.38)	**1.9e-08**
5 (least deprived)	1.3 (1.13, 1.49)	**2.4e-04**

Crude odds ratios (OR) for all variables shown in the table (OR > 1.00 mean greater odds of attendance).

CI; Confidence interval, MODY; maturity onset diabetes of the young, PTAL; public transport accesibility level, IMD; index of multiple deprivation.

Bold p-values show statistically significant results.

D

Ethnic disparities in progression rates of sight-threatening diabetic retinopathy in diabetic eye screening

D.1 Supplementary tables

Table D.1: Incidence rates of sight-threatening diabetic retinopathy per 100 person-years by follow-up period with 95% confidence intervals.

Characteristic	0-1yr	1-2yr	2-3yr	3-4yr	4-5yr	5-10yr
Overall	0.86 (0.82 - 0.90)	2.18 (2.11 - 2.24)	2.09 (2.03 - 2.16)	2.26 (2.19 - 2.34)	2.48 (2.39 - 2.57)	3.10 (2.99 - 3.20)
Age groups						
Less than 45 years	0.90 (0.81 - 0.99)	2.38 (2.23 - 2.53)	2.39 (2.22 - 2.56)	2.82 (2.62 - 3.01)	3.32 (3.09 - 3.55)	4.89 (4.58 - 5.20)
45 to <55 years	0.86 (0.78 - 0.95)	2.29 (2.15 - 2.43)	2.26 (2.12 - 2.41)	2.25 (2.09 - 2.40)	2.85 (2.66 - 3.03)	3.49 (3.26 - 3.71)
55 to <65 years	0.85 (0.77 - 0.93)	2.04 (1.91 - 2.17)	1.94 (1.81 - 2.08)	2.07 (1.92 - 2.22)	2.00 (1.85 - 2.15)	2.54 (2.35 - 2.72)
65 years and over	0.84 (0.77 - 0.91)	2.06 (1.94 - 2.18)	1.90 (1.78 - 2.01)	2.09 (1.96 - 2.23)	2.08 (1.93 - 2.22)	2.28 (2.11 - 2.45)
Sex						
Female	0.78 (0.72 - 0.84)	2.00 (1.91 - 2.09)	2.02 (1.92 - 2.12)	2.15 (2.04 - 2.26)	2.29 (2.17 - 2.41)	2.89 (2.74 - 3.04)
Male	0.93 (0.87 - 0.99)	2.33 (2.24 - 2.42)	2.16 (2.06 - 2.26)	2.36 (2.25 - 2.47)	2.65 (2.53 - 2.77)	3.29 (3.14 - 3.44)
Ethnicity						
White	0.76 (0.69 - 0.82)	1.80 (1.70 - 1.90)	1.76 (1.66 - 1.87)	1.92 (1.80 - 2.04)	1.87 (1.75 - 2.00)	2.37 (2.21 - 2.52)
South Asian	0.85 (0.78 - 0.92)	2.28 (2.16 - 2.39)	2.12 (2.00 - 2.23)	2.40 (2.27 - 2.53)	2.74 (2.59 - 2.89)	3.62 (3.43 - 3.80)
Black	1.08 (0.97 - 1.19)	2.75 (2.56 - 2.93)	2.63 (2.44 - 2.82)	2.59 (2.38 - 2.80)	3.05 (2.81 - 3.29)	3.65 (3.36 - 3.93)
Any other Asian	0.84 (0.67 - 1.01)	2.26 (1.98 - 2.54)	2.04 (1.76 - 2.33)	2.57 (2.23 - 2.91)	2.87 (2.49 - 3.25)	2.80 (2.40 - 3.21)
Other	1.07 (0.80 - 1.34)	1.81 (1.46 - 2.16)	2.39 (1.96 - 2.83)	2.16 (1.72 - 2.61)	2.53 (2.02 - 3.05)	3.46 (2.81 - 4.11)
Mixed	0.75 (0.41 - 1.09)	1.98 (1.42 - 2.54)	2.65 (1.95 - 3.36)	3.00 (2.17 - 3.83)	3.44 (2.46 - 4.42)	3.31 (2.25 - 4.37)
Chinese	1.16 (0.59 - 1.73)	2.13 (1.35 - 2.92)	2.29 (1.42 - 3.16)	1.41 (0.67 - 2.15)	1.44 (0.64 - 2.24)	1.56 (0.66 - 2.46)

Table D.1: Incidence rates of sight-threatening diabetic retinopathy per 100 person-years by follow-up period with 95% confidence intervals.

Characteristic	0-1yr	1-2yr	2-3yr	3-4yr	4-5yr	5-10yr
Unknown	0.91 (0.57 - 1.26)	4.18 (3.36 - 5.00)	5.20 (3.88 - 6.51)	3.77 (2.03 - 5.51)	4.06 (1.73 - 6.39)	2.02 (-0.10 - 4.15)
Baseline DR grade						
No retinopathy	0.21 (0.19 - 0.23)	0.70 (0.66 - 0.74)	0.83 (0.78 - 0.88)	1.08 (1.02 - 1.14)	1.51 (1.43 - 1.59)	2.30 (2.20 - 2.40)
Retinopathy in one eye	1.23 (1.10 - 1.37)	3.63 (3.40 - 3.87)	3.79 (3.53 - 4.05)	4.61 (4.31 - 4.92)	4.33 (4.01 - 4.65)	5.05 (4.68 - 5.42)
Retinopathy in both eyes	6.04 (5.69 - 6.39)	14.48 (13.94 - 15.03)	12.79 (12.21 - 13.37)	11.57 (10.95 - 12.19)	10.75 (10.08 - 11.41)	9.30 (8.61 - 9.99)

Table D.2: Sensitivity analysis using incidence rate of referable diabetic retinopathy per 100 person-years by follow-up period defined by 95% confidence intervals. People from the earliest 2 years of study period were excluded.

Characteristic	0-1yr	1-2yr	2-3yr	3-4yr	4-5yr	5-8yr
Overall	0.65 (0.60 - 0.71)	1.65 (1.56 - 1.74)	1.56 (1.46 - 1.66)	1.69 (1.57 - 1.81)	2.37 (2.21 - 2.54)	2.99 (2.76 - 3.22)
Age groups						
Less than 45 years	0.88 (0.76 - 1.01)	1.98 (1.79 - 2.17)	1.92 (1.71 - 2.13)	2.31 (2.04 - 2.57)	3.34 (2.97 - 3.72)	3.87 (3.36 - 4.38)
45 to <55 years	0.57 (0.47 - 0.67)	1.58 (1.41 - 1.75)	1.67 (1.47 - 1.87)	1.48 (1.27 - 1.69)	2.42 (2.11 - 2.73)	2.94 (2.52 - 3.37)
55 to <65 years	0.54 (0.44 - 0.65)	1.36 (1.19 - 1.53)	1.28 (1.09 - 1.46)	1.59 (1.36 - 1.83)	1.90 (1.60 - 2.19)	2.39 (1.97 - 2.80)
65 years and over	0.59 (0.48 - 0.70)	1.64 (1.45 - 1.83)	1.29 (1.10 - 1.49)	1.29 (1.07 - 1.52)	1.64 (1.34 - 1.94)	2.64 (2.17 - 3.12)
Sex						
Female	0.53 (0.46 - 0.60)	1.37 (1.25 - 1.49)	1.30 (1.17 - 1.43)	1.42 (1.26 - 1.59)	2.06 (1.83 - 2.28)	2.66 (2.34 - 2.98)
Male	0.76 (0.68 - 0.84)	1.89 (1.76 - 2.02)	1.78 (1.64 - 1.93)	1.91 (1.74 - 2.09)	2.64 (2.41 - 2.88)	3.27 (2.94 - 3.60)
Ethnicity						
White	0.51 (0.42 - 0.59)	1.40 (1.25 - 1.54)	1.40 (1.24 - 1.56)	1.61 (1.41 - 1.81)	1.88 (1.62 - 2.14)	2.21 (1.86 - 2.56)
South Asian	0.73 (0.63 - 0.82)	1.64 (1.49 - 1.79)	1.46 (1.31 - 1.62)	1.80 (1.60 - 1.99)	2.51 (2.25 - 2.78)	3.22 (2.85 - 3.60)
Black	0.72 (0.58 - 0.87)	2.25 (1.99 - 2.51)	1.93 (1.65 - 2.20)	1.59 (1.31 - 1.88)	2.75 (2.31 - 3.18)	4.04 (3.38 - 4.70)
Any other Asian	0.67 (0.43 - 0.91)	1.72 (1.33 - 2.11)	1.43 (1.03 - 1.83)	1.52 (1.06 - 1.98)	2.79 (2.06 - 3.51)	3.15 (2.18 - 4.11)
Other	0.92 (0.54 - 1.29)	1.59 (1.08 - 2.09)	2.54 (1.81 - 3.26)	1.68 (0.98 - 2.38)	2.42 (1.43 - 3.42)	3.19 (1.78 - 4.59)
Mixed	0.73 (0.28 - 1.17)	0.88 (0.37 - 1.39)	2.14 (1.25 - 3.03)	2.43 (1.29 - 3.57)	3.23 (1.65 - 4.81)	2.56 (0.81 - 4.30)

Table D.2: Sensitivity analysis using incidence rate of referable diabetic retinopathy per 100 person-years by follow-up period defined by 95% confidence intervals. People from the earliest 2 years of study period were excluded.

Characteristic	0-1yr	1-2yr	2-3yr	3-4yr	4-5yr	5-8yr
Chinese	0.66 (0.04 - 1.27)	1.32 (0.42 - 2.23)	1.68 (0.53 - 2.83)	0.46 (-0.25 - 1.17)	2.68 (0.73 - 4.63)	0.00 (0.00 - 0.00)
Unknown	0.87 (0.20 - 1.54)	3.01 (1.56 - 4.45)	2.05 (0.42 - 3.69)	4.15 (0.88 - 7.41)	2.56 (-0.97 - 6.10)	3.33 (-2.06 - 8.73)
Baseline DR grade						
No retinopathy	0.18 (0.15 - 0.21)	0.60 (0.54 - 0.66)	0.68 (0.61 - 0.75)	0.91 (0.81 - 1.00)	1.48 (1.34 - 1.62)	2.13 (1.92 - 2.35)
Retinopathy in one eye	1.20 (0.97 - 1.44)	3.41 (3.01 - 3.81)	3.65 (3.19 - 4.11)	3.94 (3.39 - 4.50)	5.32 (4.57 - 6.07)	6.76 (5.68 - 7.83)
Retinopathy in both eyes	6.87 (6.13 - 7.61)	16.72 (15.56 - 17.88)	13.99 (12.70 - 15.28)	12.56 (11.07 - 14.04)	14.96 (13.03 - 16.90)	13.61 (11.20 - 16.03)

D. Ethnic disparities in progression rates of sight-threatening diabetic retinopathy in diabetic eye screening

Table D.3: Incidence rates of any diabetic retinopathy (people with R0M0 at first screen, n = 107,701) and sight-threatening diabetic retinopathy (people with R0M0 and R1M0 at first screen, n = 137,591) per 100 person-years by ethnic group.

Ethnicity	**Any DR IR (95% CI)**	**STDR IR (95% CI)**
White	1.07 (1.07 - 1.07)	1.77 (1.77 - 1.77)
South Asian	1.69 (1.69 - 1.69)	2.44 (2.44 - 2.44)
Black	1.98 (1.98 - 1.98)	2.68 (2.68 - 2.68)
Any other Asian	1.38 (1.38 - 1.38)	2.24 (2.24 - 2.25)
Other	1.72 (1.71 - 1.72)	2.33 (2.32 - 2.33)
Mixed	1.58 (1.57 - 1.60)	2.41 (2.40 - 2.43)
Chinese	0.89 (0.87 - 0.91)	1.65 (1.63 - 1.67)
Unknown	1.24 (1.23 - 1.25)	2.61 (2.59 - 2.62)

Table D.4: Cumulative incidence rate of any diabetic retinopathy per 100 person-years by follow-up with 95% confidence intervals.

Characteristic	Year 1	Year 2	Year 3	Year 4	Year 5	Year 10
Overall	0.78 (0.73 - 0.82)	1.40 (1.34 - 1.46)	1.47 (1.41 - 1.53)	1.50 (1.44 - 1.56)	1.52 (1.46 - 1.59)	1.49 (1.43 - 1.55)
Age groups						
Less than 45 years	0.92 (0.82 - 1.03)	1.61 (1.48 - 1.75)	1.75 (1.61 - 1.90)	1.87 (1.72 - 2.02)	1.96 (1.81 - 2.12)	2.05 (1.89 - 2.20)
45 to <55 years	0.76 (0.67 - 0.85)	1.52 (1.39 - 1.64)	1.62 (1.50 - 1.75)	1.64 (1.51 - 1.77)	1.66 (1.53 - 1.79)	1.63 (1.50 - 1.75)
55 to <65 years	0.79 (0.70 - 0.88)	1.28 (1.17 - 1.39)	1.30 (1.19 - 1.42)	1.29 (1.18 - 1.41)	1.29 (1.18 - 1.41)	1.22 (1.11 - 1.33)
65 years and over	0.67 (0.60 - 0.75)	1.25 (1.14 - 1.35)	1.27 (1.17 - 1.38)	1.29 (1.19 - 1.39)	1.30 (1.20 - 1.41)	1.23 (1.13 - 1.33)
Sex						
Female	0.75 (0.69 - 0.82)	1.39 (1.30 - 1.47)	1.45 (1.37 - 1.54)	1.47 (1.38 - 1.56)	1.49 (1.40 - 1.58)	1.46 (1.37 - 1.55)
Male	0.79 (0.73 - 0.86)	1.41 (1.33 - 1.49)	1.48 (1.39 - 1.56)	1.52 (1.43 - 1.60)	1.55 (1.47 - 1.64)	1.51 (1.43 - 1.60)
Ethnicity						
White	0.60 (0.54 - 0.67)	1.07 (0.99 - 1.16)	1.09 (1.00 - 1.18)	1.09 (1.00 - 1.18)	1.11 (1.02 - 1.20)	1.07 (0.99 - 1.16)
South Asian	0.81 (0.74 - 0.89)	1.54 (1.43 - 1.64)	1.65 (1.54 - 1.76)	1.71 (1.60 - 1.82)	1.74 (1.62 - 1.85)	1.69 (1.58 - 1.80)
Black	1.10 (0.97 - 1.23)	1.80 (1.64 - 1.97)	1.90 (1.73 - 2.07)	1.95 (1.78 - 2.12)	2.00 (1.82 - 2.17)	1.98 (1.81 - 2.15)
Any other Asian	0.79 (0.60 - 0.97)	1.51 (1.26 - 1.77)	1.51 (1.25 - 1.76)	1.48 (1.22 - 1.73)	1.48 (1.22 - 1.73)	1.38 (1.13 - 1.63)
Other	0.88 (0.60 - 1.16)	1.46 (1.10 - 1.81)	1.64 (1.26 - 2.01)	1.74 (1.36 - 2.13)	1.75 (1.37 - 2.14)	1.72 (1.33 - 2.10)
Mixed	0.66 (0.30 - 1.02)	1.49 (0.95 - 2.03)	1.48 (0.95 - 2.02)	1.43 (0.91 - 1.96)	1.42 (0.90 - 1.95)	1.58 (1.03 - 2.14)
Chinese	0.81 (0.27 - 1.35)	1.26 (0.58 - 1.93)	1.02 (0.42 - 1.63)	0.98 (0.38 - 1.57)	1.05 (0.43 - 1.66)	0.89 (0.33 - 1.46)

Table D.4: Cumulative incidence rate of any diabetic retinopathy per 100 person-years by follow-up with 95% confidence intervals.

Characteristic	Year 1	Year 2	Year 3	Year 4	Year 5	Year 10
Unknown	0.41 (0.14 - 0.68)	0.99 (0.58 - 1.40)	1.14 (0.70 - 1.58)	1.19 (0.74 - 1.64)	1.23 (0.77 - 1.68)	1.24 (0.78 - 1.70)

Table D.5: Semi-parametric multivariable Cox proportional hazards model for interval censored data.

Characteristic	HR 95% CI	p-value
Age (per 5 year increase)	0.92 (0.91 - 0.93)	**7.5e-129**
Age groups		
<45 years	1.00	
45 to <55 years	0.80 (0.75 - 0.84)	**5.1e-23**
55 to <65 years	0.61 (0.56 - 0.66)	**9.7e-82**
65 years and over	0.56 (0.5 - 0.61)	**4.2e-112**
Sex		
Female	1.00	
Male	1.04 (1 - 1.07)	**0.028**
Baseline DR grade†		
No retinopathy	1.00	
Retinopathy in one eye	8.00 (7.96 - 8.05)	**3.5e-2209**
Retinopathy in both eyes	3.07 (3.03 - 3.11)	**1.0e-632**
Ethnicity		
White	1.00	

†No retinopathy; R0M0 (both eyes), retinopathy in one eye; R1M1 in one eye, retinopathy in both eyes; R1M0 in both eyes.

Hazard ratios (HR) are mutually adjusted for all factors shown in the table.

HR greater than 1 imply greater hazards for vision-threatening diabetic retinopathy (DR).

Bold p-values show statistically significant results.

CI; confidence interval, IMD; index of multiple deprivation.

Table D.5: Semi-parametric multivariable Cox proportional hazards model for interval censored data.

Characteristic	HR 95% CI	p-value
South Asian	1.37 (1.33 - 1.41)	**1.9e-51**
Black	1.58 (1.53 - 1.63)	**9.1e-76**
Any other Asian	1.26 (1.18 - 1.34)	**1.4e-09**
Other	1.30 (1.2 - 1.39)	**1.2e-07**
Mixed	1.38 (1.23 - 1.53)	**1.9e-05**
Chinese	0.98 (0.75 - 1.22)	0.888
Unknown	1.38 (1.16 - 1.59)	**0.003**
Duration of diabetes (per 5 years)	1.15 (1.14 - 1.16)	**3.3e-136**
Type of diabetes		
Type 2	1.00	
Type 1	1.02 (0.94 - 1.11)	0.594
Other	0.71 (0.19 - 1.24)	0.198
Missing	1.25 (1.12 - 1.37)	**5.5e-04**
IMD		
1 (Most deprived)	1.00	
2	1.04 (0.98 - 1.1)	0.239
3	1.02 (0.96 - 1.08)	0.444
4	0.98 (0.92 - 1.05)	0.586

[†]No retinopathy; R0M0 (both eyes), retinopathy in one eye; R1M1 in one eye, retinopathy in both eyes; R1M0 in both eyes.

Hazard ratios (HR) are mutually adjusted for all factors shown in the table.

HR greater than 1 imply greater hazards for vision-threatening diabetic retinopathy (DR).

Bold p-values show statistically significant results.

CI; confidence interval, IMD; index of multiple deprivation.

Table D.5: Semi-parametric multivariable Cox proportional hazards model for interval censored data.

Characteristic	**HR 95% CI**	**p-value**
5 (least deprived)	0.93 (0.85 - 1.01)	0.064
Missing	1.09 (-0.79 - 2.97)	0.925

[†]No retinopathy; R0M0 (both eyes), retinopathy in one eye; R1M1 in one eye, retinopathy in both eyes; R1M0 in both eyes.

Hazard ratios (HR) are mutually adjusted for all factors shown in the table.

HR greater than 1 imply greater hazards for vision-threatening diabetic retinopathy (DR).

Bold p-values show statistically significant results.

CI; confidence interval, IMD; index of multiple deprivation.

Table D.6: Multivariable Cox proportional hazards model for right censored data with development of any diabetic retinopathy (DR) as outcome of interest.

Characteristic	HR 95% CI	p-value
Age (per 5-year increase)	0.990.98, 0.99	**2.4e-12**
Age categories		
<45yr	1.00	
45 to <55yr	0.900.87, 0.93	**3.9e-11**
55 to <65yr	0.810.78, 0.84	**4.8e-39**
65yr and over	0.870.84, 0.90	**6.8e-18**
Sex		
Female	1.00	
Male	1.061.03, 1.08	**1.5e-07**
Ethnicity		
White	1.00	
South Asian	1.031.00, 1.06	**0.021**
Black	1.031.00, 1.06	0.070
Any other Asian	0.960.92, 1.01	0.096
Other	1.091.02, 1.16	**0.006**
Mixed	1.030.94, 1.13	0.550
Chinese	1.060.94, 1.20	0.318
Unknown	1.361.21, 1.54	**5.7e-07**
Duration of diabetes (per 5-year increase)	1.181.17, 1.19	**1.1e-377**
Type of diabetes		
Type 2	1.00	
Type 1	1.361.28, 1.44	**2.5e-26**
Other	1.010.77, 1.32	0.951

Hazard ratios (HR) are mutually adjusted for all factors shown in the table.

HR greater than 1 imply greater hazards for vision-threatening diabetic retinopathy (DR).

Bold p-values show statistically significant results.

CI; confidence interval, IMD; index of multiple deprivation.

Table D.6: Multivariable Cox proportional hazards model for right censored data with development of any diabetic retinopathy (DR) as outcome of interest.

Characteristic	**HR 95% CI**	**p-value**
Missing	1.251.16, 1.35	**7.6e-09**
Deprivation (IMD quintiles)		
1	1.00	
2	0.990.96, 1.03	0.692
3	0.980.95, 1.02	0.338
4	0.980.94, 1.02	0.318
5	0.970.93, 1.01	0.152
Missing	1.781.05, 3.02	**0.032**

Hazard ratios (HR) are mutually adjusted for all factors shown in the table.

HR greater than 1 imply greater hazards for vision-threatening diabetic retinopathy (DR).

Bold p-values show statistically significant results.

CI; confidence interval, IMD; index of multiple deprivation.

D.2 Supplementary figures

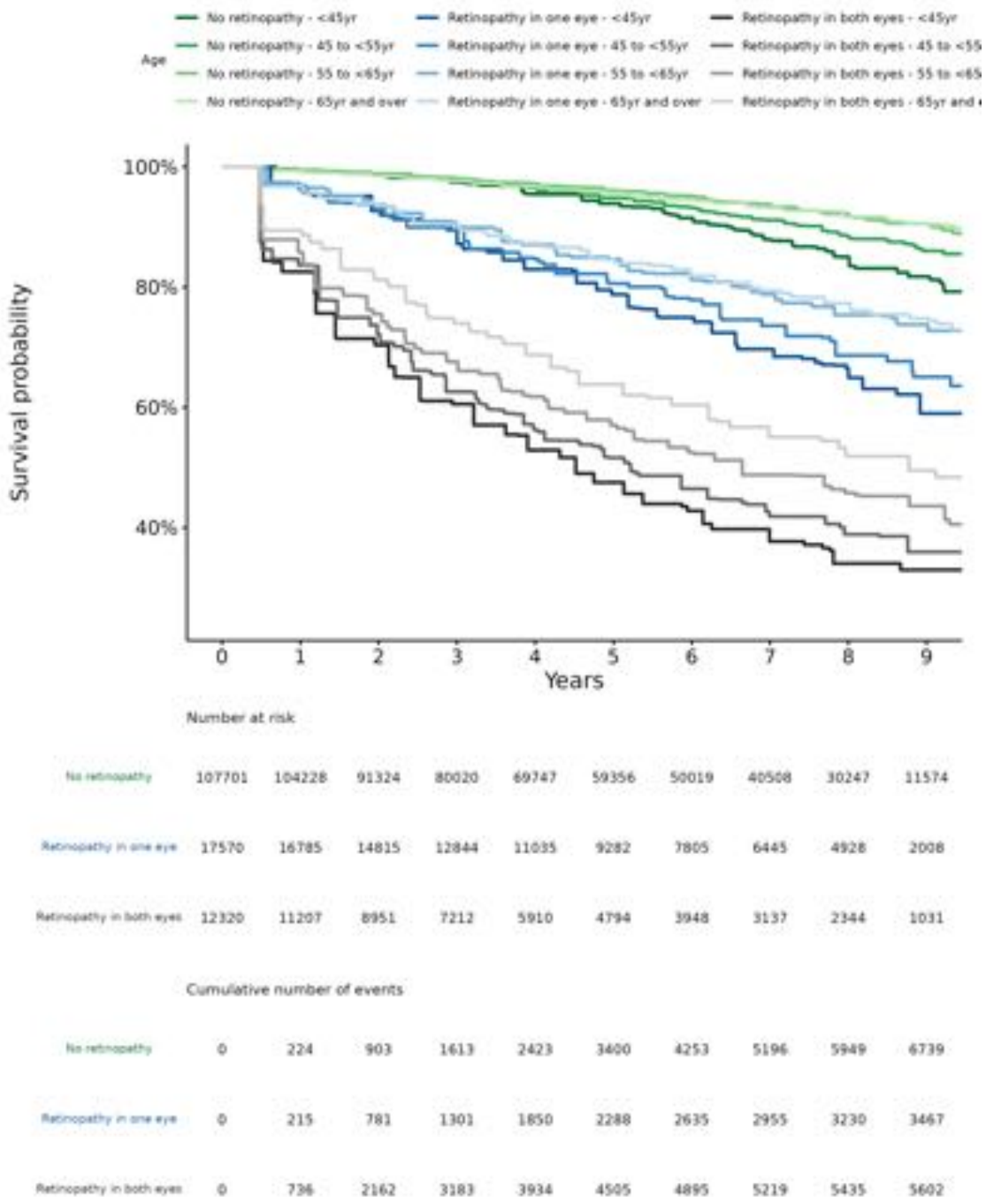


Figure D.1: Survival plot for development of sight-threatening diabetic retinopathy fitted with interval censoring and the Turnbull estimator stratified by baseline diabetic retinopathy grade and age.

E

Prediction of diabetes complications at point of diabetic eye screening, a streamlined approach to individualised preventive care

E.1 Supplementary tables

Table E.1: Prediction modelling strategies for all-cause mortality

Variable	Class	Levels	Base model	DR grade model	DESP model	Medical history model	Clinical measures model	Medication history model
Age	Continuous	-	* **	* **	* **	* **	* **	* **
Ethnicity	Categorical (8 levels)	White, South Asian, Black, Any other Asian, Other, Mixed, Chinese, unknown	* **	* **	* **	* **	* **	* **
Diabetic retinopathy grade	Categorical (7 levels)	R0M0, R1M0, R1M1, R2M0, R2M1, R3M0, R3M1		* **	* **	* **	* **	* **
Diabetic retinopathy in contralateral eye	Categorical (2 levels)	Equal, Better		* **	* **	* **	* **	* **
Type of diabetes	Categorical (4 levels)	Type 2, Type 1, Other, Missing			* **	* **	* **	* **
Duration of diabetes	Continuous	-			* **	* **	* **	**
Index of Multiple Deprivation	Categorical (6 levels)	5, 4, 3, 2, 1, Missing			* **	* **	* **	* **

Mean arterial pressure is calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure.

LDL-C; Low-density lipoprotein cholesterol, HDL-C; High-density lipoprotein cholesterol.

Coloured cell indicate the variable was tested in backward elimination.

* = Variable included in male models.

** = Variable included in female models.

Table E.1: Prediction modelling strategies for all-cause mortality

Variable	Class	Levels	Base model	DR grade model	DESP model	Medical history model	Clinical measures model	Medication history model
Hypertension	Binary	Yes, No				*	* **	
Chronic kidney disease	Binary	Yes, No				* **	* **	* **
History of myocardial infarction	Binary	Yes, No				* **	* **	* **
History of stroke	Binary	Yes, No				* **	* **	* **
Smoking history	Categorical (3 levels)	Non-smoker, smoker, ex-smoker				* **	* **	* **
Body mass index	Continuous	-					* **	* **
HbA1c	Continuous	-					* **	* **
Mean arterial pressure	Continuous	-					* **	* **
Total cholesterol	Continuous	-					* **	* **
Triglycerides	Continuous	-					* **	* **

Mean arterial pressure is calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure.

LDL-C; Low-density lipoprotein cholesterol, HDL-C; High-density lipoprotein cholesterol.

Coloured cell indicate the variable was tested in backward elimination.

* = Variable included in male models.

** = Variable included in female models.

Table E.1: Prediction modelling strategies for all-cause mortality

Variable	Class	Levels	Base model	DR grade model	DESP model	Medical history model	Clinical measures model	Medication history model
LDL-C/HDL-C	Continuous	-					* **	* **
Insulin use	Binary	Yes, No						* **
Non-insulin hypoglycaemics use	Binary	Yes, No						* **
Lipid lowering use	Binary	Yes, No						* **
Calcium channel blocker use	Binary	Yes, No						* **
Beta blocker use	Binary	Yes, No						* **
Alpha blocker use	Binary	Yes, No						* **
Renin angiotensin blocker use	Binary	Yes, No						*

Diuretic use	Binary	Yes, No	* **

Mean arterial pressure is calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure.

LDL-C; Low-density lipoprotein cholesterol, HDL-C; High-density lipoprotein cholesterol.

Coloured cell indicate the variable was tested in backward elimination.

* = Variable included in male models.

** = Variable included in female models.

Table E.2: Prediction modelling strategies for sight-threatening diabetic retinopathy (STDR).

Variable	Class	Levels	Base model	DESP model	DESP + HbA1c model	Medical history model	Clinical measures model	Medication history model
Age	Continuous	-	*	*	*	*	*	*
Sex	Categorical (2 levels)	Male, Female	*			*	*	*
Ethnicity	Categorical (8 levels)	White, South Asian, Black, Any other Asian, Other, Mixed, Chinese, unknown	*	*	*	*	*	*
Diabetic retinopathy grade	Categorical (3 levels)	No retinopathy, retinopathy in one eye, retinopathy in both eyes		*	*	*	*	*
Type of diabetes	Categorical (4 levels)	Type 2, Type 1, Other, Missing		*	*	*	*	*
Duration of diabetes	Continuous	-		*	*	*	*	*
Index of Multiple Deprivation	Categorical (6 levels)	5, 4, 3, 2, 1, Missing		*	*	*	*	*
HbA1c	Continuous	-			*	*	*	*
Hypertension	Binary	Yes, No						

Mean arterial pressure is calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure.

LDL-C; Low-density lipoprotein cholesterol, HDL-C; High-density lipoprotein cholesterol.

Coloured cell indicate the variable was tested in backward elimination.

* = Variable included in STDR models.

Table E.2: Prediction modelling strategies for sight-threatening diabetic retinopathy (STDR).

Variable	Class	Levels	Base model	DESP model	DESP + HbA1c model	Medical history model	Clinical measures model	Medication history model
Chronic kidney disease	Binary	Yes, No				*	*	*
History of myocardial infarction	Binary	Yes, No					*	
History of stroke	Binary	Yes, No				*	*	
Smoking history	Categorical (3 levels)	Non-smoker, smoker, ex-smoker				*	*	*
Body mass index	Continuous	-					*	*
Mean arterial pressure	Continuous	-					*	*
Total cholesterol	Continuous	-					*	*
Triglycerides	Continuous	-						
LDL-C/HDL-C	Continuous	-					*	
Insulin use	Binary	Yes, No						*

Mean arterial pressure is calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure.

LDL-C; Low-density lipoprotein cholesterol, HDL-C; High-density lipoprotein cholesterol.

Coloured cell indicate the variable was tested in backward elimination.

* = Variable included in STDR models.

Table E.2: Prediction modelling strategies for sight-threatening diabetic retinopathy (STDR).

Variable	Class	Levels	Base model	DESP model	DESP + HbA1c model	Medical history model	Clinical measures model	Medication history model
Non-insulin hypoglycaemics use	Binary	Yes, No						*
Lipid lowering use	Binary	Yes, No						
Calcium channel blocker use	Binary	Yes, No						
Beta blocker use	Binary	Yes, No						
Alpha blocker use	Binary	Yes, No						*
Renin angiotensin blocker use	Binary	Yes, No						

Diuretic use	Binary	Yes, No	*

Mean arterial pressure is calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure.

LDL-C; Low-density lipoprotein cholesterol, HDL-C; High-density lipoprotein cholesterol.

Coloured cell indicate the variable was tested in backward elimination.

* = Variable included in STDR models.

Table E.3: Male multivariable fractional polynomial base model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^3)	6.02	0.05	0.00e+00**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	-10.90	0.48	8.87e-115**
ethnicitySouth Asian	-0.30	0.02	3.21e-50**
ethnicityBlack	-0.25	0.02	6.27e-25**
ethnicityAny other Asian	-0.45	0.05	2.28e-23**
ethnicityOther	-0.11	0.05	2.79e-02*
ethnicityMixed	-0.16	0.08	5.41e-02
ethnicityChinese	-0.72	0.14	1.22e-07**
ethnicityUnknown	1.23	0.03	0.00e+00**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.4: Male multivariable fractional polynomial diabetic retinopathy grades model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^3)	6.09	0.05	0.00e+00**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	-10.78	0.48	3.87e-112**
ethnicitySouth Asian	-0.34	0.02	2.08e-61**
ethnicityBlack	-0.29	0.02	3.13e-32**
ethnicityAny other Asian	-0.49	0.05	4.43e-27**
ethnicityOther	-0.15	0.05	2.95e-03**
ethnicityMixed	-0.23	0.08	4.00e-03**
ethnicityChinese	-0.72	0.14	1.09e-07**
ethnicityUnknown	1.19	0.03	0.00e+00**
bl_comb_grade_clean_uR1M0	0.31	0.02	4.36e-40**
bl_comb_grade_clean_uR1M1	0.56	0.04	4.92e-49**
bl_comb_grade_clean_uR2M0	0.86	0.07	2.29e-36**
bl_comb_grade_clean_uR2M1	0.88	0.05	5.92e-77**
bl_comb_grade_clean_uR3M0	1.11	0.08	1.56e-41**
bl_comb_grade_clean_uR3M1	1.20	0.06	7.33e-78**
grade_ou_minBetter	-0.18	0.03	3.21e-12**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.5: Male multivariable fractional polynomial diabetic eye screening programme data model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^2)	10.70	0.48	9.41e-110**
I((age_at_bl/100) ^3)	-4.11	0.46	3.38e-19**
ethnicitySouth Asian	-0.34	0.02	1.85e-62**
ethnicityBlack	-0.33	0.02	5.05e-41**
ethnicityAny other Asian	-0.49	0.05	1.65e-26**
ethnicityOther	-0.20	0.05	1.00e-04**
ethnicityMixed	-0.23	0.08	4.12e-03**
ethnicityChinese	-0.69	0.14	3.93e-07**
ethnicityUnknown	0.98	0.04	2.38e-170**
bl_comb_grade_clean_uR1M0	0.22	0.02	5.20e-19**
bl_comb_grade_clean_uR1M1	0.41	0.04	8.90e-26**
bl_comb_grade_clean_uR2M0	0.65	0.07	2.38e-21**
bl_comb_grade_clean_uR2M1	0.72	0.05	1.16e-49**
bl_comb_grade_clean_uR3M0	0.90	0.08	6.12e-27**
bl_comb_grade_clean_uR3M1	1.01	0.07	1.16e-53**
imd_quint_clean2	-0.06	0.03	2.51e-02*
imd_quint_clean3	-0.15	0.03	4.02e-07**
imd_quint_clean4	-0.26	0.03	3.67e-17**
imd_quint_clean5	-0.34	0.04	2.52e-22**
imd_quint_cleanMissing	-0.00	0.04	9.26e-01
type_diab_groupedType 1	0.19	0.05	2.35e-04**
type_diab_groupedOther	0.34	0.20	8.81e-02
type_diab_groupedMissing	0.44	0.03	2.40e-40**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.5: Male multivariable fractional polynomial diabetic eye screening programme data model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((duration_diab_desp/10) ^1)	0.23	0.02	5.22e-24**
I((duration_diab_desp/10) ^2)	-0.03	0.01	6.79e-08**
grade_ou_minBetter	-0.13	0.03	6.64e-07**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.6: Male multivariable fractional polynomial targeted medical history model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^2)	10.24	0.49	3.53e-98**
I((age_at_bl/100) ^3)	-3.96	0.46	1.45e-17**
ethnicitySouth Asian	-0.34	0.02	5.85e-60**
ethnicityBlack	-0.28	0.03	9.68e-30**
ethnicityAny other Asian	-0.43	0.05	1.00e-20**
ethnicityOther	-0.19	0.05	3.17e-04**
ethnicityMixed	-0.27	0.08	8.96e-04**
ethnicityChinese	-0.61	0.14	5.67e-06**
ethnicityUnknown	0.97	0.04	1.03e-168**
smoker	0.51	0.02	2.66e-104**
bl_comb_grade_clean_uR1M0	0.21	0.02	5.68e-18**
bl_comb_grade_clean_uR1M1	0.41	0.04	4.04e-25**
bl_comb_grade_clean_uR2M0	0.63	0.07	1.25e-19**
bl_comb_grade_clean_uR2M1	0.71	0.05	4.32e-48**
bl_comb_grade_clean_uR3M0	0.84	0.08	1.46e-23**
bl_comb_grade_clean_uR3M1	1.01	0.07	1.65e-53**
has_ckd	0.28	0.02	2.90e-54**
has_had_stroke	0.37	0.02	1.09e-54**
type_diab_groupedType 1	0.20	0.05	1.23e-04**
type_diab_groupedOther	0.31	0.20	1.13e-01
type_diab_groupedMissing	0.44	0.03	1.62e-40**
has_had_mi	0.29	0.02	3.91e-39**
imd_quint_clean2	-0.05	0.03	6.00e-02
imd_quint_clean3	-0.11	0.03	7.40e-05**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.6: Male multivariable fractional polynomial targeted medical history model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
imd_quint_clean4	-0.21	0.03	3.42e-12**
imd_quint_clean5	-0.28	0.04	5.41e-15**
imd_quint_cleanMissing	0.04	0.04	4.10e-01
I((duration_diab_desp/10) ^1)	0.19	0.02	1.90e-16**
I((duration_diab_desp/10) ^2)	-0.03	0.01	4.36e-05**
exsmoker	0.10	0.02	2.60e-09**
grade_ou_minBetter	-0.13	0.03	5.47e-07**
has_hypertension	0.08	0.02	9.03e-06**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.7: Male multivariable fractional polynomial clinical measures model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^2)	11.93	0.56	1.50e-101**
I((age_at_bl/100) ^3)	-5.45	0.53	1.39e-24**
ethnicitySouth Asian	-0.35	0.02	8.27e-49**
ethnicityBlack	-0.26	0.03	6.57e-21**
ethnicityAny other Asian	-0.39	0.05	8.31e-15**
ethnicityOther	-0.19	0.06	8.86e-04**
ethnicityMixed	-0.35	0.09	1.31e-04**
ethnicityChinese	-0.77	0.16	1.70e-06**
ethnicityUnknown	0.99	0.04	3.20e-141**
smoker	0.53	0.03	6.59e-92**
has_ckd	0.30	0.02	7.56e-52**
bl_comb_grade_clean_uR1M0	0.18	0.03	7.61e-12**
bl_comb_grade_clean_uR1M1	0.33	0.04	7.50e-15**
bl_comb_grade_clean_uR2M0	0.55	0.08	1.02e-12**
bl_comb_grade_clean_uR2M1	0.60	0.05	2.18e-27**
bl_comb_grade_clean_uR3M0	0.72	0.10	1.56e-13**
bl_comb_grade_clean_uR3M1	0.88	0.07	4.60e-32**
has_had_stroke	0.36	0.03	4.81e-44**
I((hba1c_dcct_index/10) ^0.5)	-6.12	0.82	8.53e-14**
I((hba1c_dcct_index/10) ^1)	3.97	0.45	5.75e-19**
type_diab_groupedType 1	0.19	0.06	1.41e-03**
type_diab_groupedOther	0.26	0.22	2.34e-01
type_diab_groupedMissing	0.41	0.04	2.13e-29**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.7: Male multivariable fractional polynomial clinical measures model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
has_had_mi	0.29	0.02	5.24e-31**
imd_quint_clean2	-0.05	0.03	7.39e-02
imd_quint_clean3	-0.10	0.03	1.49e-03**
imd_quint_clean4	-0.19	0.03	2.55e-08**
imd_quint_clean5	-0.25	0.04	6.07e-11**
imd_quint_cleanMissing	0.01	0.05	8.63e-01
exsmoker	0.15	0.02	1.32e-15**
has_hypertension	0.16	0.02	6.22e-15**
I((duration_diab_desp/10) ^1)	0.09	0.01	5.67e-15**
I((map/100) ^2)	-2.27	0.19	5.53e-33**
I((map/100) ^2 * log((map/100)))	4.52	0.38	1.78e-32**
grade_ou_minBetter	-0.09	0.03	1.18e-03**
I(((total_cholesterol_index + 0.1)/10) ^0.5)	-3.57	0.67	8.24e-08**
I(((total_cholesterol_index + 0.1)/10) ^0.5 * log(((total_cholesterol_index + 0.1)/10)))	3.21	0.57	1.61e-08**
I((bmi_index/10) ^-1)	35.98	1.74	5.58e-95**
I((bmi_index/10) ^-0.5)	-42.62	2.09	7.87e-93**
I(triglycerides_index ^-2)	-0.07	0.02	1.99e-05**
I(triglycerides_index ^-2 * log(triglycerides_index))	-0.04	0.01	5.85e-06**
log((ldl_hdl_index + 0.1))	-0.53	0.13	6.44e-05**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.7: Male multivariable fractional polynomial clinical measures model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((ldl_hdl_index + 0.1) ^0.5)	0.74	0.19	1.26e-04**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.8: Male multivariable fractional polynomial medication use model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^2)	6.70	0.09	0.00e+00**
I((age_at_bl/100) ^2 * log((age_at_bl/100)))	-5.05	0.52	5.96e-22**
ethnicitySouth Asian	-0.34	0.02	8.29e-46**
ethnicityBlack	-0.31	0.03	7.25e-28**
ethnicityAny other Asian	-0.38	0.05	1.59e-14**
ethnicityOther	-0.18	0.06	1.21e-03**
ethnicityMixed	-0.38	0.09	2.66e-05**
ethnicityChinese	-0.78	0.16	1.36e-06**
ethnicityUnknown	0.96	0.04	2.14e-131**
smoker	0.54	0.03	7.83e-96**
diuretics_use	0.35	0.02	8.57e-66**
insulins_use	0.38	0.02	5.17e-58**
has_ckd	0.24	0.02	2.17e-32**
has_had_stroke	0.32	0.03	1.52e-34**
bl_comb_grade_clean_uR1M0	0.14	0.03	8.59e-08**
bl_comb_grade_clean_uR1M1	0.26	0.04	1.26e-09**
bl_comb_grade_clean_uR2M0	0.46	0.08	2.24e-09**
bl_comb_grade_clean_uR2M1	0.48	0.06	6.30e-18**
bl_comb_grade_clean_uR3M0	0.58	0.10	3.06e-09**
bl_comb_grade_clean_uR3M1	0.72	0.08	8.02e-22**
I((hba1c_dcct_index/10) ^1)	-0.87	0.21	2.77e-05**
I((hba1c_dcct_index/10) ^1 * log((hba1c_dcct_index/10)))	1.62	0.23	3.05e-12**
type_diab_groupedType 1	0.06	0.06	2.97e-01

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.8: Male multivariable fractional polynomial medication use model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
type_diab_groupedOther	0.22	0.22	3.19e-01
type_diab_groupedMissing	0.37	0.04	5.69e-24**
imd_quint_clean2	-0.05	0.03	1.36e-01
imd_quint_clean3	-0.09	0.03	5.77e-03**
imd_quint_clean4	-0.16	0.03	1.47e-06**
imd_quint_clean5	-0.23	0.04	3.97e-09**
imd_quint_cleanMissing	0.02	0.05	7.05e-01
exsmoker	0.14	0.02	1.10e-13**
has_had_mi	0.19	0.03	9.66e-13**
beta_blockers_use	0.10	0.02	1.43e-06**
lipid_lowering_use	-0.08	0.02	1.84e-04**
alpha_blockers_use	0.09	0.02	1.01e-04**
I((map/100) ^2)	-1.96	0.19	1.10e-24**
I((map/100) ^2 * log((map/100)))	3.92	0.38	1.86e-24**
I(((total_cholesterol_index + 0.1)/10) ^0.5)	-2.97	0.67	8.05e-06**
I(((total_cholesterol_index + 0.1)/10) ^0.5 * log(((total_cholesterol_index + 0.1)/10)))	2.86	0.57	4.36e-07**
ccbs_use	-0.06	0.02	7.13e-03**
grade_ou_minBetter	-0.08	0.03	8.34e-03**
non_insulin_hypoglycaemics_use	0.08	0.02	1.37e-03**
I((bmi_index/10) ^-1)	33.84	1.76	1.43e-82**
I((bmi_index/10) ^-0.5)	-39.28	2.11	2.24e-77**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.8: Male multivariable fractional polynomial medication use model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
renin_angiotensin_blockers_use	0.06	0.02	2.38e-02*
I(triglycerides_index ^-2)	-0.07	0.02	1.74e-04**
I(triglycerides_index ^-2 * log(triglycerides_index))	-0.04	0.01	3.34e-05**
log((ldl_hdl_index + 0.1))	-0.54	0.13	5.27e-05**
I((ldl_hdl_index + 0.1) ^0.5)	0.73	0.19	1.50e-04**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.9: Female multivariable fractional polynomial base model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^3)	6.09	0.05	0.00e+00**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	-10.45	0.51	3.86e-93**
ethnicitySouth Asian	-0.31	0.02	1.54e-38**
ethnicityBlack	-0.35	0.03	1.56e-37**
ethnicityAny other Asian	-0.49	0.05	1.87e-19**
ethnicityOther	-0.32	0.06	2.78e-07**
ethnicityMixed	-0.23	0.09	1.22e-02*
ethnicityChinese	-0.52	0.13	6.78e-05**
ethnicityUnknown	1.21	0.03	6.80e-268**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.10: Female multivariable fractional polynomial diabetic retinopathy grades model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^3)	6.07	0.05	0.00e+00**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	-10.21	0.51	6.14e-89**
ethnicitySouth Asian	-0.35	0.02	9.32e-48**
ethnicityBlack	-0.40	0.03	3.85e-49**
ethnicityAny other Asian	-0.51	0.05	2.65e-21**
ethnicityOther	-0.38	0.06	1.74e-09**
ethnicityMixed	-0.31	0.09	1.04e-03**
ethnicityChinese	-0.50	0.13	1.20e-04**
ethnicityUnknown	1.19	0.03	4.39e-256**
bl_comb_grade_clean_uR1M0	0.41	0.03	1.28e-53**
bl_comb_grade_clean_uR1M1	0.72	0.04	6.67e-67**
bl_comb_grade_clean_uR2M0	0.92	0.08	1.32e-28**
bl_comb_grade_clean_uR2M1	1.11	0.06	1.02e-77**
bl_comb_grade_clean_uR3M0	1.27	0.10	6.74e-40**
bl_comb_grade_clean_uR3M1	1.39	0.08	8.54e-68**
grade_ou_minBetter	-0.25	0.03	4.29e-17**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.11: Female multivariable fractional polynomial diabetic eye screening programme data model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^3)	6.01	0.06	0.00e+00**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	-10.32	0.52	4.93e-89**
ethnicitySouth Asian	-0.36	0.02	6.49e-49**
ethnicityBlack	-0.44	0.03	6.26e-59**
ethnicityAny other Asian	-0.50	0.05	1.71e-20**
ethnicityOther	-0.40	0.06	2.19e-10**
ethnicityMixed	-0.30	0.09	1.47e-03**
ethnicityChinese	-0.51	0.13	9.28e-05**
ethnicityUnknown	1.01	0.04	1.96e-141**
bl_comb_grade_clean_uR1M0	0.31	0.03	2.88e-29**
bl_comb_grade_clean_uR1M1	0.57	0.04	1.46e-39**
bl_comb_grade_clean_uR2M0	0.70	0.08	6.48e-17**
bl_comb_grade_clean_uR2M1	0.92	0.06	6.67e-52**
bl_comb_grade_clean_uR3M0	1.08	0.10	7.46e-29**
bl_comb_grade_clean_uR3M1	1.19	0.08	5.91e-49**
type_diab_groupedType 1	0.23	0.06	2.81e-04**
type_diab_groupedOther	0.13	0.22	5.59e-01
type_diab_groupedMissing	0.42	0.04	1.04e-29**
imd_quint_clean2	-0.08	0.03	1.01e-02*
imd_quint_clean3	-0.17	0.03	8.32e-08**
imd_quint_clean4	-0.21	0.03	6.99e-10**
imd_quint_clean5	-0.38	0.04	1.25e-20**
imd_quint_cleanMissing	-0.02	0.05	6.99e-01

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.11: Female multivariable fractional polynomial diabetic eye screening programme data model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((duration_diab_desp/10) ^1)	0.21	0.02	2.47e-35**
I((duration_diab_desp/10) ^3)	-0.01	0.00	3.76e-12**
grade_ou_minBetter	-0.19	0.03	2.36e-10**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.12: Female multivariable fractional polynomial targeted medical history model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^3)	5.79	0.06	0.00e+00**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	-9.88	0.52	6.80e-81**
ethnicitySouth Asian	-0.25	0.03	2.39e-22**
ethnicityBlack	-0.34	0.03	2.02e-33**
ethnicityAny other Asian	-0.38	0.05	5.09e-12**
ethnicityOther	-0.32	0.06	4.57e-07**
ethnicityMixed	-0.22	0.09	2.07e-02*
ethnicityChinese	-0.35	0.13	7.31e-03**
ethnicityUnknown	1.05	0.04	2.02e-150**
bl_comb_grade_clean_uR1M0	0.30	0.03	8.07e-28**
bl_comb_grade_clean_uR1M1	0.54	0.04	1.71e-35**
bl_comb_grade_clean_uR2M0	0.67	0.08	1.53e-15**
bl_comb_grade_clean_uR2M1	0.90	0.06	4.48e-49**
bl_comb_grade_clean_uR3M0	1.01	0.10	1.70e-25**
bl_comb_grade_clean_uR3M1	1.17	0.08	2.36e-47**
smoker	0.54	0.03	5.43e-65**
has_ckd	0.28	0.02	1.82e-43**
has_had_stroke	0.36	0.03	1.21e-39**
has_had_mi	0.38	0.03	5.71e-31**
type_diab_groupedType 1	0.18	0.06	3.71e-03**
type_diab_groupedOther	0.12	0.22	5.78e-01
type_diab_groupedMissing	0.43	0.04	2.86e-30**
imd_quint_clean2	-0.08	0.03	1.10e-02*
imd_quint_clean3	-0.16	0.03	8.86e-07**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.12: Female multivariable fractional polynomial targeted medical history model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
imd_quint_clean4	-0.18	0.03	1.90e-07**
imd_quint_clean5	-0.33	0.04	4.33e-16**
imd_quint_cleanMissing	-0.01	0.05	8.82e-01
I((duration_diab_desp/10) ^1)	0.18	0.02	1.04e-26**
I((duration_diab_desp/10) ^3)	-0.01	0.00	2.73e-09**
exsmoker	0.17	0.02	2.42e-12**
grade_ou_minBetter	-0.18	0.03	3.10e-09**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.13: Female multivariable fractional polynomial clinical measures model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^3)	5.99	0.07	0.00e+00**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	-12.23	0.61	4.31e-88**
ethnicitySouth Asian	-0.21	0.03	9.27e-13**
ethnicityBlack	-0.28	0.03	1.87e-17**
ethnicityAny other Asian	-0.32	0.06	1.04e-07**
ethnicityOther	-0.30	0.07	1.29e-05**
ethnicityMixed	-0.19	0.10	6.93e-02
ethnicityChinese	-0.34	0.14	1.79e-02*
ethnicityUnknown	1.12	0.05	3.47e-131**
smoker	0.55	0.03	3.94e-57**
bl_comb_grade_clean_uR1M0	0.27	0.03	2.85e-18**
bl_comb_grade_clean_uR1M1	0.45	0.05	2.74e-20**
bl_comb_grade_clean_uR2M0	0.58	0.10	1.47e-09**
bl_comb_grade_clean_uR2M1	0.77	0.07	3.61e-29**
bl_comb_grade_clean_uR3M0	0.87	0.12	5.06e-14**
bl_comb_grade_clean_uR3M1	1.04	0.09	5.94e-30**
has_ckd	0.28	0.02	1.63e-37**
I((hba1c_dcct_index/10) ^0.5)	-10.90	0.98	7.70e-29**
I((hba1c_dcct_index/10) ^1)	6.66	0.54	1.70e-35**
has_had_stroke	0.33	0.03	9.01e-26**
type_diab_groupedType 1	0.21	0.07	2.97e-03**
type_diab_groupedOther	-0.01	0.29	9.72e-01
type_diab_groupedMissing	0.41	0.04	1.19e-21**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.13: Female multivariable fractional polynomial clinical measures model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
has_had_mi	0.34	0.04	2.17e-20**
imd_quint_clean2	-0.07	0.03	4.50e-02*
imd_quint_clean3	-0.15	0.04	3.62e-05**
imd_quint_clean4	-0.18	0.04	2.29e-06**
imd_quint_clean5	-0.30	0.04	2.58e-11**
imd_quint_cleanMissing	-0.03	0.06	6.07e-01
exsmoker	0.19	0.03	2.47e-13**
I((duration_diab_desp/10) ^1)	0.15	0.02	7.13e-16**
I((duration_diab_desp/10) ^3)	-0.00	0.00	3.00e-05**
grade_ou_minBetter	-0.15	0.03	5.70e-06**
I((bmi_index/10) ^-0.5)	39.39	1.78	4.92e-109**
log((bmi_index/10))	11.50	0.52	5.67e-110**
has_hypertension	0.11	0.03	8.30e-06**
I(triglycerides_index ^-0.5)	-0.31	0.06	5.89e-07**
log(ldl_hdl_index)	-0.08	0.04	2.17e-02*
I(log(ldl_hdl_index) ^2)	0.15	0.03	1.25e-06**
I((map/100) ^-1)	1.39	0.21	7.21e-11**
I((map/100) ^3)	0.49	0.09	1.48e-08**
log(((total_cholesterol_index + 0.1)/10))	-2.14	0.26	2.77e-16**
I(((total_cholesterol_index + 0.1)/10) ^0.5)	5.92	0.81	2.10e-13**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.13: Female multivariable fractional polynomial clinical measures model for all-cause mortality.

Variable	Coefficient	Standard error	p-value

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.14: Female multivariable fractional polynomial medication use model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^3)	5.92	0.07	0.00e+00**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	-12.13	0.62	1.14e-85**
ethnicitySouth Asian	-0.17	0.03	1.90e-09**
ethnicityBlack	-0.32	0.03	5.55e-22**
ethnicityAny other Asian	-0.30	0.06	7.49e-07**
ethnicityOther	-0.29	0.07	3.48e-05**
ethnicityMixed	-0.20	0.11	5.90e-02
ethnicityChinese	-0.31	0.14	3.12e-02*
ethnicityUnknown	1.10	0.05	3.26e-125**
smoker	0.57	0.03	2.37e-60**
bl_comb_grade_clean_uR1M0	0.22	0.03	1.67e-12**
bl_comb_grade_clean_uR1M1	0.36	0.05	3.42e-13**
bl_comb_grade_clean_uR2M0	0.47	0.10	1.23e-06**
bl_comb_grade_clean_uR2M1	0.65	0.07	1.39e-20**
bl_comb_grade_clean_uR3M0	0.72	0.12	7.18e-10**
bl_comb_grade_clean_uR3M1	0.90	0.09	2.16e-22**
diuretics_use	0.29	0.02	5.00e-33**
has_ckd	0.23	0.02	1.17e-25**
insulins_use	0.32	0.03	4.31e-28**
has_had_stroke	0.30	0.03	3.48e-22**
type_diab_groupedType 1	0.09	0.07	2.03e-01
type_diab_groupedOther	-0.08	0.29	7.72e-01
type_diab_groupedMissing	0.40	0.04	1.52e-20**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.14: Female multivariable fractional polynomial medication use model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I((hba1c_dcct_index/10) ^1)	-2.15	0.25	4.20e-18**
I((hba1c_dcct_index/10) ^1 * log((hba1c_dcct_index/10)))	3.22	0.28	2.78e-30**
has_had_mi	0.27	0.04	1.83e-12**
exsmoker	0.19	0.03	3.93e-13**
imd_quint_clean2	-0.08	0.03	2.11e-02*
imd_quint_clean3	-0.15	0.04	1.77e-05**
imd_quint_clean4	-0.19	0.04	1.28e-06**
imd_quint_clean5	-0.30	0.04	5.11e-11**
imd_quint_cleanMissing	-0.04	0.06	4.62e-01
lipid_lowering_use	-0.17	0.03	3.78e-10**
alpha_blockers_use	0.18	0.03	9.80e-11**
grade_ou_minBetter	-0.13	0.03	1.28e-04**
beta_blockers_use	0.08	0.02	2.15e-04**
non_insulin_hypoglycaemics_use	0.13	0.03	4.85e-06**
I(triglycerides_index ^-0.5)	-0.30	0.06	2.32e-06**
I((duration_diab_desp/10) ^2)	0.06	0.01	6.93e-06**
I((duration_diab_desp/10) ^2 * log((duration_diab_desp/10)))	-0.04	0.01	2.34e-05**
ccbs_use	-0.07	0.02	4.68e-03**
I((map/100) ^-0.5)	2.71	0.51	1.11e-07**
I((map/100) ^3)	0.46	0.10	3.01e-06**
log(ldl_hdl_index)	-0.10	0.04	9.79e-03**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.14: Female multivariable fractional polynomial medication use model for all-cause mortality.

Variable	Coefficient	Standard error	p-value
I(log(ldl_hdl_index) ^2)	0.15	0.03	2.17e-06**
log(((total_cholesterol_index + 0.1)/10))	-2.11	0.27	9.13e-15**
I(((total_cholesterol_index + 0.1)/10) ^0.5)	5.96	0.84	9.90e-13**
I((bmi_index/10) ^-0.5)	38.90	1.77	1.01e-106**
log((bmi_index/10))	11.19	0.52	3.20e-104**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.15: Multivariable fractional polynomial base model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
I((age_at_bl/100) ^-2)	0.17	0.01	5.56e-82**
I((age_at_bl/100) ^-2 * log((age_at_bl/100)))	0.08	0.00	1.32e-64**
ethnicitySouth Asian	0.24	0.02	1.29e-34**
ethnicityBlack	0.39	0.02	2.67e-65**
ethnicityAny other Asian	0.17	0.04	1.95e-06**
ethnicityOther	0.23	0.05	1.42e-06**
ethnicityMixed	0.28	0.07	1.19e-04**
ethnicityChinese	-0.09	0.11	3.88e-01
ethnicityUnknown	0.68	0.10	2.39e-12**
sexMale	0.14	0.02	1.02e-18**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.16: Multivariable fractional polynomial diabetic eye screening programme data model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
bl_grade_ou_comb_gradesRetinopathy in one eye	1.07	0.02	0.00e+00**
bl_grade_ou_comb_gradesRetinopathy in both eyes	2.01	0.02	0.00e+00**
I((age_at_bl/100) ^3)	-0.22	0.09	9.36e-03**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	8.42	0.45	7.92e-79**
I((duration_diab_desp/10) ^1)	0.76	0.02	3.70e-219**
I((duration_diab_desp/10) ^1 * log((duration_diab_desp/10)))	-0.42	0.02	3.20e-104**
ethnicitySouth Asian	0.28	0.02	1.01e-44**
ethnicityBlack	0.44	0.02	1.17e-78**
ethnicityAny other Asian	0.20	0.04	1.44e-08**
ethnicityOther	0.23	0.05	7.85e-07**
ethnicityMixed	0.33	0.07	3.57e-06**
ethnicityChinese	-0.02	0.11	8.56e-01
ethnicityUnknown	0.52	0.10	1.62e-07**
type_diab_groupedType 1	-0.05	0.04	1.90e-01
type_diab_groupedOther	-0.28	0.26	2.78e-01
type_diab_groupedMissing	0.28	0.06	1.72e-06**
imd_quint_clean2	0.04	0.03	1.52e-01
imd_quint_clean3	0.03	0.03	2.77e-01
imd_quint_clean4	-0.02	0.03	4.97e-01
imd_quint_clean5	-0.07	0.04	4.21e-02*
imd_quint_cleanMissing	0.45	0.41	2.69e-01

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.16: Multivariable fractional polynomial diabetic eye screening programme data model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
sexMale	0.06	0.02	1.65e-04**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.17: Multivariable fractional polynomial diabetic eye screening programme with glycated haemoglobin (HbA1c) data model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
bl_grade_ou_comb_gradesRetinopathy in one eye	1.03	0.02	0.00e+00**
bl_grade_ou_comb_gradesRetinopathy in both eyes	1.86	0.02	0.00e+00**
I((hba1c_dcct_index/10) ^-2)	-1.84	0.03	0.00e+00**
I((hba1c_dcct_index/10) ^-2 * log((hba1c_dcct_index/10)))	-1.29	0.02	0.00e+00**
I((duration_diab_desp/10) ^0.5)	1.08	0.06	1.96e-67**
I((duration_diab_desp/10) ^1)	-0.35	0.04	8.54e-23**
ethnicitySouth Asian	0.29	0.02	1.50e-42**
ethnicityBlack	0.43	0.02	2.02e-68**
ethnicityAny other Asian	0.28	0.04	5.48e-14**
ethnicityOther	0.25	0.05	2.69e-07**
ethnicityMixed	0.36	0.08	3.07e-06**
ethnicityChinese	0.10	0.11	3.76e-01
ethnicityUnknown	0.49	0.11	3.31e-06**
I((age_at_bl/100) ^3)	0.47	0.09	1.21e-07**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	7.18	0.47	1.48e-52**
type_diab_groupedType 1	-0.11	0.04	5.18e-03**
type_diab_groupedOther	-0.16	0.28	5.56e-01
type_diab_groupedMissing	0.28	0.06	4.64e-06**
imd_quint_clean2	0.03	0.03	3.53e-01

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.17: Multivariable fractional polynomial diabetic eye screening programme with glycated haemoglobin (HbA1c) data model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
imd_quint_clean3	0.01	0.03	7.30e-01
imd_quint_clean4	-0.02	0.03	5.21e-01
imd_quint_clean5	-0.06	0.04	1.04e-01
imd_quint_cleanMissing	0.52	0.41	2.08e-01
sexMale	0.02	0.02	1.40e-01

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.18: Multivariable fractional polynomial targeted medical history model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
bl_grade_ou_comb_gradesRetinopathy in one eye	1.03	0.02	0.00e+00**
bl_grade_ou_comb_gradesRetinopathy in both eyes	1.86	0.02	0.00e+00**
I((hba1c_dcct_index/10) ^-2)	-1.84	0.03	0.00e+00**
I((hba1c_dcct_index/10) ^-2 * log((hba1c_dcct_index/10)))	-1.29	0.02	0.00e+00**
I((duration_diab_desp/10) ^0.5)	1.07	0.06	1.96e-66**
I((duration_diab_desp/10) ^1)	-0.34	0.04	1.19e-22**
ethnicitySouth Asian	0.28	0.02	1.99e-38**
ethnicityBlack	0.42	0.02	7.12e-63**
ethnicityAny other Asian	0.27	0.04	7.88e-13**
ethnicityOther	0.25	0.05	5.58e-07**
ethnicityMixed	0.36	0.08	3.34e-06**
ethnicityChinese	0.09	0.11	4.22e-01
ethnicityUnknown	0.48	0.11	5.53e-06**
I((age_at_bl/100) ^3)	0.39	0.09	2.67e-05**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	7.10	0.47	4.03e-51**
type_diab_groupedType 1	-0.11	0.04	5.34e-03**
type_diab_groupedOther	-0.17	0.28	5.52e-01
type_diab_groupedMissing	0.29	0.06	3.86e-06**
has_ckd	0.07	0.03	1.03e-02*

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.18: Multivariable fractional polynomial targeted medical history model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
exsmoker	-0.05	0.02	1.47e-02*
has_had_stroke	0.09	0.04	2.08e-02*
smoker	-0.05	0.03	4.32e-02*
imd_quint_clean2	0.03	0.03	3.67e-01
imd_quint_clean3	0.01	0.03	8.10e-01
imd_quint_clean4	-0.02	0.03	4.36e-01
imd_quint_clean5	-0.07	0.04	7.99e-02
imd_quint_cleanMissing	0.53	0.41	2.01e-01
sexMale	0.04	0.02	3.10e-02*

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.19: Multivariable fractional polynomial clinical measures model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
bl_grade_ou_comb_gradesRetinopathy in one eye	1.02	0.02	0.00e+00**
bl_grade_ou_comb_gradesRetinopathy in both eyes	1.85	0.02	0.00e+00**
I((hba1c_dcct_index/10) ^-2)	-1.80	0.03	0.00e+00**
I((hba1c_dcct_index/10) ^-2 * log((hba1c_dcct_index/10)))	-1.27	0.02	0.00e+00**
I((duration_diab_desp/10) ^0.5)	1.12	0.07	8.85e-66**
I((duration_diab_desp/10) ^1)	-0.35	0.04	1.99e-21**
ethnicitySouth Asian	0.24	0.02	1.45e-25**
ethnicityBlack	0.40	0.03	2.78e-53**
ethnicityAny other Asian	0.24	0.04	1.39e-09**
ethnicityOther	0.20	0.05	8.85e-05**
ethnicityMixed	0.34	0.08	2.41e-05**
ethnicityChinese	0.05	0.12	6.85e-01
ethnicityUnknown	0.44	0.11	9.04e-05**
I((age_at_bl/100) ^3)	0.34	0.10	4.37e-04**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	7.36	0.49	1.47e-50**
I((map/100) ^1)	0.65	0.09	1.23e-13**
I((bmi_index/10) ^1)	-0.11	0.02	5.71e-12**
type_diab_groupedType 1	-0.13	0.04	1.82e-03**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.19: Multivariable fractional polynomial clinical measures model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
type_diab_groupedOther	-0.22	0.30	4.68e-01
type_diab_groupedMissing	0.29	0.06	5.20e-06**
has_ckd	0.07	0.03	7.73e-03**
imd_quint_clean2	0.02	0.03	4.01e-01
imd_quint_clean3	0.01	0.03	7.77e-01
imd_quint_clean4	-0.03	0.03	3.11e-01
imd_quint_clean5	-0.08	0.04	4.62e-02*
imd_quint_cleanMissing	0.57	0.41	1.68e-01
smoker	-0.06	0.03	3.46e-02*
has_had_mi	0.08	0.04	4.60e-02*
has_had_stroke	0.09	0.04	3.05e-02*
exsmoker	-0.05	0.02	4.02e-02*
sexMale	0.01	0.02	7.16e-01
I((ldl_hdl_index + 0.1) ^1)	0.23	0.07	1.64e-03**
I((ldl_hdl_index + 0.1) ^1 * log((ldl_hdl_index + 0.1)))	-0.12	0.04	1.96e-03**
log(((total_cholesterol_index + 0.1)/10))	-1.36	0.31	1.37e-05**
I(((total_cholesterol_index + 0.1)/10) ^0.5)	4.40	0.94	2.79e-06**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.20: Multivariable fractional polynomial medication use model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
bl_grade_ou_comb_gradesRetinopathy in one eye	1.01	0.02	0.00e+00**
bl_grade_ou_comb_gradesRetinopathy in both eyes	1.82	0.02	0.00e+00**
I((hba1c_dcct_index/10) ^-2)	0.85	0.02	6.97e-254**
I((hba1c_dcct_index/10) ^-1)	-4.10	0.08	0.00e+00**
insulins_use	0.28	0.02	8.20e-37**
ethnicitySouth Asian	0.25	0.02	1.67e-27**
ethnicityBlack	0.38	0.03	1.01e-47**
ethnicityAny other Asian	0.23	0.04	2.06e-09**
ethnicityOther	0.20	0.05	6.91e-05**
ethnicityMixed	0.32	0.08	6.11e-05**
ethnicityChinese	0.06	0.12	6.18e-01
ethnicityUnknown	0.43	0.11	1.47e-04**
I((duration_diab_desp/10) ^0.5)	1.00	0.07	8.01e-52**
I((duration_diab_desp/10) ^1)	-0.34	0.04	5.49e-20**
non_insulin_hypoglycaemics_use	0.30	0.03	8.92e-22**
I((age_at_bl/100) ^3)	0.45	0.10	5.07e-06**
I((age_at_bl/100) ^3 * log((age_at_bl/100)))	7.06	0.49	3.19e-46**
I((bmi_index/10) ^1)	-0.11	0.02	3.10e-12**
I((map/100) ^1)	0.72	0.09	3.35e-16**

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.20: Multivariable fractional polynomial medication use model for sight-threatening diabetic retinopathy (STDR).

Variable	Coefficient	Standard error	p-value
type_diab_groupedType 1	-0.10	0.05	3.02e-02*
type_diab_groupedOther	-0.23	0.30	4.41e-01
type_diab_groupedMissing	0.29	0.06	6.85e-06**
has_ckd	0.06	0.03	4.03e-02*
diuretics_use	-0.07	0.02	9.38e-04**
smoker	-0.06	0.03	2.68e-02*
alpha_blockers_use	0.09	0.03	4.40e-03**
exsmoker	-0.05	0.02	3.85e-02*
imd_quint_clean2	0.02	0.03	4.49e-01
imd_quint_clean3	0.01	0.03	8.41e-01
imd_quint_clean4	-0.03	0.03	3.35e-01
imd_quint_clean5	-0.07	0.04	7.51e-02
imd_quint_cleanMissing	0.63	0.41	1.24e-01
I(((total_cholesterol_index + 0.1)/10) ^1)	0.35	0.08	1.51e-05**
sexMale	0.03	0.02	1.37e-01

Continuous variable transformation is shown where appropriate.
HR, Hazard ratio.
* p-value < 0.05.
** p-value < 0.01.

Table E.21: Missing values for continuous variables in cohort of people with diabetes for all-cause mortality (N =176,751).

Variable	N missing	Percent missing
LDL-cholesterol	48,712	27.6
Triglycerides	44,679	25.3
HDL-cholesterol	28,638	16.2
Total cholesterol	15,602	8.8
HbA1c	13,129	7.4
Body mass index	12,948	7.3
Mean arterial pressure	10,506	5.9
Systolic blood pressure	10,496	5.9
Diastolic blood pressure	10,493	5.9
Age	0	0.0
Duration of diabetes	0	0.0

Table E.22: Missing value rates in continuous variable recording for people with non sight-threatening diabetic retinopathy at baseline.

Variable	N missing	Percent missing
LDL-cholesterol	36,125	26.3
Triglycerides	33,122	24.1
HDL-cholesterol	21,188	15.4
Total cholesterol	10,764	7.8
HbA1c	9,371	6.8
Body mass index	8,780	6.4
Mean arterial pressure	6,862	5.0
Systolic blood pressure	6,853	5.0
Diastolic blood pressure	6,852	5.0
Age	0	0.0
Duration of diabetes	0	0.0

Table E.23: Apparent sight-threatening diabetic retinopathy discrimination (C-statistic), Bayes Information Criterion (BIC), baseline survival probability, and model call with continuous variable transformations.

Model	C-statistic (95% CI)	BIC	Baseline survival at 5 years	Call
Base	0.559 (0.554-0.564)	365844.6	0.908	coxph(formula = survival::Surv(time_days, event_ref) ~ I((age_at_bl/100) ^-2) + I((age_at_bl/100) ^-2 * log((age_at_bl/100))) + ethnicity + sex, data = desp_imp)
DESP data	0.775 (0.771-0.779)	351354.2	0.935	coxph(formula = survival::Surv(time_days, event_ref) ~ bl_grade_ou_comb_grades + I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + I((duration_diab_desp/10) ^1) + I((duration_diab_desp/10) ^1 * log((duration_diab_desp/10))) + ethnicity + type_diab_grouped + imd_quint_clean + sex, data = desp_imp)
HbA1c	0.804 (0.800-0.808)	314729.0	0.945	coxph(formula = survival::Surv(time_days, event_ref) ~ bl_grade_ou_comb_grades + I((hba1c_dcct_index/10) ^-2) + I((hba1c_dcct_index/10) ^-2 * log((hba1c_dcct_index/10))) + I((duration_diab_desp/10) ^0.5) + I((duration_diab_desp/10) ^1) + ethnicity + I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + type_diab_grouped + imd_quint_clean + sex, data = desp_imp)
Medical history	0.804 (0.800-0.808)	314747.4	0.945	coxph(formula = survival::Surv(time_days, event_ref) ~ bl_grade_ou_comb_grades + I((hba1c_dcct_index/10) ^-2) + I((hba1c_dcct_index/10) ^-2 * log((hba1c_dcct_index/10))) + I((duration_diab_desp/10) ^0.5) + I((duration_diab_desp/10) ^1) + ethnicity + I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + type_diab_grouped + has_ckd + exsmoker + has_had_stroke + smoker + imd_quint_clean + sex, data = desp_imp %>% tidyr::drop_na(hba1c_dcct_index))

Table E.23: Apparent sight-threatening diabetic retinopathy discrimination (C-statistic), Bayes Information Criterion (BIC), baseline survival probability, and model call with continuous variable transformations.

Model	C-statistic (95% CI)	BIC	Baseline survival at 5 years	Call
Clinical measures	0.805 (0.801-0.809)	295286.1	0.945	coxph(formula = survival::Surv(time_days, event_ref) ~ bl_grade_ou_comb_grades + I((hba1c_dcct_index/10) ^-2) + I((hba1c_dcct_index/10) ^-2 * log((hba1c_dcct_index/10))) + I((duration_diab_desp/10) ^0.5) + I((duration_diab_desp/10) ^1) + ethnicity + I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + I((map/100) ^1) + I((bmi_index/10) ^1) + type_diab_grouped + has_ckd + imd_quint_clean + smoker + has_had_mi + has_had_stroke + exsmoker + sex + I((ldl_hdl_index + 0.1) ^1) + I((ldl_hdl_index + 0.1) ^1 * log((ldl_hdl_index + 0.1))) + log(((total_cholesterol_index + 0.1)/10)) + I(((total_cholesterol_index + 0.1)/10) ^0.5), data = desp_imp)
Medication use	0.807 (0.803-0.811)	295057.7	0.945	coxph(formula = survival::Surv(time_days, event_ref) ~ bl_grade_ou_comb_grades + I((hba1c_dcct_index/10) ^-2) + I((hba1c_dcct_index/10) ^-1) + insulins_use + ethnicity + I((duration_diab_desp/10) ^0.5) + I((duration_diab_desp/10) ^1) + non_insulin_hypoglycaemics_use + I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + I((bmi_index/10) ^1) + I((map/100) ^1) + type_diab_grouped + has_ckd + diuretics_use + smoker + alpha_blockers_use + exsmoker + imd_quint_clean + I(((total_cholesterol_index + 0.1)/10) ^1) + sex, data = desp_imp)

Table E.24: Apparent all-cause mortality discrimination (C-statistic), Bayes Information Criterion (BIC), baseline survival probability, and model call with continuous variable transformations in males.

Model	C-statistic (95% CI)	BIC	Baseline survival at 5 years	Call
Base	0.806 (0.802-0.809)	339419.0	0.952	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + ethnicity, data = desp_male)
Diabetic retinopathy	0.812 (0.809-0.815)	338653.8	0.953	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + ethnicity + bl_comb_grade_clean_u + grade_ou_min, data = desp_male)
DESP data	0.815 (0.812-0.818)	338217.6	0.955	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^2) + I((age_at_bl/100) ^3) + ethnicity + bl_comb_grade_clean_u + imd_quint_clean + type_diab_grouped + I((duration_diab_desp/10) ^1) + I((duration_diab_desp/10) ^2) + grade_ou_min, data = desp_male)
Medical history	0.822 (0.819-0.825)	337086.2	0.956	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^2) + I((age_at_bl/100) ^3) + ethnicity + smoker + bl_comb_grade_clean_u + has_ckd + has_had_stroke + type_diab_grouped + has_had_mi + imd_quint_clean + I((duration_diab_desp/10) ^1) + I((duration_diab_desp/10) ^2) + exsmoker + grade_ou_min + has_hypertension, data = desp_male)

Table E.24: Apparent all-cause mortality discrimination (C-statistic), Bayes Information Criterion (BIC), baseline survival probability, and model call with continuous variable transformations in males.

Model	C-statistic (95% CI)	BIC	Baseline survival at 5 years	Call
Clinical measures	0.827 (0.823-0.830)	278002.0	0.960	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^2) + I((age_at_bl/100) ^3) + ethnicity + smoker + has_ckd + bl_comb_grade_clean_u + has_had_stroke + I((hba1c_dcct_index/10) ^0.5) + I((hba1c_dcct_index/10) ^1) + type_diab_grouped + has_had_mi + imd_quint_clean + exsmoker + has_hypertension + I((duration_diab_desp/10) ^1) + I((map/100) ^2) + I((map/100) ^2 * log((map/100))) + grade_ou_min + I(((total_cholesterol_index + 0.1)/10) ^0.5) + I(((total_cholesterol_index + 0.1)/10) ^0.5 * log(((total_cholesterol_index + 0.1)/10))) + I((bmi_index/10) ^-1) + I((bmi_index/10) ^-0.5) + I(triglycerides_index ^-2) + I(triglycerides_index ^-2 * log(triglycerides_index)) + log((ldl_hdl_index + 0.1)) + I((ldl_hdl_index + 0.1) ^0.5), data = desp_male)
Medication use	0.831 (0.828-0.835)	277391.6	0.961	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^2) + I((age_at_bl/100) ^2 * log((age_at_bl/100))) + ethnicity + smoker + diuretics_use + insulins_use + has_ckd + has_had_stroke + bl_comb_grade_clean_u + I((hba1c_dcct_index/10) ^1) + I((hba1c_dcct_index/10) ^1 * log((hba1c_dcct_index/10))) + type_diab_grouped + imd_quint_clean + exsmoker + has_had_mi + beta_blockers_use + lipid_lowering_use + alpha_blockers_use + I((map/100) ^2) + I((map/100) ^2 * log((map/100))) + I(((total_cholesterol_index + 0.1)/10) ^0.5) + I(((total_cholesterol_index + 0.1)/10) ^0.5 * log(((total_cholesterol_index + 0.1)/10))) + ccbs_use + grade_ou_min + non_insulin_hypoglycaemics_use + I((bmi_index/10) ^-1) + I((bmi_index/10) ^-0.5) + renin_angiotensin_blockers_use + I(triglycerides_index ^-2) + I(triglycerides_index ^-2 * log(triglycerides_index)) + log((ldl_hdl_index + 0.1)) + I((ldl_hdl_index + 0.1) ^0.5), data = desp_male)

Table E.25: Apparent all-cause mortality discrimination (C-statistic), Bayes Information Criterion (BIC), baseline survival probability, and model call with continuous variable transformations in females.

Model	C-statistic (95% CI)	BIC	Baseline survival at 5 years	Call
Base	0.817 (0.813-0.820)	255622.6	0.961	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + ethnicity, data = desp_female)
Diabetic retinopathy	0.824 (0.820-0.828)	254860.5	0.963	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + ethnicity + bl_comb_grade_clean_u + grade_ou_min, data = desp_female)
DESP data	0.827 (0.823-0.830)	254524.6	0.963	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + ethnicity + bl_comb_grade_clean_u + type_diab_grouped + imd_quint_clean + I((duration_diab_desp/10) ^1) + I((duration_diab_desp/10) ^3) + grade_ou_min, data = desp_female)
Medical history	0.832 (0.829-0.836)	253762.8	0.964	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + ethnicity + bl_comb_grade_clean_u + smoker + has_ckd + has_had_stroke + has_had_mi + type_diab_grouped + imd_quint_clean + I((duration_diab_desp/10) ^1) + I((duration_diab_desp/10) ^3) + exsmoker + grade_ou_min, data = desp_female)

Table E.25: Apparent all-cause mortality discrimination (C-statistic), Bayes Information Criterion (BIC), baseline survival probability, and model call with continuous variable transformations in females.

Model	C-statistic (95% CI)	BIC	Baseline survival at 5 years	Call
Clinical measures	0.837 (0.833-0.840)	203495.1	0.970	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + ethnicity + smoker + bl_comb_grade_clean_u + has_ckd + I((hba1c_dcct_index/10) ^0.5) + I((hba1c_dcct_index/10) ^1) + has_had_stroke + type_diab_grouped + has_had_mi + imd_quint_clean + exsmoker + I((duration_diab_desp/10) ^1) + I((duration_diab_desp/10) ^3) + grade_ou_min + I((bmi_index/10) ^-0.5) + log((bmi_index/10)) + has_hypertension + I(triglycerides_index ^-0.5) + log(ldl_hdl_index) + I(log(ldl_hdl_index) ^2) + I((map/100) ^-1) + I((map/100) ^3) + log(((total_cholesterol_index + 0.1)/10)) + I(((total_cholesterol_index + 0.1)/10) ^0.5), data = desp_female)
Medication use	0.840 (0.836-0.844)	203136.1	0.970	coxph(formula = survival::Surv(tt_death, ev_death) ~ I((age_at_bl/100) ^3) + I((age_at_bl/100) ^3 * log((age_at_bl/100))) + ethnicity + smoker + bl_comb_grade_clean_u + diuretics_use + has_ckd + insulins_use + has_had_stroke + type_diab_grouped + I((hba1c_dcct_index/10) ^1) + I((hba1c_dcct_index/10) ^1 * log((hba1c_dcct_index/10))) + has_had_mi + exsmoker + imd_quint_clean + lipid_lowering_use + alpha_blockers_use + grade_ou_min + beta_blockers_use + non_insulin_hypoglycaemics_use + I(triglycerides_index ^-0.5) + I((duration_diab_desp/10) ^2) + I((duration_diab_desp/10) ^2 * log((duration_diab_desp/10))) + ccbs_use + I((map/100) ^-0.5) + I((map/100) ^3) + log(ldl_hdl_index) + I(log(ldl_hdl_index) ^2) + log(((total_cholesterol_index + 0.1)/10)) + I(((total_cholesterol_index + 0.1)/10) ^0.5) + I((bmi_index/10) ^-0.5) + log((bmi_index/10)), data = desp_female)

Table E.26: Net benefit per 1000 people with diabetes by threshold probability in working age population (All-cause mortality prediction).

Model	**5%**	**10%**	**20%**	**30%**
Male				
Base model	5.8	1.9	0.7	0.0
Diabetic retinopathy grades	6.9	2.5	0.7	0.2
DESP	7.3	3.1	0.8	0.2
Medical history	8.3	3.8	1.2	0.5
Clinical measures	9.5	4.6	1.5	0.6
Prescription use	10.2	5.4	1.8	0.8
Female				
Base model	2.0	1.3	0.1	0.0
Diabetic retinopathy grades	3.3	1.5	0.3	0.0
DESP	3.8	1.6	0.5	0.1
Medical history	4.4	2.1	0.5	0.2
Clinical measures	5.2	2.6	0.8	0.3
Prescription use	5.6	2.8	1.0	0.3

Table E.27: Net benefit per 1000 people with diabetes by threshold probability in working age population (Sight-threatening diabetic retinopathy prediction).

Model	**5%**	**10%**	**20%**	**30%**
Prescription use	59.7	47.2	31.2	20.8
Clinical measures	59.5	46.8	30.9	20.4
Medical history	59.3	46.5	30.3	20.3
DESP and HbA1c	59.3	46.3	30.3	20.3
DESP	54.3	42.8	28.1	17.5
Base model	46.7	3.9	0.3	0.0

E.2 Supplementary figures

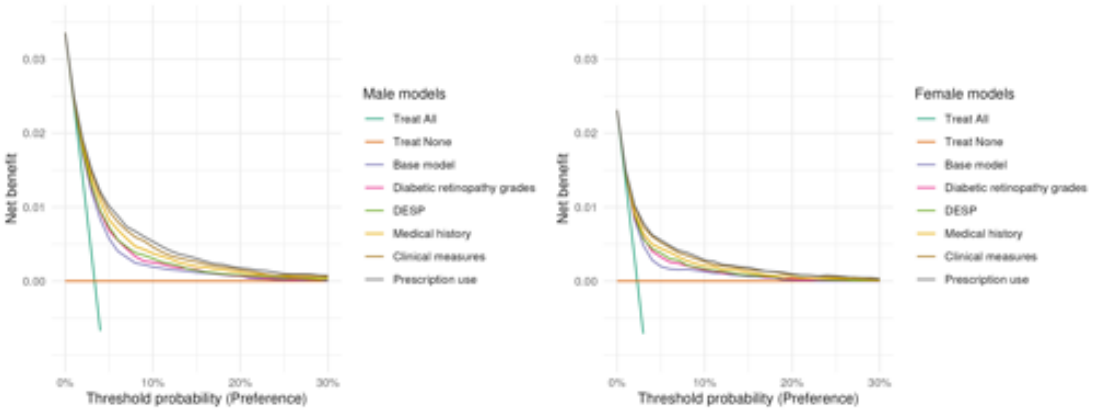


Figure E.1: Decision curve analysis for all-cause mortality models in working age population.

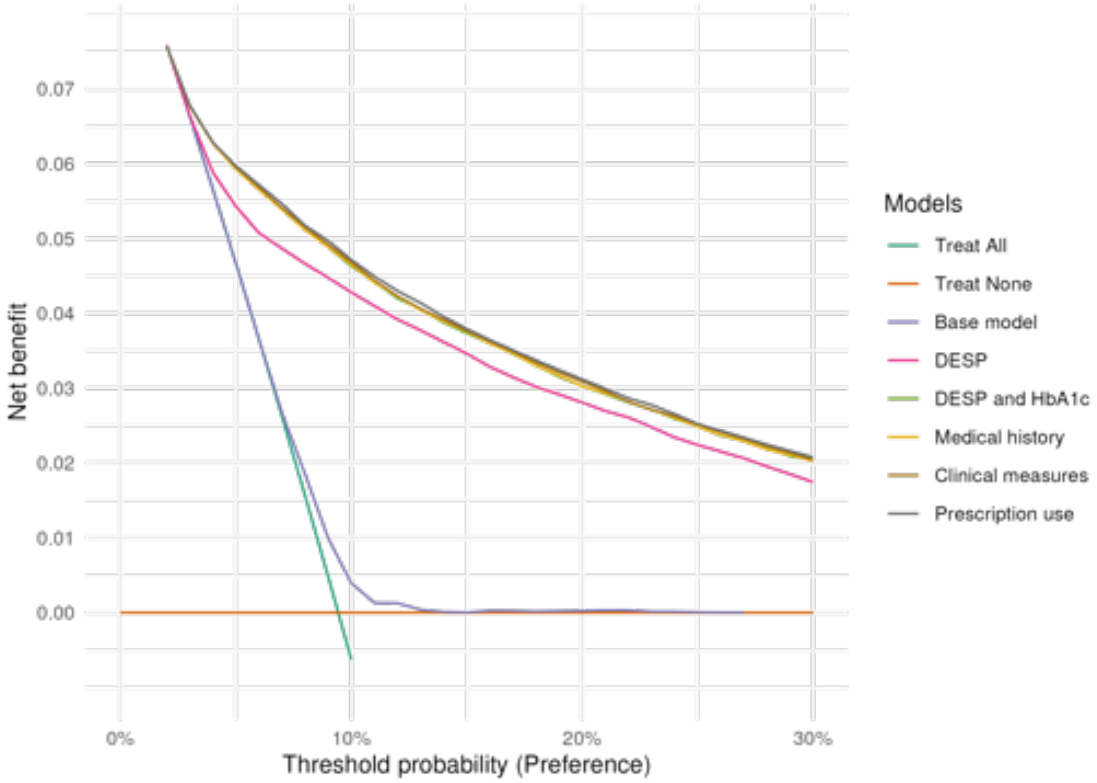


Figure E.2: Decision curve analysis for STDR models in working age population.

F

Declaration forms for published and submitted work

F.1 Formal registration of visual impairment in people with diabetic retinopathy significantly underestimates the scale of the problem: a retrospective cohort study at a tertiary care eye hospital service in the UK

Declaration Form: referencing doctoral candidate's own published work(s) in thesis

Published manuscript:
Olvera-Barrios A, Mishra AV, Schwartz R, Khatun M, Seltene M, Rutkowska C, et al. Formal registration of visual impairment in people with diabetic retinopathy significantly underestimates the scale of the problem: a retrospective cohort study at a tertiary care eye hospital service in the UK. British Journal of Ophthalmology [Internet]. 2022 Oct 14; Available from: https://bjo.bmj.com/content/early/2022/10/14/bjo-2022-321910

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F.2 Effect of ethnicity and other sociodemographic factors on attendance at diabetic eye screening: a 12-month retrospective cohort study

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Olvera-Barrios A, Seltene M, Heeren TFC, Chambers R, Bolter L, Tufail A, et al. Effect of ethnicity and other sociodemographic factors on attendance at diabetic eye screening: a 12-month retrospective cohort study. BMJ Open. 2021 Sep 17;11(9):e046264

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F.3 Ethnic disparities in progression rates for sight-threatening diabetic retinopathy in diabetic eye screening: a population-based retrospective cohort study

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F.4 Two-year recall for people with no diabetic retinopathy: a multi-ethnic population-based retrospective cohort study using real-world data to quantify the effect

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Olvera-Barrios A, Rudnicka AR, Anderson J, Bolter L, Chambers R, Warwick AN, et al. Two-year recall for people with no diabetic retinopathy: a multi-ethnic population-based retrospective cohort study using real-world data to quantify the effect. British Journal of Ophthalmology. Aug 2023; 0:1-7. Available from: https://doi.org/10.1136%2Fbjo-2023-324097

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F.5 Comparison of true-colour wide-field confocal scanner imaging with standard fundus photography for diabetic retinopathy screening

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Olvera-Barrios A, Heeren TF, Balaskas K, Chambers R, Bolter L, Tufail A, et al. Comparison of true-colour wide-field confocal scanner imaging with standard fundus photography for diabetic retinopathy screening. Br J Ophthalmol. 2020 Nov;104(11):1579–84.

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