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DIABETIC Medicine

RESEARCH ARTICLE

Is diabetic retinopathy screening worthwhile among people first diagnosed with diabetes at older ages? A cohort study of Norfolk diabetic retinopathy screening programme

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Abstract

Aims: England's Diabetic Eye Disease Screening Programme offers screening to every resident over age 12 with diabetes, starting as soon as possible after diagnosis and repeated annually. People first diagnosed with diabetes at older ages have shorter life expectancy and therefore may be less likely to benefit from screening and treatment. To inform decisions about whether diabetic eye screening policy should be stratified by age, we investigated the probability of receiving treatment according to age at first screening episode.

Methods: This was a cohort study of participants in the Norfolk Diabetic Retinopathy Screening Programme from 2006 to 2017, with individuals' programme data linked to hospital treatment and death data recorded up to 2021. We estimated and compared the probability, annual incidence and screening costs of receiving retinal laser photocoagulation or intravitreal injection and of death, in age groups defined by age at first screening episode.

Results: The probability of death increased with increasing age at diagnosis, while the probability of receiving either treatment decreased with increasing age. The estimated cost of screening per person who received either or both treatments was £18,608 among all participants, increasing with age up to £21,721 in those aged 70–79 and £26,214 in those aged 80–89.

Conclusions: Diabetic retinopathy screening is less effective and less cost-effective with increasing age at diagnosis of diabetes, because of the increasing probability of death before participants develop sight-threatening diabetic retinopathy and can benefit from treatment. Upper age limits on entry into screening programmes or risk stratification in older age groups may, therefore, be justifiable.

KEYWORDS

diabetic complications, diabetic retinopathy, diagnostic screening programs, Intravitreal injections, laser therapy

1 | INTRODUCTION

The growing burden of diabetes and treatment of diabetes-related complications is costly. In the United Kingdom (UK), the annual cost of diabetes care to the National Health Service (NHS) was estimated at £9.8 billion in 2012.[1] These costs will continue to rise as the population with diabetes grows. In the UK in 2021, there were approximately 4.9 million people living with diabetes. This is projected to rise to 5.5 million by 2030.[2] This creates problems for the UK Diabetic Eye Screening programmes, as the number of individuals requiring screening now far exceeds the 1.4 million people who were invited when the programme was introduced in 2003. There is, therefore, a need to re-evaluate the screening programme and determine whether there are lower risk groups who could be screened less frequently. The NHS intends to implement risk stratification based on individuals' screening results and other risk factors, in order to optimize screening intervals and improve the cost-effectiveness of the programme.[3]

Age may be another prognostic factor relevant to risk stratification and screening policy. At present in the UK, all people with diabetes over the age of 12 years are invited to annual retinopathy screening appointments, with no upper age limit. This differs from other UK national screening programmes which have upper age limits including 74 years for bowel cancer, 71 for breast cancer and 65 for cervical cancer.[4] These age restrictions are in place because in older people the value of screening is reduced by the increasing probability of death due to other causes occurring before screening and treatment can be beneficial, and additionally because older people have fewer years of benefit from treatment before death.

Type 2 diabetes is often and increasingly first diagnosed at older ages. For example, in the Norfolk Diabetic Eye Disease Screening Programme from 2006 to 2017, 38% of people with diabetes screened for the first time were aged 70 years or over (Table 1). The average time taken from diagnosis of type 2 diabetes to development of any grade of diabetic retinopathy is 8–9 years,[5] with sight-threatening retinopathy usually taking at least 10 years to develop, by which time many of those originally aged 70 and over would have died.

Most other UK studies of diabetic retinopathy progression have used routinely collected screening programme data, in which follow-up ends at the time that potentially sight-threatening (R2 or R3) retinopathy or maculopathy (M1) is first detected, and the individual is referred to a specialist ophthalmology clinic for further assessment, confirmation of diagnosis and treatment by laser photocoagulation or intravitreal injection. As individuals are only likely to benefit from screening if their retinopathy or maculopathy is treated, linkage of screening programme data with hospital treatment data is necessary to identify individuals likely to have benefited.

Novelty Statement

- *What is already known?* There is a need to evaluate the UK diabetic retinopathy screening programme to ensure that screening is effective and cost-effective. Risk stratification may be needed to optimize screening intervals and cost-effectiveness.
- *What this study has found?* Diabetic retinopathy screening is less effective and less cost-effective with increasing age at diagnosis of diabetes, because of the increasing probability of death before participants develop sight-threatening diabetic retinopathy and can benefit from treatment.
- *What are the implications of this study?* Upper age limits on entry into the diabetic retinopathy screening programme or risk stratification in older age groups may be justifiable.

We examined data from the Norfolk Diabetic Eye Disease Screening Programme from 2006 to 2017, linked with hospital treatment data from 2007 to 2021, aiming:

(i) to estimate the probability, annual incidence and screening cost of retinal laser photocoagulation and intravitreal injection,
(ii) to estimate the time from first screening episode until treatment or death,
(iii) to estimate time from treatment to death and
(iv) to compare these outcomes between subgroups defined by age at first screening episode.

2 | METHODS

The population of this cohort study was made up of all people with diabetes participating in the Norfolk Diabetic Eye Disease Screening programme who were screened for the first time between 20 December 2006 and 14 March 2017. The three study outcomes were first episode of retinal laser photocoagulation, first episode of intravitreal injection and death. Individuals were followed up from the date of their first screening episode until they had their first laser or intravitreal injection or died, or until follow-up was censored (on 2nd July 2020 for laser and 7th September 2020 for intravitreal injection, as determined by available data). The maximum possible duration of

TABLE 1 Probability, annual incidence and screening cost of retinal laser.

Age at first screen (years)	No. individuals	% by age	No. receiving retinal laser[a]	% receiving laser	95%CI[d]	95%CI[d]	Person years at risk of laser[a]	Annual incidence of laser %[a]	95%CI[e]	95%CI[e]	Ratio No. screens: No. receiving laser[b]	Screening cost per person receiving laser (£)[c]
0–49	7862	17.5	225	2.86	2.50	3.25	81,219	0.28	0.24	0.32	288	11,808
50–59	7768	17.3	162	2.09	1.78	2.43	77,792	0.21	0.18	0.24	332	13,612
60–69	12,063	26.8	154	1.28	1.08	1.49	119,222	0.13	0.11	0.15	486	19,926
70–79	11,423	25.4	93	0.81	0.66	1.00	102,933	0.09	0.07	0.11	673	27,593
80–89	5326	11.8	18	0.34	0.20	0.53	36,419	0.05	0.03	0.08	1140	46,740
≥90	573	1.3	1	0.17	0.00	0.97	2640	0.04	0.001	0.21	1378	56,498
Total	45,015	100.0	653	1.45	1.34	1.57	420,225	0.16	0.14	0.17	451	18,491

[a]Follow-up censored at date of latest first laser 20/7/2021.
[b]Follow-up censored at date of latest screening episode 14/3/2017.
[c]Assuming cost is £41 per screening episode.[6]
[d]CI confidence interval: Binomial.
[e]CI confidence interval: Poisson.

follow-up was, therefore, 14 years and 7 months for laser, and 13 years and 9 months for intravitreal injection.

Screening programme data were obtained from the Norfolk Diabetic Eye Disease Screening Programme database. The data included age and date at every screening episode, from 20th December 2006 until 14th March 2017, and date of death from 9th February 2007 until 20th July 2021. Dates of retinal laser photocoagulation and intravitreal injection were extracted from hard copy medical records held by the Ophthalmology Department of the Norfolk and Norwich University Hospital NHS Trust, which managed and treated all participants referred from the screening programme after detection of sight-threatening retinopathy or maculopathy. Dates of first laser treatment were available from 9th February 2007 until 20th July 2021. Dates of first intravitreal injection were available from 8th April 2010 (when this treatment first became available) until 7th September 2020. Hospital treatment data are held separately from Screening Programme Data. Because Screening Programme participants with sight-threatening retinopathy are referred to, and surgically treated by, the Norfolk and Norwich University Hospital NHS Trust only, we assumed that participants who did not have laser surgery recorded until 20 July 2021, or intravitreal injection recorded until 10 July 2021, had not received the respective treatments, regardless of whether or not they continued to be screened.

Screening programme and hospital treatment data were electronically linked using individuals' NHS numbers and then anonymized.

We carried out statistical analyses to estimate the probability and incidence rates of each outcome, as follows. We calculated the probability of experiencing each outcome during follow-up, with binomial confidence intervals. For each individual, we calculated the time at risk of each outcome, that is, the number of days from first screening episode until first laser, first injection, death or censorship. Censorship dates were the date of the latest retinal laser recorded (for time to laser and time to death) and the date of the latest intravitreal injection (for time to injection). Annual incidence rates were calculated using counts and aggregated time at risk of each outcome, with Poisson confidence intervals. These probabilities and incidence rates were calculated for the whole cohort and for subgroups defined by age at first screening episode. We carried out an additional analysis of time from first treatment until death in participants who had received either retinal laser, intravitreal injection, or both treatments, to indicate the maximum duration of possible benefit from treatment.

To compare statistically the risks of each outcome between age strata, we carried out separate survival analyses for each outcome, with times to outcome event or

censorship as defined above, and with age categories at first screening episode as explanatory variables. For each outcome, we plotted Kaplan-Meier survival curves, stratified by age category, and compared hazards of each outcome with Cox proportional hazards regression models. To assess the proportionality of hazards between age categories, we plotted complementary log-log plots for each outcome and, after each Cox model, tested for proportionality based on Schoenfeld residuals. Finally, to account for the competing risk of death during time to retinal laser or injection, we carried out competing risk regression analyses, with laser or injection as primary outcomes and with death as competing risk. We used competing risks regression because we assumed that risk of death was likely to be associated with risk of retinopathy and maculopathy progression and treatment and was thus an informative reason for censorship when analysing time to treatment. The age groups 80–89 and 90 or above were combined for survival analyses because of the small numbers treated in the older group.

We calculated the number of screening episodes per person who received retinal laser or intravitreal injection or either treatment. We estimated the average screening cost per person treated by assuming that each screening episode cost an average of £41, adjusted for inflation to 2022 prices.[6] We restricted the analysis to the period for which screening episode data were available.

Ethical considerations. The study protocol was approved by the East of England—Cambridge Central Research Ethics Committee (reference 19/EE/0084). The study was a retrospective service evaluation using medical record data, carried out in collaboration with the medical personnel responsible for patient care, with no risk to participants and without influencing their medical care. Participants' consent for medical records to be used for this research was not obtained because it was not feasible, because of the large study population, use of retrospective data recorded up to 14 years earlier and prior deaths of many participants. Confidentiality of data was ensured by removal of personal identifiers after data linkage, which was carried out by the clinical co-investigators.

3 | RESULTS

The cohort comprised 45,015 participants, of whom 653 (1.5%) received retinal laser, 642 (1.4%) received intravitreal injection and 13,592 (30.2%) died during follow-up (Tables 1–3). Thirty-five per cent of participants were aged under 60 years at first screening episode, 52% were aged 60–79, and 13% were aged 80 or older. With increasing age at first screening episode, probabilities of receiving laser or injection were less likely, and probability of death was more likely (Tables 1–3). Of 5326 participants aged 80-89 at first screening episode, 18 (0.34%) received laser, 33 (0.62%) received injection and 3849 (72.3%) died during follow-up. Of 573 participants aged 90 or over at first screening episode, 1 (0.17%) received laser, 2 (0.35%) received injection and 488 (85.2%) died during follow-up.

The median duration of follow-up for analysis of time to retinal laser was 12.3 years (range 0.01–14.6, interquartile range (IQR) 8.1–13.5 years). The median duration of follow-up for analysis of time to intravitreal injection was 8.8 years (range 0.01–13.7, IQR 5.2–12.2 years). The annual incidences of laser, injection and death were 0.16%, 0.14% and 2.8% respectively (Tables 1–3). Annual incidence of retinal laser and of intravitreal injection decreased, and annual incidence of death increased, with increasing age (Tables 1–3; Figure 1). Complementary log-log plots and Schoenfeld residual tests showed that hazards were proportional between age groups for death and laser as outcomes but not for injection as outcome. The Cox regression models showed that, compared to participants aged under 50 at first screening, those aged 80 or over were 91% less likely to receive retinal laser (hazard ratio (HR) 0.09), 47% less likely to receive intravitreal injection (HR 0.63) and 16.5 times as likely to die at any time during follow-up (Table 4). When the competing risk of death was taken into account, those aged 80 or over were 92% less likely to receive retinal laser (subhazard ratio (SHR) 0.08) and were 70% less likely to receive intravitreal injection (SHR 0.30) at any time during follow-up, compared to those aged under 50 (Table 5). Those aged 70–79 were 76% less likely to receive retinal laser (subhazard ratio (SHR) 0.24), and 53% less likely to receive intravitreal injection (SHR 0.47) at any time during follow-up, compared to those aged under 50 (Table 5).

Risk of death after treatment increased with increasing age at first screening episode, with 51% of those aged 70–79 and 67% of those aged 80 or above dying during follow-up (Table 6). Among those treated and who died, median survival time from first treatment to death was 8.0 years and increased with age, with 8.7 years of median survival in those aged 70–79 and 10.0 years of median survival in those aged 80 and above.

The number of screening episodes and screening cost per person who received laser were 451 and £18,491 in the whole cohort, increasing from 288 episodes and £11,808 for participants aged under 50 up to 1378 episodes and £56,498 for participants aged 90 and over (Table 1). The number of screening episodes and screening cost per person who received intravitreal injection were 551 and £22,591 in the whole cohort, increasing from 503 episodes and £20,623 for participants aged under 50 up to 689 episodes and £28,249 for participants aged 90 and over (Table 2). The number of screening

TABLE 2 Probability, annual incidence and screening cost of intravitreal injection and screening cost of receiving either or both treatments.

Age at first screen (years)	No. individuals	No. receiving injection[a]	% receiving injection	95%CI[d]	95%CI[d]	Person years at risk of injection[a]	Annual incidence of injection %[a]	95%CI[e]	95%CI[e]	Ratio No. screens: No. receiving injection[b]	Screening cost per person receiving injection (£)[c]	No. receiving retinal laser or injection or both[b]	Ratio No. screens: No. receiving laser or injection or both[b]	Screening cost per person receiving laser or injection or both (£)[c]
0-49	7862	146	1.86	1.57	2.18	76,776	0.19	0.16	0.22	503	20,623	182	404	16,544
50-59	7768	165	2.12	1.82	2.47	75,010	0.22	0.19	0.26	397	16,277	185	354	14,518
60-69	12,063	186	1.54	1.33	1.78	119,858	0.16	0.13	0.18	551	22,591	210	488	20,009
70-79	11,423	110	0.96	0.79	1.16	117,628	0.09	0.08	0.11	708	29,028	147	530	21,721
80-89	5326	33	0.62	0.43	0.87	53,994	0.06	0.04	0.09	775	31,775	40	639	26,214
≥90	573	2	0.35	0.04	1.26	5368	0.04	0.00	0.13	689	28,249	2	689	28,249
Total	45,015	642	1.43	1.32	1.54	448,635	0.14	0.13	0.15	551	22,591	766	454	18,608

[a]Follow-up censored at date of latest first injection 7/9/2020.
[b]Follow-up censored at date of latest screening episode 14/3/2017.
[c]Assuming cost is £41 per screening episode.
[d]CI confidence interval: Binomial.
[e]CI confidence interval: Poisson.

episodes and screening cost per person who received either retinal laser or intravitreal injection, or both, were 454 and £18,608 in the whole cohort, increasing up to 689 episodes and £28,249 for participants aged 90 and over (Table 2).

4 | DISCUSSION

Our study demonstrates that as a person's age at first screening increases, their likelihood of receiving active treatment for sight-threatening diabetic retinopathy with retinal laser or intravitreal injections decreases. The decline in annual incidence of treatment is most pronounced for laser treatment at >60 years of age and for injection treatment at >70 years of age. This suggests that the probability of benefiting from screening by receiving treatment reduces with increasing age at first screening, while the cost of screening per person treated increases. For each person who received either retinal laser or intravitreal injections, or both, the cost, per person treated, of screening participants aged 90 and over rose by 200% compared to the cohort as a whole. Overall, our findings demonstrate that as age increases the likelihood of receiving active treatment declines (earlier for laser and later for injections) and the cost of screening per person treated rises with increasing age. Screening costs per person treated were slightly lower for laser than for intravitreal injections, partly because the latter treatment was not available before 2010. This is predictable as most participants treated with laser are those with proliferative diabetic retinopathy which is far more prevalent in younger age groups, while injection treatment for diabetic macular oedema is common across most age groups apart from the very oldest cohort.

Several cohort studies evaluating real-world screening programmes have shown that increased screening intervals could safely be adopted in certain groups of participants by stratifying their risk according to baseline screening outcomes.[7–13] However, like most studies which interrogate screening data, they may overestimate the benefits of screening, as the end point of these studies is the identification of sight-threatening diabetic retinopathy and referral of the patient to specialist care. They do not take into account whether active treatment was undertaken, which is necessary to benefit the patient. Treatment may not be carried out for several reasons including that it was not indicated after further specialist examination, retinopathy did not progress to treatable proliferative retinopathy or maculopathy, or due to participants' refusal of treatment, loss to follow-up or death. In such cases, individuals have not benefited from screening.

TABLE 3 Probability and annual incidence of death.

Age at first screen (years)	No. individuals	No. who died	% who died	Person year at risk of death[a]	Annual incidence of death %	95%CI[b]	95%CI[b]
0–49	7862	406	5.2	84,168	0.5	0.4	0.5
50–59	7768	882	11.4	82,444	1.0	1.0	1.1
60–69	12,063	2581	21.4	131,237	2.0	1.9	2.0
70–79	11,423	5385	47.1	128,103	4.2	4.1	4.3
80–89	5326	3849	72.3	58,815	6.5	6.3	6.8
≥90	573	488	85.2	5881	8.3	7.6	9.1
Total	45,015	13,591	30.2	490,648	2.8	2.7	2.8

[a]Follow-up censored at date of latest first laser 20/7/2021.

[b]CI confidence interval (Poisson).

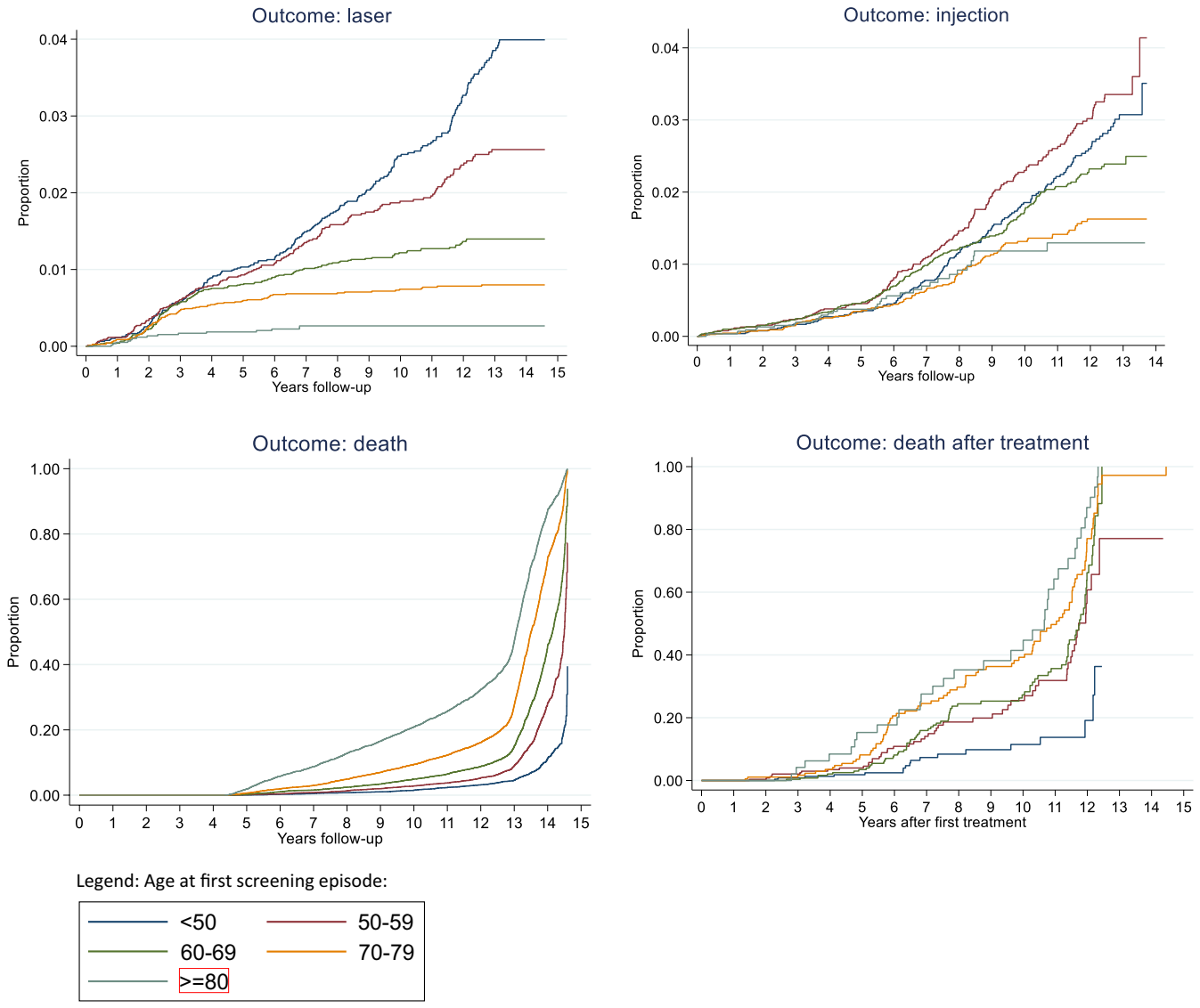

FIGURE 1 Kaplan-Meier estimates of proportions reaching each outcome by age group (EPS files attached).

One study followed a cohort of participants from the North Wales community screening programme beyond referral until laser treatment. They found that in the group with no retinopathy at initial screening, <0.1% of participants required laser therapy at 2 years, rising to 0.2% (cumulative) at 3 years.[12] The presence of any retinopathy

TABLE 4 Time from first screening episode to laser, intravitreal injection and death: Cox regression models.

Age at first screen (years)	Laser				Injection				Death			
	Hazard ratio	95%CI		*p*	Hazard ratio	95%CI		*p*	Hazard ratio	95%CI		*p*
0–49 (reference)												
50–59	0.71	0.58	0.87	0.001	1.20	0.95	1.50	0.121	2.6	2.3	2.9	<0.001
60–69	0.43	0.35	0.52	<0.001	0.90	0.72	1.11	0.323	4.7	4.2	5.2	<0.001
70–79	0.25	0.20	0.32	<0.001	0.63	0.49	0.81	<0.001	9.5	8.6	10.5	<0.001
≥80	0.09	0.05	0.15	<0.001	0.63	0.43	0.92	0.015	16.5	14.9	18.3	<0.001

TABLE 5 Time from first screening episode to laser and intravitreal injection, adjusted for competing risk of death: competing risk regression models.

Age at first screen (years)	Laser				Injection			
	Subhazard ratio	95%CI		*p*	Subhazard ratio	95%CI		*p*
0–49 (reference)								
50–59	0.71	0.58	0.87	0.001	1.15	0.92	1.43	0.229
60–69	0.42	0.34	0.52	<0.001	0.81	0.65	1.01	0.057
70–79	0.24	0.19	0.31	<0.001	0.47	0.37	0.60	<0.001
≥80	0.08	0.05	0.13	<0.001	0.30	0.21	0.43	<0.001

Abbreviation: SHR, subhazard ratio.

at screening was the strongest independent predictor of future laser therapy. Large studies have found that 65%–70% of their population with diabetes had no retinopathy at screening,[15,16] and our previous study of this Norfolk diabetic screening population found that 80% of participants had no retinopathy on their initial screening examination,[11] suggesting that costs could be reduced by screening such individuals less often.

Few studies have specifically investigated the prevalence and treatment of sight-threatening diabetic retinopathy in older age groups. The Oulu Eye Study from Finland analysed a population of 500 people aged >70 years and found that in spite of a high prevalence of previously undiagnosed diabetes, the prevalence of sight-threatening diabetic retinopathy was low (R2/R3 = 3.5%, M1 = 8%). Of those participants with sight-threatening diabetic retinopathy at screening, treatment with laser was indicated in 1.8% for proliferative disease and 6.2% for maculopathy,[16] leading the authors to question the cost-effectiveness of retinopathy screening in this age group. However, their treatment rates far exceed our finding that only 0.6% and 0.8% of our ≥70 cohort required laser or injection treatment respectively.

A strength of our study is the use of a large, comprehensive, population-based data source, similar to other diabetic screening programme studies.[7–14] A particular strength is a long duration of follow-up which includes data from each patient's first screening episode up until they had their first laser or injection treatment or died. This allowed analysis of the likelihood of a patient receiving treatment while taking into account the competing risk of death. This analysis demonstrated that those ≥80 or over were 92% less likely to receive retinal laser and 70% less likely to receive intravitreal injection compared to those aged <50. While 0.9% of the ≥80 cohort received active treatment, 74% died during follow-up. In this age cohort, the annual incidence of laser or injection was 0.05% and 0.06%, respectively, compared to an annual incidence of death of 8.3%. A limitation of the study was that we did not also investigate the additional prognostic value of screening test results, or other risk factors, within each age stratum. This was because the relatively small numbers of people aged over 70 who were treated restricted the statistical power for such analysis, and also because the detailed additional reporting required would have distracted from our primary focus on age at first screen. Another limitation was that we assumed that participants did not receive treatment if there was no record of their treatment held by the Norfolk and Norwich University Hospital. This is likely to be correct for almost all participants because only that hospital provides retinal laser photocoagulation and intravitreal injection for diabetic eye disease in the National Health Service in Norfolk. It is possible

TABLE 6 Time from first treatment (laser or injection) until death among treated participants.

Age at first screen (years)	No. died / no. treated	%	Survival time: years from treatment to death in those who died			Cox regression model		
			Median	Range	Interquartile range	Hazard ratio	95%CI	*p*
0–49	18/305	5.9	6.5	2.3–12.2	5.1–9.6	1.0	(reference)	
50–59	52/274	20.0	7.3	1.5–12.4	5.3–11.4	2.8	1.6-4.8	<0.001
60–69	81/292	27.7	7.7	2.6–12.5	6.4–11.4	3.3	2.0-5.5	<0.001
70–79	94/184	51.1	8.7	1.4–14.7	5.8–11.5	4.8	2.9-7.9	<0.001
≥80	35/52	67.3	10.0	2.8–12.3	6.1–11.6	6.4	3.6-6.1	<0.001
All ages	280/1107	25.3	8.0	1.4–14.5	5.8–11.4			

that some participants may have been treated outside Norfolk or in private hospitals, but such cases are very uncommon and would not have been a result of participation in the Norfolk Screening Programme, and so would not be directly relevant to the aims of this study.

Previous studies have suggested that annual screening for all people with diabetes may not be cost-effective.[16,17,18] Our study roughly estimated cost-effectiveness in each age cohort by calculating the average screening cost per person treated by assuming that each screening episode cost an average of £41,[6] without considering effectiveness of treatment. It showed that the screening cost per person treated increased steeply above age 80 years, which suggests that the cost-effectiveness of screening would be improved by screening those diagnosed at older ages less frequently or not at all, while also reducing the burden of testing on older people. However, as only 8% of all screening episodes were in those >80 at diagnosis, this would not greatly reduce the overall cost of screening programmes. Furthermore, the finding of 10 years of median survival after treatment among those aged ≥80 (Table 6) suggests that those treated could indeed receive substantial benefit from screening and treatment before death.

5 | CONCLUSIONS

Our study demonstrates that diabetic retinopathy screening is less effective and less cost-effective with increasing age, because of the competing risk of death before participants can benefit from treatment. This suggests that implementing an upper age limit for the screening programme may be appropriate. However, given the finding of a 10-year median survival after treatment in our oldest cohort, a risk stratification approach may be more appropriate as it would enable older people to be treated, but with more efficient screening. The results of initial and subsequent screening tests have been shown to be a sound basis for risk stratification,[3,11] so that participants with no detectable retinopathy should have longer intervals between subsequent screens. Information on other risk factors such as duration of diabetes and glycaemic and blood pressure control could also inform risk stratification. Considering the demographic changes in the age of the UK population and increasing incidence of diabetes, continuing to screen the population according to the current paradigm could lead to significant increases in scope and cost over time without conferring adequate health benefits in older age groups.

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CONFLICT OF INTEREST STATEMENT

No potential conflicts of interest relevant to this article are reported.

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