Retrospective Write-Up for Vision Research

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Abstract

Neovascular age-related Macular Degeneration (nAMD) represents one of the leading causes of blindness in both developed and developing countries. This paper examines inequalities and variations in visual outcomes for people being treated for nAMD, the reasons behind any variation.

nAMD began to be treated via intraocular injections With Anti-Vascular Endothelial Growth Factors (anti-VEGF) after 2006. This paper draws on the landmark trials that first established the safety and efficacy of anti-VEGF therapy for nAMD.

Using a systematic review previously published by the authors, this paper investigated whether there were factors that could be identified from the dataset that influenced how effective anti-VEGF therapy is in reducing visual loss in patients with nAMD. This paper highlights the importance of being able to identify modifiable factors, such as number of anti-VEGF injections received, that could lead to better visual outcomes for these patients. This paper then goes on to examine levels of variation in visual outcome in nAMD nationally in the UK, as well as further investigating any influencing factors that could not be identified in the previously published systematic review. This was done using a large real-world dataset of over 26,00 patients from seven hospitals. These highlighted significant levels of variation, but struggled to identify definitively further influencing factors, such as ethnicity or social deprivation. This could be because there genuinely was not an associated relationship between these factors and visual outcomes, but certainly in the case of ethnicity, it is particularly apparent that there was an overwhelmingly white population, so there may have not been enough ethnic variation to detect any effect of ethnicity.

Keywords: • Neo vascular age-related macular degeneration • Anti-VEGF • Gene therapy• Retina

Introduction

Objectives

A previously published systematic review by the authors of this work, Gill et al. studied demographic and clinical factors that influence variation in visual outcomes in patients with Neovascular Age-Related Macular Degeneration (nAMD) when they are being treated with Anti-Vascular Endothelial Growth Factor (anti-VEGF). This review found that age at baseline, number of anti-VEGF injections and visual acuity at baseline contribute to the success of anti-VEGF treatment for nAMD. However, it was not established what impact factors such as ethnicity, smoking or social deprivation has on the success of treatment. To explore such factors an analysis of a real-world dataset was undertaken. The objectives of this work were:

- To establish how variation in letterscore, number of anti-VEGF injections received and compliance with guideline recommendations of the number of injections (3 months and 12 months) can be explained by social deprivation.
- To establish how much variation in patients developing bilateral nAMD can be explained by social deprivation.
- To establish how much variation in visual loss of >15 letters can be explained by smoking status.

Background

Pathogenesis of nAMD: AMD can be dry and wet (or neovascular). Dry AMD accounts for approximately 85% of total AMD cases and is characterized by a mild to moderate loss of central vision, with retention of peripheral vision [1-3]. In dry AMD onset is insidious and gradual, with loss of vision occurring over a period of months to years. There is currently no NHS funded licensed treatment for dry AMD, although research into this continues. Genetics plays a crucial role in whether dry AMD progresses to advanced or wet AMD, as do lifestyle choices such as smoking, obesity, lack of exercise, and diet lacking fruit and green vegetables. Although wet, or nAMD only accounts for 10%-15% of total AMD cases, it causes 80% of cases of blindness [2-6]. nAMD differs clinically from the dry form by the presence of RPE detachment, leakage from choroid blood vessels due to increased levels of VEGF. This leads to scar or glial tissue and macular hard exudates . nAMD is also characterized by an acute onset and can develop in a matter of days to weeks. Optical Coherence Tomography (OCT) is a non-invasive procedure that uses light waves to form an image of all the layers of the retina. Figures 1 and 2 respectively below shows an OCT image of a normal retina and a retina with nAMD.

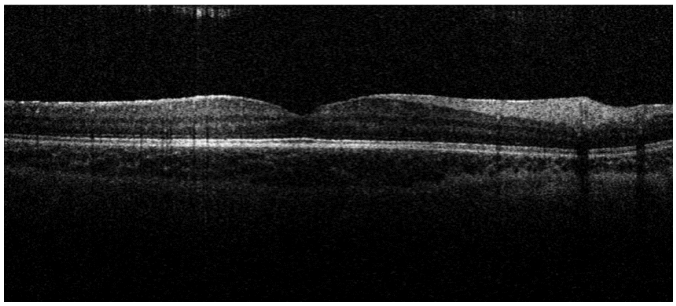

Figure 1. OCT image of a normal macular region.

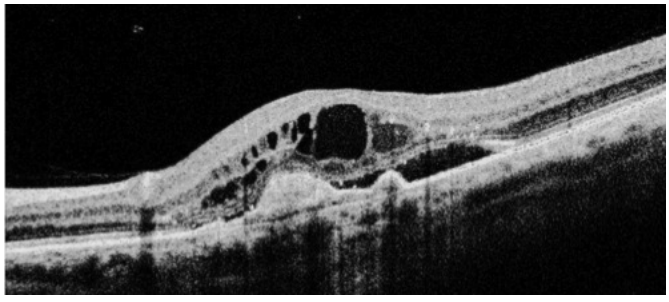

Figure 2. OCT image of a retina with nAMD, showing fluid within and beneath the retina (the black spaces) and therefore a greater retinal thickness

Treatment for nAMD

Although anti-VEGF is not a curative treatment for nAMD, the aim of its use is to slow disease progression and maintain optimal vision for as long as possible [7,8].

Ranibizumab and Aflibercept are the two most used licensed treatments in the UK, and intravitreal injections are given directly into the vitreous (the gel-like fluid that fills the eye) under drops of local anesthetic. Aflibercept is usually administered, with a three-month loading phase treatment (where a patient with newly diagnosed nAMD is given an initial once-monthly dose of anti-VEGF for three months) [9-11]. During the loading phase, injections are given on a four-weekly basis. In order to prevent ocular infection, administration of anti-VEGF follows peri-orbital skin cleansing, ocular surface sterilisation, orbital draping, and insertion of a sterile lid speculum. Overall, patients who receive regular anti-VEGF therapy for nAMD can expect to slow the progression of the disease overall, and are likely to retain their sight, even though visual acuity tends to worsen over time. However, some patients will still lose their sight [12].

Global costs of nAMD

The World Health Organisation ranks AMD as the third global cause of blindness after cataract and glaucoma [13]. nAMD is not only a leading cause of blindness in developing countries, but also a significant burden. Large scale epidemiological studies highlight that nAMD prevalence is increasing in developing countries such as India, because of a rise in life expectancy [1,14]. Global estimates of the cost of AMD are $343 billion dollars, including $255 billion dollars in direct healthcare costs [13]. In the UK, nAMD represents a significant use of NHS resources.

Variation in visual outcomes

Despite anti-VEGF therapy showing significant improvements in visual prognosis overall, there are variations in the visual outcomes of patients with nAMD who are treated with anti-VEGF therapy. Therefore, there is a need to understand the levels of this variation, and possible causes.

Materials and Methods

Background to the dataset

The data used in this study came from an Electronic Medical Records (EMR) database managed by a company called Medisoft. In 2021, there were 80 ophthalmology departments across the UK that use this EMR system as part of their nAMD pathway. This system records information on:

Age in years and months at the time of first EMR entry for nAMD.

- Age in years and months at the time of first intravitreal injection of anti-VEGF drugs for nAMD.Gender.
- Visual acuity (measured in both ETDRS letter score and Snellen) for both eyes.
- The time of first injection and at each prior or subsequent assessment visit.
- Date of each subsequent assessment / injection visit.
- Re-treatment criteria, decision and if relevant reason(s) for permanently stopping treatment.
- Details of the injection process (including indication for injection, drug used, dose, site, anaesthesia used, and complications).
- Defined clinical examination findings at each visit related to neovascular AMD.
- Date of other ophthalmic procedure or investigation performed during follow up (ocular surgery, or procedures, retinal imaging, blindness registration).
- Grade and job title of the person administering the injections and recording the assessment data.
- Whether treatment was initiated elsewhere, or part of the treatment occurred at another centre.

Data management

Ethical approval: Health Research Authority (HRA) and Health Sciences Departmental Research Governance approvals were sought, and approval granted in December 2018.

Approaching sites: Sites known to contribute data to the EMR system as part of their nAMD pathway were invited by letter to access their data. Sites were selected to take part based on the members of the AMD users' group [15]. Written consent was required from the medical retina lead and Caldicott Guardian at each site for their EMR nAMD data to be extracted and used as part of the study. Figure 3 gives a flow diagram of the recruitment process. There were three inner city teaching hospitals, and the other four sites were district hospitals.All eligible sites who were using the EMR system were approached to take part in the study. No sites were excluded. Sites were only not included if they declined to take part or failed to reply.

Figure 3. Recruitment process flowchart diagram.

Extraction of data: Copies of signed consent forms from participating sites were sent to Medisoft, who extracted and anonymised the data from these sites, which dated from 2008 to 2017. They were then transferred electronically in a password protected electronic link, as Comma-Separated Values (CSV) files. These files were then imported into Stata version 15, with the later data analysis taking place in Stata version 16. Data were stored securely on a University of York's networked drive with password protection and never stored on any temporary media. No personal identifiable information was sent or used as part of this study. On receipt of the data, it was processed in accordance with the Data Protection Act 1998. The data were extracted during December 2018. The cleaning process took place between January 2018 and August 2021. It is common in ophthalmic research to count both number of eyes and patient numbers. Therefore, therefore both patient numbers and numbers of eyes has been reported in this analysis. At each site A to G, there were a total of 5,013 patients (473 eyes), 1726 patients (2,720 eyes), 1726 patients (2,095 eyes), 1,457 patients (2,133 eyes), 875 patients (1,037 eyes), 2,583 patients (3,911 eyes) and 905 patients (1,337 eyes).

Cleaning and merging: The files were received as separate text files for demographics, medical history, cataract surgery history, ocular medical history, visual acuity, injection history, injector grade history and injected drug history. Each was imported into Stata version 15 and variables reformatted where necessary. During the merging process, several decisions had to be made about the data. One of these was how to identify which VA assessment belonged to which study time point, as the VA assessments occurred with differing regularities. It was decided that the nearest VA assessment to each study time point would be used, as long as it was within two weeks either side of the time point. If two VA assessments were present two weeks either side of the time point, the assessment in the two weeks after the time point was used. The baseline VA assessment was identified as the nearest assessment that took place before the first anti-VEGF injection.

Exclusion criteria: Eyes with Central Retinal Vein Occlusion (CRVO), BRVO, traumatic eye injury and cataract surgery within 3 months were excluded from the analysis. The reasons for this are detailed in Table 1. The exclusion criteria were identified from the retrospective dataset (Table 2).

Table 1. Reasons for exclusion criteria.

Exclusion Criteria	Reason
CRVO diagnosis	Eye may already be being treated with anti-VEGF for CRVO, so difficult to attribute any visual effects purely to treatment for nAMD.
BRVO diagnosis	Eye may already be being treated with anti-VEGF for CRVO, so difficult to attribute any visual effects purely to treatment for nAMD.
Traumatic eye injury	Eye injury could lead to decreased visual acuity that makes it difficult to understand the effects of anti-VEGF therapy for nAMD.
Cataract surgery within 3 months	Recent cataract surgery can lead to increased visual acuity, so would be difficult to tell if any changes in visual acuity were due to the cataract surgery or anti-VEGF treatment for nAMD.

Table 2. Demographic factors to be analyzed.

IMD score	a score from 0 – 100 (shows the amount of social deprivation, with a score of 0 representing the least deprivation)
Smoking status	current smoker, ex- smoker, never smoked.
Ethnicity	ethnicity category expressed by patient
IMD decile	ordinal categories from 1- 10 (ranks local authority area of patients in order of levels of social deprivation, with 1 having the least social deprivation).
Age	age in years at time of first EMR entry
Bilaterality	a patient having or developing two eyes with nAMD.

Known factors

- Gender: It was found by the systematic review previously published by the authors of this work that gender does not have a significant impact on visual outcome, so was not analyzed in any regression models [16].
- Age: It was found from the review that higher age at baseline led to poorer visual outcomes [16]. Although age as a patient characteristic was not planned to be analyzed in any regression models, it was deemed important to be able to describe the age profile of the patients in the dataset.
- Baseline VA: It was clear from the systematic review that baseline VA had a strong impact on visual outcome in the short and long-term [16]. It was therefore decided not to explore this as a characteristic of interest in the models in this study.
- Number of injections: the review also found that number of injections had a significant impact on visual outcome. However, it was decided to investigate how patient characteristics were associated with number of injections received [16].

Factors with limited evidence

- Other health conditions such as diabetes, heart disease and diabetes: although the systematic review was unable to find any data on such factors, after cleaning of the retrospective data it became clear that due to insufficient data on such factors, it would be unable to run any models on them in this analysis [16].
- Smoking: the systematic review was unable to find any data on the impact of smoking on visual outcome, so this was included in analyses [16].
- Social deprivation: there was similarly no data from the review on how social deprivation affected visual outcomes and number of injections received, so it was decided to include this patient characteristic in the analysis [16].
- Ethnicity: the review was unable to find significant data on how ethnicity affected visual outcome [16].
- Bilaterality: It was unknown from the systematic review whether developing nAMD in two eyes affected visual outcome long-term.

Statistical methods

The relationship between visual outcome (measured in letter score) and social deprivation (measured in IMD score) will be explored using a covariance pattern mixed-effect linear regression model, because letterscore is a repeated measure. Bilaterality, smoking and ethnicity will be included as fixed effects. Because of the very low numbers of non-white patients in the sample (2.2%), different non-white ethnicities were all grouped into one category. It is recognised that this does not reflect differences between the different groups. Eyes were clustered by patient in the model, as it was felt that where two eyes in the analysis came from the same patient, they were more likely to be more similar than two eyes from two different patients. Variable coefficients, 95% confidence intervals and p-values will be reported. Because site G did not measure visual acuity in letterscore, but in LogMar, in order to see if visual outcomes were particularly different at site G compared to other sites, LogMar measurements at all sites were converted into letterscore. Site G was then included in an analysis of all sites.

The relationship between number of injections received and social deprivation (measured in IMD score) will be explored using a Poisson regression model. A Poisson regression model was used because the number of injections variable was count data over varying periods of time in the study between patients. Bilaterality, ethnicity and smoking will be controlled for and included as fixed effects and eyes as a random effect. The relationship between compliance with the recommended number of injections at three months (3 injections), and 12 months (8 injections) will be explored using odds ratio models. The relationship between bilaterality and IMD Decile will also be explored using a logistic regression model, controlling for ethnicity and smoking as fixed effects and eyes as a random effect. The relationship between smoking and vision loss of >15 letters will be explored using an odds ratio model controlling for ethnicity and IMD Score as fixed effects and eyes as a random effect.

Results

Descriptive statistics

One of the categorical variables used in the models was how many people had both of their eyes or just one of their eyes treated for nAMD in the study. Nearly 70% of patients in the study only had one eye being treated for nAMD. This shows a similar distribution of patients with only one eye being treated for nAMD, with Site E having a particularly high proportion of patients being unilateral (84.4%). There were nearly twice as many females as males in the sample (Tables 3 and 4). This is likely to be because females generally tend to live longer than males and hence are more likely to have nAMD [17]. This distribution was largely reflected at site level. Data on IMD score were available for 10,663 cases in the dataset. This score can range from 0-100. No one in the dataset scored the top range of IMD score. The mean IMD score across all sites was 20 for further information (Figures 4-7). However, there was a very large range, of more than 80. Between sites, Site E had the lowest mean IMD score (10), therefore having the least amount of social deprivation. Site E also had the lowest standard deviation, with its highest level of social deprivation only reaching 40. Site C had the highest mean score, but site D had the highest range (80). The variable is positively skewed, with most values being under 40. This suggests that overall, more than half of patients in the whole dataset are in the lower half of IMD scores. Each site was positively skewed. It is also recognized that Figure 4 shows a more significant amount of variation in visual acuity at Site G, and this could be due to either a smaller sample size at Site G, or the fact that LogMar scores were transformed into ETDRS equivalent. Site G was the site with the smallest number of patients. This could be meaningful in terms of it's irregular visual outcome pattern.

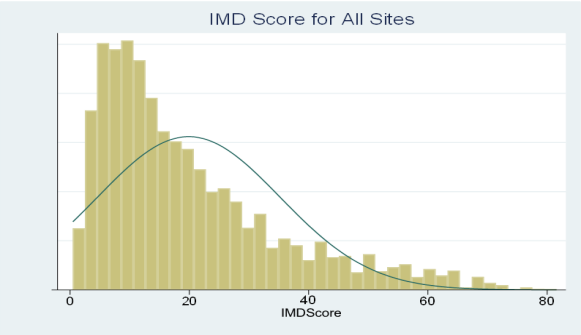

Figure 4. Frequency distribution for IMD score.

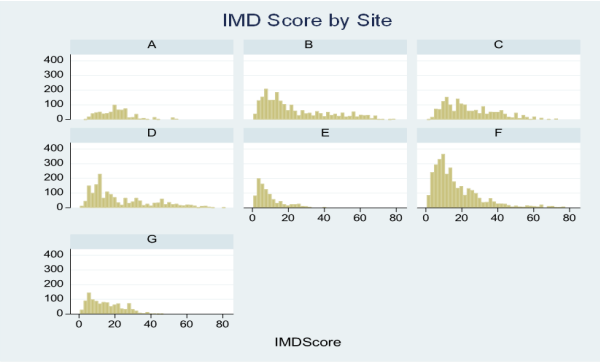

Figure 5. Frequency distribution of IMD Score by site.

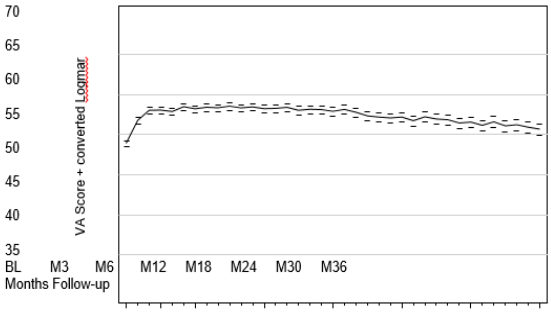

Figure 6.Visual acuity at all time-points.

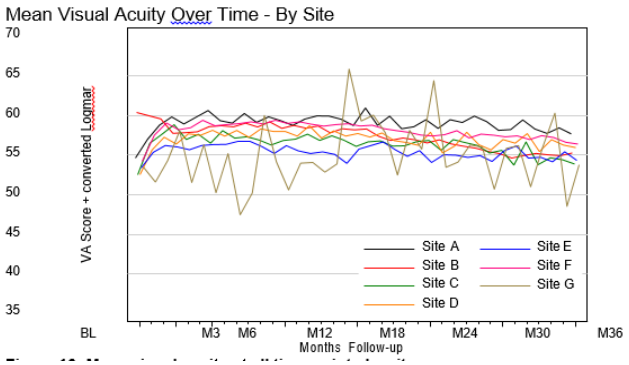

Figure 7. Mean visual acuity at all time-points by site.

Regression Models

IMD Score on Letterscore and LogMar: The results are presented in Table 3. Controlling for bilaterality, ethnicity and smoking status, higher IMD scores appeared to be associated with lower letterscores and lower LogMar over 36 months. Although they were not statistically significant in the models.

Table 3. Multiple regression output for IMD score effect on letterscore and LogMAR, controlling for bilaterality, ethnicity and smoking.

Variable	Coefficient	95% CI	Overall *P* Value
Letter scores (14,093 eyes and 12,623 patients)			
Constant	80.81	56.03, 105.59	<0.01
IMD Score	-0.6	-0.16, 0.03	0.21
Bilaterality*	-4.81	-8.10, 1.53	<0.00
Ethnicity**	-16.51	-39.73, 6.70	0.13
Smoking	-0.74	-2.85, 1.38	0.49
LogMar (14,093 eyes and 10,688 patients)			
Constant	78.5	52.81, 104.14	<0.01
IMD Score	-0.13	-1.33, -0.10	0.2
Bilaterality*	-1.82	-4.64, -1.00	0.2
Ethnicity**	-17.23	-41.61, 7.12	0.16
Smoking	-0.71	-2.74, 1.23	0.45
***Bilaterality**= having two eyes in the study			
**Being non-white			

IMD Score and Number of Injections: The results are presented in Table 4. Higher IMD scores were not associated with the number of injections received. There were 11,823 eyes and 10,688 patients.

Table 4. Poisson regression output for IMD score effect on number of injections, controlling for bilaterality, ethnicity and smoking

Variable	Coefficient	95% CI	P Value
Constant	62.65	56.21, 69.08	<0.01
IMD Score	-0.07	-0.1.5, -0.01	0.08
Bilaterality*	-4.62	-0.36, -1.95	<0.01
Smoking	-0.14	-0.18,1.80	0.87
Ethnicity**	0.04	-0.36, 0.29	<0.01
*Bilaterality= having two eyes in the study			
**Ethnicity=being non-white			

IMD score and treatment compliance: There were 11,823 eyes and 9553 patients at both 3 months and 12 months. The results are presented in Table 5. IMD scores appeared to be associated with compliance with recommended treatment levels at 3 months and 12 months in this study sample, but the odds ratios (OR=0.99) were so small this does not translate into a meaningful finding.

Table 5. OR output for IMD score effect on compliance with recommended number of injections at 3 months and 12 months, controlling for bilaterality, ethnicity and smoking at all sites.

	3 Months			12 Months		
Variable	Odds Ratio	95% CI	P Value	Odds Ratio	95% CI	P Value
Constant	6.22	2.31, 16.8	<0.01	0.25	0.23, 0.43	<0.01
IMD Score	0.99	0.98, 1.1	<0.01	0.99	0.99, 0.1	<0.01
Bilaterality*	1.82	1.35, 2.44	<0.01	1.3	1.12, 1.52	<0.01
Smoking	0.88	0.76,	0.09	0.92	0.82,	0.09

		1.02			1.02	
Ethnicity**	0.94	0.42, 2.1	0.87	1.23	0.42, 2.1	0.87
*Bilaterality=having two eyes in the study **Ethnicity=being non-white						

IMD decile and bilateral nAMD: In all IMD deciles, there were more patients with one eye impacted in the study rather than both. The IMD decile with the greatest proportion of bilateral patients was decile one (21%). The IMD decile with the lowest proportion of bilateral patients was decile 4 (17%). Controlling for ethnicity and smoking status, over 36 months IMD decile was not associated with developing nAMD in both eyes.

Table 6. Logistic regression output for IMD decile and bilaterality for all sites controlling for smoking and ethnicity.

Variable	Coefficient	95% CI	P Value
Constant*	1.3	1.2, 1.4	<0.01
IMD Decile	0	-0.0, 0.0	0.97
Smoking	0	-0.0, 0.0	0.1
Ethnicity**	-0.1	-0.0, 0.03	0.1

Association between smoking status and visual loss at all sites: There was no evidence of an association found in this study between smoking and visual loss of >15 letters at 36 months (Tables 6 and 7).

Table 7. Odds ratio output for smoking status effect on visual loss of >15 letters, controlling for bilaterality, ethnicity and smoking at all sites.

Variable	Odds Ratio	95% CI	Overall *P* Value
Constant	-0.4	-8.5, 239.0	0
IMD Score	1	0.1, 1.0	0.33
Bilaterality*	0.5	0.3, 0.7	<0.00
Smoking	1.1	0.8, 1.3	1.3
Ethnicity**	0.9	0.2, 3.9	0.92
*Bilaterality= having two eyes in the study			
**Being non-white			

Discussion

The overall aim of this analysis was to explain variation in both visual outcomes and number of injections received across seven NHS ophthalmology departments. This study is one of a number of UK studies that have used EMR data to look at a wide variety of causes of variation in visual outcome in patients with nAMD being treated with anti-VEGF therapy, and variation in treatment delivery [18]. This is an important issue because the ability to explain as much variation in visual outcome as possible could enable clinicians to better target treatment regimens and could therefore improve visual outcomes in nAMD generally. It is also important to be able to explain variation from a real-world dataset such as the one used in this study, because clinical practice often fails to replicate the levels of treatment from clinical trials.There were 14,093 eyes in the study at baseline, and 2,772 at the final time-point of 36 months. The visual outcome pattern of an initial three-month spike in visual acuity, followed by a gradual decline was seen in most patients, which concurs with findings by other relevant recent studies. The reasons for loss of patients at 36 months could not be clearly identified in this study [19]. One reason for this attrition is likely to be in part due to death, as the patients in this study were of an older age. However, it did appear that those with lower starting VA at baseline and older age were less likely to still be receiving treatment at 36 months. Older adults not receiving treatment at 36 months could be largely due to other health conditions and/or problems with transport preventing them from getting to clinic for regular monitoring and treatment. Patients who had lower baseline VA were also less likely to receive the recommended treatment in year one.

In this study, the regression models used did not find an association between higher social deprivation and lower visual outcomes. Although they were not statistically significant, the models suggest that those with higher levels of social deprivation had worse visual outcomes. However, data from a UK cohort study looking at social deprivation and being classed as having low vision due to a range of causes that found that people who were classed as low vision were more likely to live in socially deprived areas. It is also acknowledged that as this dataset spans several years of people being treated, clinical guidelines have changed regarding treatment patterns and the involvement of allied health care professions in monitoring and treatment. This could have also impacted on the number of injections patients in this study received. However, even in those eyes that were still being treated at 36 months, the initial gains made at 3 months did fall at each time-point, appearing to show initial gains were unable to be maintained long-term. This suggests that there is a physiological rather than social or service-related cause for this, which is outside of the scope of this study to identify. However, social deprivation itself did not explain variation in numbers of injections, and this is similar in other studies showing that patients with better baseline VA tend to receive more injections. This points back to the findings of this study and other current literature described above, that social deprivation does have a small effect on visual outcome, and number of injections received is more a product of low VA.

This study was also unable to show that smoking status explained variation in visual loss at 36 months. A recent study in Australia investigated the relationship between smoking and visual outcomes agreed with the findings in this study, where it found that although being a current smoker led to a lower age of developing nAMD, visual outcome was not significantly affected at 12 months. In addition, another large systematic review found no evidence of smoking having an effect on visual outcome [20]. This study was unable to analyse any other social behaviours or health conditions, such as diabetes or heart disease, because of a lack of reliable reporting on this in the dataset, a fact that is consistent with general problems of working with real-world data.

Limitations

This study did have some important limitations. The first of these is the fall in numbers of eyes from baseline to 36 months; however other studies in this field using real- world data also share this limitation [21]. The study population was strongly primarily white, and in order to meaningfully be able to include ethnicity in the models, ethnicity had to be divided between white and non-white. It is recognised that this was a crude approach and may have not been able to detect differences between each ethnic group. This study was also unable to analyse the impact of other health conditions, such as heart disease or diabetes, because there was too much inconsistency in reporting of past medical history in the dataset to carry out meaningful analyses.

Future research areas to be explored

There are further questions to be answered in this field. These include:

- Do patients with higher levels of social deprivation get diagnosed later or have more difficulty accessing services (for example regular optician checks)? If so, how could this be addressed?
- As social deprivation did not explain variation in number of injections received and compliance with the recommended number of treatments, what other factors explain this? Is it more likely that it is issues with services being able to deliver enough injections, or is it more that there is something inherent about patients that are less compliant with treatment? For example, in those patients that are less compliant, are they older and have less access to transport to hospital? Or is it a reflection of general compliance with healthcare interventions generally? Or instead of focusing on the number of injections, it could be more effective to look at how there can be closer monitoring and personalization of

treatment, such as in individual treatment patterns that are delivered.

Conclusion

Social deprivation was not found to have an impact on visual outcomes in the patients in this study over 36 months. Social deprivation did not influence the number of injections received or whether the optimum treatment level was achieved in year 1. Neither did smoking have any influence on whether patients lost more than 15 letters. However, the potential association between increased social deprivation and poorer outcomes is an important finding, as it sits within a bigger picture of inequalities across healthcare access and outcomes and raises questions about whether patients with higher social deprivation are being diagnosed later for nAMD, and therefore having poorer visual outcomes as a result.

If there had been better information on ethnicity, and more sites with more variation in the ethnic background of patients, would there have been more variation in visual outcome? Would it be possible to identify whether certain ethnicities had particularly better or worse outcomes? If so, work needs to be done on addressing any inequalities.

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