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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 United Kingdom

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We thank the editor and reviewers for their useful comments. A point-by-point response follows.

Comment	Response	Change
Reviewer: 1		
Comments to the Author		
Congratulations on completing this audit. You make a compelling case for the importance of this work both in terms of recognising the burden of visual impairment in diabetes and in assessing the degree to which patients are able to access social support via the certification process. Please find some comments below for your action:	We thank you for your useful comments.	
Methods, Pg 6, line 33: Remove "the negative base 10"	Thank you this has been deleted.	Methods Page 5 Line 158 (0.6 logarithm of the minimum angle of resolution (logMAR) equivalent)
Methods, Pg 6, line 41: Please explain how you obtained the rank scores of the index of multiple deprivation for your cohort? What is the source of this data, what factors impact the score etc?	Thank you, IMD is an established measure of relative socio-economic status derived from the post-code. It is a recognized national statistic used in population health research and in government reports to examine for example social patterns in health and behaviours. More detail on the extraction for IMD has been included in our methods section. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019	Methods Page 5 Line 172 - 176 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] Patient's postcodes were linked to their IMD scores before data extraction, and only the IMD scores were used for analysis.
Discussion, Pg 11, line 10: add "…patients with VI who were eligible for certification were not certified.." as patients can have VI and not be eligible for certification.	This has been added into our discussion section.	Discussion Page 10 Line 303 - 305 Between 2016 and 2019, 84% of the study cohort, and 74% of working age patients with VI who were eligible for certification

		were not certified visually impaired.
Discussion, Pg 11, line 12: make clear that sex differences were present in rates of VI, but not in the likelihood of being certified. Because this sentence follows a discussion of rates not certified, this may be easily missed by the reader.	Thank you, we have modified the start of the sentence accordingly.	Discussion Page 10 Line 305 - 307 For VI, sex differences were present, with males having less odds than females for VI, however, there were no sex differences in odds of certification.
Discussion, Pg 12, line 36: Fix references	This has been corrected. Thank you.	Discussion Page 11 Line 357 …however, evidence of the role of age at menopause on development of STDR remains contradictory. [26,27]
Discussion, Pg 13, lines 17-24: The finding that age is associated with greater odds for VI is not unexpected. Even though the finding is in the context of a cohort with DR, I expect the older patients in this cohort also have a range of age-related ocular comorbidities (see further point below). Though I agree 'the psychological impact of certifying a disability along with hope of VA improvement from patient and/or clinician perspectives, and the nature of injection services focussed on treatment delivery, rather than counselling and administrative activities like CVI' are important points to raise, they all exist independent of age, so I suggest this be a separate point.	Two changes on the discussion section have been made to address this point.	Discussion Page 11 Line 362 - 265 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.[28] Discussion Page 12 Line 387 - 393 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,[34] along with hope of VA improvement from patient and/or clinician perspectives, and the nature of injection services focussed on treatment delivery, rather

		than counselling and administrative activities like CVI, might explain the associations with VI in older individuals.
Additional points:		
As your methodology is based on a visual acuity cut off, please present your VA data fully, at least for those who can be classified as VI. For example, perhaps most of the 325 with VI are just slightly worse 6/24 and so potentially consultants are holding off in case there is some improvement in VA? Or are they considerably worse and still not registered indicating the opportunity to discuss / offer certification really has been missed?	Thank you for raising this useful point. Median and interquartile range as measures of central tendency and spread, respectively, have been included in our Results section.	Results Page 7 Line 226 - 231 A total of 68 patients were certified VI during the study period (9 CVI per 1000 patients) and 38/68 (49%) had diabetic retinopathy recorded as the primary cause of VI (see supplementary table 2). Median (interquartile range) final VA in logMAR was 0.00 (0.00 – 0.20) for non-VI-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).
I find Figure 2 quite difficult to digest. Could a sentence be added to aid understanding?	Thank you for pointing this out. We believe the trajectories for patients which change visual impairment status from eligible to not eligible (or vice versa) is informative. To further add clarification to the diagram we have made 3 changes. 1. Added more detail to the description within the results section that makes reference to figure 2. 2. We have modified the figure 2 caption. 3. We have made some minor edits to figure 2 (labels) to provide further clarity.	Results Page 7 Line 248 - 250 Figure 2 shows groups of patient VA trajectories from baseline to last visit by VI and certification status for the subset of individuals who had VI at any stage during the length of the study (n= 460). Figure 2 caption Figure 2. Sankey diagram showing trajectories in visual acuity defined visual impairment from baseline to final visit. The horizontal axis defines two time points (baseline and final visit) with vertical columns defining groups of patients according to VI status and the final column whether

		the patient was certified or not. Figure 2 has been updated.
Do you have any data on ocular comorbidities in your cohort? It is interesting that a large proportion (74%) of the 325 people with VI had no DR treatment and should be commented on. Why might this be? Are these people with end stage disease eye disease? Or cases of VI due to other ocular conditions? For me this would not invalidate the results but suggest it is not just MR consultants that aren't registering patients.	This is a good point and definitely an aspect which should be explored in future work. The treatment record was for patients who received treatment during the length of study period only, hence we do not have information available in the current dataset if the patient had already received treatment in the past in our service or in any other eye hospital service for other ocular comorbidities.	Results Page 7 Lines 250 -254 A total of 1,260/8,007 (15.7%) patients received any form of DR-related treatment during the study period (Supplementary table 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.
Please add a sentence on how certification status data were collected / accessed.	Thank you, we have added the relevant information into our methods section.	Methods Page 5 Lines 159 – 163 The Performance Audit & Failsafe Service at Moorfields Eye Hospital regularly collects CVI data 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.
To my knowledge certification data is not shared between hospitals. Is it possible that patients could have been registered elsewhere and this would not have been picked up by the audit method? Add as a limitation and also provides a chance to highlight the need for better sharing of this information for service planning etc.	This is accurate and has been added to the limitations of our study.	Discussion Page 12 Limitations Lines 427 - 431 Certification data are not shared between HES, and it is possible that patients could have been registered elsewhere, hence not recorded with our data collection method. Given evidence from larger CVI studies, it

		is unlikely that this could have an appreciably impact on our findings. Data on systemic risk factors was not available, hence we could not examine any associations between systemic risks markers and risk of VI. Nevertheless, we believe that the data does represent the presence of vision impairment in people with DR regardless of cause.
You mentioned causes of VI were taken from CVI forms. Please report the causes that were recorded on the CVI forms for the 68 people who were registered during the course of the study presented in the manuscript and comment on them.	We have included the number of patients certified due to diabetic retinopathy in our results section and included a descriptive table with the primary causes of VI registered by eye from the CVI form as supplementary material (Supplementary Table 2).	Results Page 7 Lines 226 – 228 A total of 68 patients were certified VI during the study period (9 CVI per 1000 patients) and 38/68 (49%) had diabetic retinopathy recorded as the primary cause of VI (see Supplementary Table 2).
It could be hypothesised that ophthalmologists seeing patients who need frequent evaluation and a decision made on whether treatment is indicated or not, do not have the bandwidth at that time to also initiate a conversation on certification. I would therefore be keen for 'treatment' to be included in your sub-analysis using CVI as the outcome variable, to see if the odds of being registered goes down if you are having treatment.	We have tested this hypothesis in the model with certification of visual impairment as the main outcome. When further controlling for treatment (did not receive treatment vs received treatment) in the multivariable logistic regression model, the treatment variable does not show a significant association with CVI (OR received treatment vs did not receive treatment 1.74, 95% CI 0.89 – 3.41, p-value 0.1), and the adjusted odds ratios for the other covariates remain stable. In addition, a likelihood ratio test between nested models (multivariable model without the treatment covariate vs multivariable model with the treatment covariate) showed that the addition of the treatment covariate did not significantly add information to the model (p = 0.1). We would need a larger data set to further explore the effect of treatment on CVI. Please see the corresponding change in our results section.	Results Page 8 Line 278 - 284 A sub analysis exploring CVI as outcome of interest (n=68) among those with VI (n= 325) controlling for the same covariates as our primary logistic regression model showed no significant associations (results not shown). We additionally whether receipt of diabetic retinopathy-related VI 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 (results not shown, available upon request)).

Do you have data on whether certification was offered and declined? If not, add as a limitation.	Data on the proportion of people who had an offer for certification was not available. However, we do believe further work is necessary to identify reasons for declining certification from the patient perspective, and factors associated with offering of certification from the clinician perspective.	In Discussion/Under-registration section we mention: "…further studies are necessary to obtain better VI estimates and to understand factors related to registration uptake.".
Reviewer: 2		
Comments to the Author		
This is an important study Visual impairment in indviduals with DR can be underestimated by > 80% when statistics are only based on certifications of visual impairment.	We are most grateful for your useful comments.	
1. It is said that after the implementation of systematic DR screening in UK using teleophthalmology and good glycemic control, DR is no longer the leading cause of visual impairment inn the working age population in UK. Table 1 shows almost 80% of the visual impairment (VI) to be mainly in people aged over 65 years. Kindly comment	We agree this is an important point. We would like to make reference to our Discussion – Age section where we present arguments about the proportion of patients found with visual impairment and the significant associations found on multivariable logistic regression. Important and possible underpinning factors for this are the duration of disease and other ocular comorbidities. We have also modified this section adding some detail on the possible effect of other ocular comorbidities as per reviewer 1 comments.	See reply to reviewer 1 age comment. Changes are included here for reference Discussion Page 11 Line 362 - 265 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.[28] Discussion Page 12 Line 387 - 393 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,[34] along with hope of VA improvement from patient and/or clinician perspectives,

		and the nature of injection services focussed on treatment delivery, rather than counselling and administrative activities like CVI, might explain the associations with VI in older individuals.
2. Did the duration of diabetes have any role to play in the severity of visual impairment in those with STDR? Kindly add information on the duration of diabetes an dits association to VI.	This is an interesting question, however, limited systemic data was available for analysis in this dataset which forms the basis for future research. Since it is not possible to mine this covariate from our data set available, we could not include it in our analysis.	Discussion, limitations section Page 13 Lines 430 - 431 Data on systemic risk factors was not available, hence we could not examine any associations between systemic risks markers and risk of VI.
3. Similarly it will be useful to know whether the glycemic control had a role to play in VI. Kindly provide information regarding the same if available	Future work could link primary health care records with hospital eye services data to continue this line of enquiry but was not possible with the currently available within the Hospital Eye Service audit data. Please refer to our results section limitations section, and to our paragraph referring to future research.	Results Limitations Page 13 Line Lines 430 - 431 Data on systemic risk factors was not available hence we could not examine any associations between systemic risk makers and risk of VI.
4. What are the main reasons as to why people with VI due to DR have not obtained certification of VI ? Kindly list the probable reasons and possible solutions to overcome this problem in the discussion section	This is a really important question which we have attempted to address in our discussion section by comparing findings from landmark studies available to date and findings from our study. Briefly, certification of visual impairment in England is voluntary and must be initiated by a consultant ophthalmologist, there is a delay from onset of visual impairment to certification, prolonged treatment and frequent hospital visits could interact with the psychological impact of certifying a disability, there can be hopes for visual acuity improvement from the patient or clinician perspective, there is an association with socioeconomic deprivation, and the busy environment of medical retina or injection clinics may limit at some extent, the opportunity to counsel patients and comply with the administrative process of offering and certifying a patient. We are, however, happy to consider further aspects that could be discussed in our work.	These aspects are mentioned in our discussion section where more detail on each is available through pages 10-13.

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 United Kingdom

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Short Title: Visual impairment certification rates in diabetic retinopathy

Keywords: Certification of visual impairment, diabetic retinopathy, blindness

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Synopsis/Precis

Visual impairment in patients with diabetic retinopathy can be underestimated by more than 80% when statistics are only based on certifications of visual impairment alone.

Abstract (250 words)

Aims:

To analyse the prevalence of visual impairment (VI), compare it to certification of VI (CVI), and to analyse VI associations 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 VI, defined as vision in the best eye < 6/24. We conducted a multivariable logistic regression for VI as primary outcome of interest, controlling for age, sex, type of diabetes, baseline DR grade, ethnicity, and index of multiple deprivation.

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 VI did not have CVI after a mean (SD) follow-up of 1.87 (±0.86) years. Older age, showed a positive association with VI (OR per decade rise 1.88, 95% CI 1.70-2.08; p $1.8x10^{-34}$). Males had lower risk of VI (OR 0.62, 95% CI 0.50-0.79, p $6.0x10^{-5}$), and less deprivation a graded inverse association with VI (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 vision impairment are not registered at the point-of-care which could translate to underestimation of diabetes-related VI, and all-cause VI at a national level if replicated at other centres. Further work is needed to explore rates of VI and uptake of registration.

What is already known on this topic

People with diabetes in England undergo annual diabetic eye screening, which triggers prompt referral to eye hospital services, and diabetes-related treatment regimens are covered as part of universal healthcare.

Certification of visual impairment is a valuable tool to provide assistance for patients and also to measure the causes and rates of visual disability in the UK. The certification of visual impairment due to diabetic retinopathy has decreased over the last 20 years. Since 2010, diabetic retinopathy was no longer leading cause of certification of visual impairment in England.

What this study adds

We have found a marked under-registration of visual impairment of 84% in patients with diabetic retinopathy at the largest centre for ophthalmic treatment in England.

Estimating nationwide prevalence of visual impairment on patients with diabetic retinopathy with the certification of visual impairment could substantially underestimate the problem.

How this study might affect research, practice or policy

Using rates of vision impairment in addition to rates of certification would provide valuable and complementary data towards the goal of preventing diabetes-related blindness, particularly by increasing the size of the dataset available.

Epidemiological studies assessing the causes of blindness should consider using point-of-care structured visual acuity data at different timepoints to provide more accurate estimates of the causes blindness.

Resources and public health strategies to target individuals at higher risk of blindness could be in need of reallocation if the primary causes of blindness are different than the estimations derived from CVI registries. Further work may also be needed to understand under-registration, a complex interface between patient choice and health systems.

Introduction

The number of blind people in the United Kingdom has been documented since 1851.[1,2] Reports on causes of low vision in England and Wales began in 1950.[1–3] From the 1930's, the BD8 designated forms signed by an ophthalmologist were required to certify someone as blind or visually impaired.[4,5] 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).[6] In 2013, an eye health indicator was incorporated into the Public Health Outcomes Framework in England.[7] 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 (VI): 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 benefits, public transport benefits (SSI level), as well as increased access to low vision support.

Diabetic retinopathy (DR) is a major complication of diabetes, and the leading cause of incident sight impairment and blindness in the working age population in many countries.[4,8,9] There was an estimate of 463 million people with diabetes globally in 2019, and the number is projected to rise to 700 million in 2045.[10] An early diagnosis and a timely intervention can prevent blindness. The UK implemented a systematic diabetic eye screening programme (DESP) in England in 2003, achieving nationwide coverage by 2008.[11] The English DESP offers annual photographic screening for all patients with diabetes aged ≥ 12, and as a possible result of these measures and others, DR is no longer the leading cause of CVI in England and Wales.[4,11] Patients are referred to hospital eye services (HES) when certain severity level based on retinal features is present on retinal photographs.[12]

The aim of this study was to comprehensively analyse the prevalence of VI 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 VI.

Methods

This was a retrospective study registered as an audit and approved through the research governance process at Moorfields Eye Hospital NHS Foundation Trust. The study adhered to the UK Data Protection Act 2018 and included consecutive patients referred to the medical retina service at Moorfields Eye Hospital NHS Foundation Trust with a diagnosis of referrable DR from the NHS DESP between 4 January 2016 to 1 August 2019. The main outcome measure was the prevalence of patients with VI. Moorfields Eye Hospital is the main referral centre for treatment of ophthalmic diseases in England, and serves 5 main DESPs (i.e. North Central London, North East London, North West London, South East London, and South West London DESP). Only in 2019, the hospital reviewed a total of 5,173 referrals from the DESPs.

Visual impairment was defined as best corrected VA in the better eye worse than 6/24 (0.6 logarithm of the minimum angle of resolution (logMAR) equivalent) following UK CVI Guidance definition.[6] The Performance Audit & Failsafe Service at Moorfields Eye Hospital regularly collects CVI data 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. Patients with missing data on age, sex, less than 24 weeks of follow-up, missing DR grades, and patients with no DR (R0M0) at the time of their clinical examination, were excluded from the analysis (Figure 1). Supplementary table 1 shows overall patient characteristics of excluded patients.

Visual acuity data was measured and recorded in Snellen fractions, ETDRS letter scores, and as logMAR at three different timepoints; baseline, year one and at the end of follow-up. All VA measurements were converted to logMAR based on work from Holladay *et al*.,[13] Beck *et al*.[14] and Gegori *et al*.[15] To align with UK CVI guidance,[6] the eye with best VA at each visit was selected for analysis.

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] Patient's 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 data of the English indices of deprivation 2019, where the 1st quintile was the most deprived and

the 5th quintile the least deprived.[16] IMD quintiles 4 and 5 were pooled due to small numbers with visual outcome. 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 grades (grading classification in order of increasing severity: M0, R1, M1, R2, and R3) 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. DR grades were further categorised as non-sight-threatening DR (non-STDR; comprising R1 & M0 grades), and STDR (comprising grades > R1 and/or M1). 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).

Statistical analysis

We used the software for statistical computing R (version 4.1.2) for analyses.[17] 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 VI. We conducted a multivariable logistic regression analysis with VI 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 ratio per year in age and IMD category (with decreasing levels of deprivation) were also examined given graded associations. As part of sensitivity analyses, we calculated the certification of VI 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).[18]

Results

A total of 8,007 patients (4,859/8,007; 61% male) were included for analysis. Table 1 shows the patient cohort characteristics. A total of 68 patients were certified VI during the study period (9 CVI per 1000 patients) and 38/68 (49%) had diabetic retinopathy recorded as the primary cause of VI (see Supplementary Table 2). Median (interquartile range) final VA in logMAR was 0.00 (0.00 – 0.20) for non-VI-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 1.87 years (SD ±0.86, interquartile range 1.11–2.58). There were no statistically significant differences in follow-up of certified patients (years to certification) vs. patients with VI (years followed-up with VI) 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).

Excluded patients 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 VI, 267/5,350 (5.0%) died within the study period, and none of the patients who died were eligible for VI at their baseline hospital eye service (HES) visit. Among the 5% that died, mean (IQR) time to death from the first visit was 1.2 (0.5-1.8) years.

The prevalence of VI at the final visit was 4.3% (325/8,007). Eighty four percent (272/325) of patients with VI were not certified by the last visit (Table 2), namely 34 cases with VI not certified per 1000 patients with diabetic retinopathy at HES. A total of 165/8,007 (2.1%) patients had VI at baseline and remained visually impaired by end of follow-up. The incidence rate of VI was 10.9 per 1,000 person-years (160 new VI cases during study period). Figure 2 shows groups of patient VA trajectories from baseline to last visit by VI and certification status for the subset of individuals who had VI 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 (Supplementary table 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, mean [IQR] follow-up 2.2 [1.6-2.7] years), 83% (214/258) of patients with VI were not certified by the last visit. In the subset of working age population patients (n=3,952,

mean [IQR] follow-up 1.8 [1.1-2.5] years), 74% (51/69) of patients with VI were not certified by the last visit.

Table 1 shows the results of multivariable logistic regression model with VI as the primary health outcome of interest. Every decade increase in age was associated with 88% increase in odds of having VI (p $1.8x10^{-34}$). Males showed a 38% reduction in odds of VI when compared to females (p $6.0x10^{-5}$). The majority of VI and CVI was in older adult patients (supplementary table 4). In the working age band, males had 59.4% (41/69) and 52.2% (12/23) of VI and CVI, respectively. This was reversed from 65 years and older with females having 57.4% (147/256) and 57.8% (26/45) of VI and CVI, respectively. When compared to the most deprived patients, the least deprived had a 42% reduction in the odds of VI, and per unit increase in IMD category was associated with a 17% reduction in odds of VI (p for linear trend 0.002, Table 1). Having STDR at baseline was associated with a 2.20-fold increase in odds of having VI when compared to patients with non-STDR. There were no associations with ethnicity between the main ethnic groups (Black, south Asian) when compared with whites. The other ethnic group showed significant associations with VI, however, due to the heterogeneity of this category, meaningful conclusions cannot be drawn. Type of diabetes did not show associations with VI. 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 those with VI (n= 325) controlling for the same covariates as our primary logistic regression model showed no significant associations. We additionally whether receipt of diabetic retinopathy-related VI 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 (results not shown, available upon request)).

Table 1. Patient characteristics and mutually adjusted odds ratios for visual impairment.

	Visual impairment			Multivariable logistic regression
Characteristic	**Overall, N = 8,007[1]**	**No, N = 7,682[1]**	**Yes, N = 325[1]**	**OR (95% CI); p-value[2]**
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				
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**

[1]n (column %) for categorical and mean (SD) for continuous variables.

[2]Mutually adjusted odds ratios for all variables shown in table.
Odds ratios greater than 1 imply greater odds of visual impairment.
Bold p-values represent statistically significant results.
DM; diabetes mellitus, DR; diabetic retinopathy, STDR; Sight-threatening diabetic retinopathy, IMD; index of multiple deprivation.

Table 2. 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[1]**	**Not CVI eligibile[1]**	**CVI eligible[1]**	**Overall, N = 8,007[1]**	**Not CVI eligibile[1]**	**CVI eligible[1]**
CVI						
Certified	4 (<0.1%)	1 (<0.1%)	3 (1.1%)	68 (0.8%)	15 (0.2%)	53 (16%)
Not certified	8,003 (100%)	7,731 (100%)	272 (99%)	7,939 (99%)	7,667 (100%)	272 (84%)
Total	8,007 (100%)	7,732 (100%)	275 (100%)	8,007 (100%)	7,682 (100%)	325 (100%)

[1]n (%)
Grey cells represent the number of visually impaired patients without certification of visual impairment.
CVI; certification of visual impairment.

Discussion

Our study 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 VI who were eligible for certification were not certified visually impaired. For VI, sex differences were present, with males having less odds than females for VI, however, there were no sex differences in odds of certification. Decreasing levels of deprivation were associated with less odds of VI. There were no associations with ethnicity between the major ethnic groups. Our findings suggest a remarkable under representation of VI in patients with DR when using the CVI as index of blindness.

Under-registration

CVI data represents a useful epidemiological resource for VI analysis in England, but has limitations due to uptake. Since at least 2010, there has been a reduction in CVI due to DR in England and Wales.[4,9] This contrasts with findings from global studies in which the rate of diabetes-related VI has increased, and accounts for a larger proportion of blindness/VI.[3,19] Registration of VI in England is voluntary and must be initiated by a consultant ophthalmologist.[6] In this context, it has been estimated that up to 53% of eligible patients might not be certified blind despite consultation at hospital eye services.[20,21] We have demonstrated that, at point of care, this difference is even greater, with an 84% under-registration. Derived from our study, we could expect a total of 11 new cases of VI per 1000 patients with diabetic retinopathy 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 VI 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.[20,22] We have demonstrated that there were no differences in length of follow-up of unregistered eligible patients vs registered patients in our cohort (p=0.4). Furthermore, we have shown that after exclusion of cases with ≤ 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 audits available that assess VI among patients with DR. Considering the increasing population prevalence of diabetes,[23] and the well-established English DESP,[11,23] our results suggest that the VI prevalence among patients with DR is underrepresented in CVI derived analyses, and that further studies are necessary to obtain better VI estimates and to understand factors related to registration uptake.

Sex

A recent study assessing the rates of VI impairment in Austria found an overall higher VI incidence in females than in males (32.2 vs 17.7 per 100,000 person-years).[24] In our analysis, 53.8% (175/325) of overall VI was present in females, but males showed greater rates of VI in the working age population (See supplementary table 4). These findings align with previous reports[20,24] and warrant further investigation. In our multivariable logistic regression models, males showed a 38% decrease in odds of VI (p $6.0x10^{-5}$) when compared to 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). With a mean age for reaching menopause in the UK of 51,[25] menopause can be considered a possible underpinning factor for the differences observed, however, evidence of the role of age at menopause on development of STDR remains contradictory.[26,27]

Age

In our patient cohort with DR, older patients showed greater odds for VI. Recent advances in diabetes treatment, DR treatment, and improvement in therapeutic goals, have allowed people with diabetes to experience increased life expectancies.[28] 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.[28] Considered the standard of care for DMO, ranibizumab and aflibercept intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections were approved for use in the UK in 2013 and 2015, respectively.[29,30]

Fixed and frequent dosing regimens have shown good VA outcomes with an average of 4.4 to 10.5 ETDRS letter score gain.[31,32] 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.[33] 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,[34] stressing the fact that despite repeated visits to eye hospital services, VI 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,[34] along with hope of VA improvement from patient and/or clinician perspectives, and the nature of injection services focussed on treatment delivery, rather than counselling and administrative activities like CVI, might explain the associations with VI in older individuals.

Deprivation

Socioeconomic deprivation has been associated with attendance at diabetic eye screening (DES).[23] Those from more deprived areas are less likely to attend DES appointments,[23] which is further associated with presentation to DES or HES with late STDR.[11] 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.

Strengths and limitations

The strengths of our study are as follows. We have analysed point of care data of patients with DR of the largest eye hospital in the UK. We have included a clear definition of VI based on VA following UK CVI guidance[6] 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. We have utilised a rich dataset that includes both demographic and ocular variables.

The limitations of our study are that despite the large catchment area, the results are from a single centre and might not extrapolate to other settings. We have not verified the causes of VI, 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, we have allowed sufficient time for cataract surgery to have occurred in our cohort and we 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 our data collection method. Given evidence from larger CVI studies, it is unlikely that this could have an appreciably impact on our findings. Data on systemic risk factors was not available, hence we could not examine any associations between systemic risks markers and risk of VI. Nevertheless, we believe that the data does represent the presence of vision impairment in people with DR regardless of cause. We did not account for visual field criteria for VI definition, which could have included more VI cases. Further work at a national level in both DES and HES to assess prevalence of VI as well as CVI is needed to confirm our 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, 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.

Conclusion

Our findings suggest that VI can be underrepresented by more than 80% when considering CVI data alone. This raises concerns, namely that unregistered patients are receiving inadequate support, that the CVI-driven allocation of resources for the main causes of blindness could be improved, and highlights the need to raise awareness and

understanding of CVI registration and benefits in both, patients, and healthcare providers.

Ethics approval: The study was registered as an audit and approved through through the research governance process at Moorfields Eye Hospital NHS Foundation Trust and adhered to the UK Protection Act 2018.

Conflict of Interest: None of the authors has a proprietary interest in this work.

Contributors: All authors meet ICMJE criteria for authorship. AO-B, ARR, CGO and CE designed the study. AO-B, RS, MS, MK, CR, undertook data management and processing. AO-B undertook data analysis, and ARR, CGO, CE, and AT provided statistical advice. AO-B, and AVM wrote the first draft of the report, which was critically appraised by all authors. All the authors read and approved the final draft for publication.

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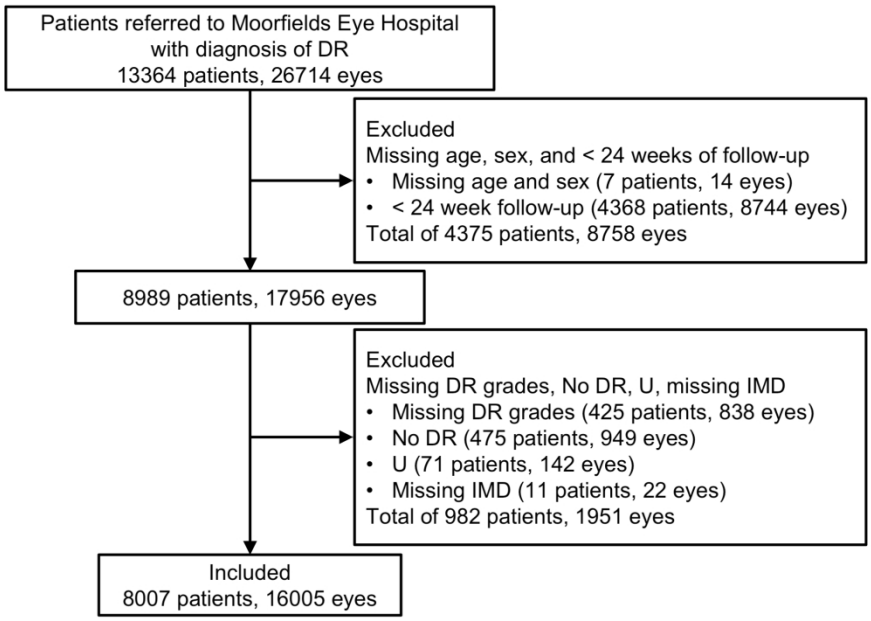

Figure 1. Diagram of exclusions.DR; diabetic retinopathy, U; ungradable, IMD; index of multiple deprivation.

495x332mm (118 x 118 DPI)

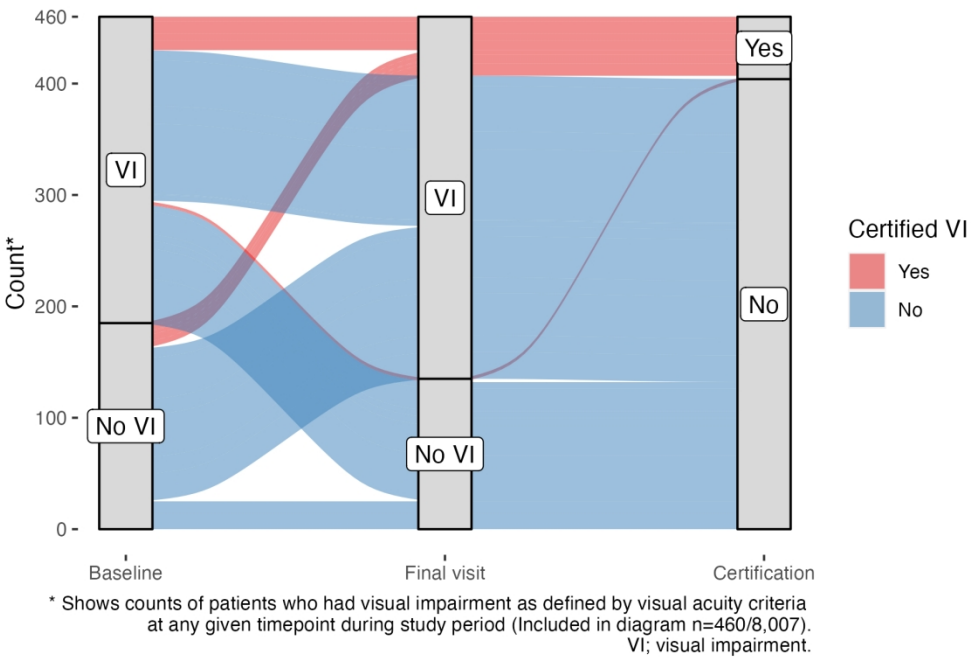

Figure 2. Sankey diagram showing trajectories in visual acuity defined visual impairment from baseline to final visit. The horizontal axis defines two time points (baseline and final visit) with vertical columns defining groups of patients according to VI status and the final column whether the patient was certified or not.

406x279mm (118 x 118 DPI)

Supplementary material.

Supplementary table 1. Characteristics of excluded patients.

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, n (column %) for categorical variables.

†Total of patients excluded, there are 7 additional cases with missing age and sex which are not shown in this table.

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

Supplementary table 2. Causes of visual impairment recorded on registration forms.

Characteristic	Left eye cause, N = 68[1]	Right eye cause, N = 68[1]
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%)

[1]n (%)

Supplementary table 3. Treatment among cohort during study period.

		Visual impairment		Certification of visual impairment	
Characteristic	**Overall, N = 8,007[1]**	**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%)

[1]n (column %)

Supplementary table 4. Visual impairment and certifications of blindness by sex. Row percentages.

	Visual impairment			Certification of visual impairment		
Characteristic	**Overall, N = 325[1]**	**Female, N = 175[1]**	**Male, N = 150[1]**	**Overall, N = 68[1]**	**Female, N = 37[1]**	**Male, N = 31[1]**
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%)

[1]n (column %)