

Baseline characteristics from the early Detection Of neovascular age-Related mAcular Degeneration in the community trial: DORADO report 1

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Abstract

Background/Objectives:

The early detection of nAMD in the community (DORADO) study aims to evaluate the persistence and adherence of individuals with intermediate AMD (iAMD) to a targeted community-based optical coherence tomography (OCT) screening programme. This report outlines the baseline characteristics of the DORADO cohort.

Subjects/Methods:

DORADO is a randomised controlled trial involving 6 UK community eye healthcare practices. Individuals aged over 50 years with a diagnosis of iAMD and best corrected visual acuity (BCVA) > 24 letters were recruited between July 2024 and April 2025. BCVA, OCT and colour fundus imaging were performed alongside the Macular Disease Quality-of-life (MacDQoL) assessment, National Eye Institute Visual Functioning Questionnaire (NEI-VFQ), EuroQoL 5-dimension 3-level (EQ-5D-3L) and the Public Health Questionnaire (PHQ9).

Results

In 253 eyes of 133 participants mean BCVA was 75.2 (SD = 13.1). Mean age was 75.6 (SD = 9.3) years, 63.9% were female, 51.9% were either ex- or current smokers, and 28.5% were from postcodes with the two lower deprivation quintiles. Prevalence of OCT biomarkers were medium drusen 62.3%, large drusen 62.3%, subretinal drusenoid deposits 37%, geographic atrophy 7.8, vitelliform lesion 4.3% and serous pigment epithelial detachment 2.7%. Mean MacDQoL average weighted impact score was - 1.0 (SD = 1.6), NEI-VFQ-25 composite score was 79.1 (SD = 23.9), EQ5D3L single summary index was 0.78 (SD = 0.2) and prevalence of mild or minimal depression was 95.8%. 60.2% of participants did not use an Amsler grid and 86.5% were not taking AREDS2 supplements.

Conclusions

The DORADO study provides a comprehensive description of a cohort of iAMD participants and the opportunity for public health intervention.

Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss in the world, predicted to affect 288 million people by 2030 (1). There are a number of classifications which categorise AMD into early (dry), intermediate (dry) and late stages (nAMD or geographic atrophy). These classifications can

be used to predict the likelihood of developing nAMD, with the risk of this developing being higher with intermediate compared with early stages (2–4).

Treatment for nAMD with intravitreal therapy is successful in halting the progression of visual loss (5). When treatment is commenced for nAMD with good vision, there is better long-term visual preservation and quality-of-life (QoL) (6, 7). The EDNA (Early detection of neovascular age-related macular degeneration) study demonstrated that spectral-domain optical coherence tomography (SD-OCT) is an excellent tool for the early detection of new nAMD compared with self-monitoring, in fellow eyes of individuals undergoing treatment for nAMD (8). The benefit of routine screening for nAMD in the first eye of individuals with intermediate AMD, is yet to be determined. There are however, multiple factors that need to be taken into consideration to establish the benefit of a targeted screening programme.

The DORADO study aims to evaluate the persistence and adherence of individuals with intermediate AMD (iAMD) in a targeted screening programme undergoing community, OCT-based assessments. The DORADO report 1 outlines the baseline characteristics of this cohort.

Subjects and Methods

The DORADO study is a randomised controlled trial involving 6 UK community eye healthcare practices (5 optometry practices and 1 community eye clinic) in North Yorkshire, West Yorkshire, North Lincolnshire and Teeside. Ethical approval was granted by the NHS Health Research Authority and Research Ethics Committee (IRAS: 331617) with ISRCTN trial registration (ISRCTN10005321). The study followed the tenets of the Declaration of Helsinki and Good Clinical Practice guidelines.

All investigators underwent trial-specific training and testing about eligibility criteria. Inclusion criteria were VA > 24 ETDRS letters, age > 50 years and a diagnosis of iAMD as per the criteria listed in Table 1. This criterion is similar to the international classification (as used in NICE Guideline 82) in that extrafoveal GA was included. However, it is important to note that there are a number of different classifications used in similar studies which may/mat not include GA (Table 2). Exclusion criteria were non-AMD macular degeneration, e.g., myopic degeneration, inherited macular dystrophy, MACTEL; diabetic macular oedema; macular haemorrhage of other causes, e.g., retinal vein occlusion; nAMD in both eyes; nAMD in one eye with the fellow eye under regular monitoring in secondary care; intraretinal or subretinal haemorrhage or the inability to consent or comply with study visits.

Following written informed consent, participants were randomised 1:1 to either the intervention or standard care arm and underwent baseline assessments.

Baseline assessments included demographics, postcode, AMD disease duration, smoking status, use of an Amsler grid and AREDS supplementation use. In addition, best corrected visual acuity (BCVA), spectral-domain OCT (SD-OCT) and colour fundus photography were also obtained. Quality-of-life was assessed using the National Eye Institute visual functioning questionnaire (NEI-VFQ-25), Macular Disease QoL (MacDQoL), Public Health Questionnaire (PHQ9) and EuroQoL (EQ-5D-3L).

BCVA (refracted or with distance glasses), was performed using either an ETDRS (Early Treatment of Diabetic Retinopathy Study) letter score or Snellen visual acuity. Snellen visual acuity was subsequently converted to an ETDRS letter score (9). Both eyes were enrolled as the study eye if they met the eligibility criteria. When assessing the better seeing (BSE) or worse seeing eyes (WSE), if both eligible eyes had the same VA, the right eye was selected as the BSE. Macular cube SD-OCT and colour fundus photography were performed using the routinely available technologies at the investigating site (Heidelberg, Nidek, Optopol).

Further assessments were performed in the intervention arm at four additional 3-monthly visits or in the standard care arm at one 12-month visit (10).

Descriptive statistics were used to define participant age, gender, smoking status, index of multiple deprivation (IMD) quintile scores, Amsler grid use and AREDS supplementation. Postcodes were used to derive the IMD quintile score using the UK Government English indices of deprivation tool (<https://imd-by-postcode.opendatacommunities.org/imd/2019>). Descriptive statistics were also used to analyse BCVA, disease duration, prevalence of OCT biomarkers for both eyes. Baseline QoL scores are reported as mean (SD) and median (IQR) for the NEI-VFQ-25 composite and subscales scores, MacDQoL average weighted impact (AWI) score, General-QoL and AMD-specific QoL scores, EQ-5D-3L single summary index (SSI) score and visual analogue score (VAS) score, and total PHQ9 score. Normality was assessed using the Shapiro-Wilk test.

To examine which baseline factors independently predict QoL, a hierarchical linear regression was performed separately for the BSE and WSE. Four outcomes were examined: NEI-VFQ-25 composite score, MacDQoL AWI score, EQ-5D-3L SSI and PHQ9 total score. Predictors were entered in 10 sequential blocks: Block 1: sociodemographic factors (age, gender); Block 2, VA; Block 3, disease duration (months); Blocks 4–9, individual SD-OCT biomarkers entered as separate pairs (medium drusen, large drusen, SDD, GA, vitelliform lesion and serous PED); Block 10, behavioural and lifestyle factors (current smoker versus never smoked, ex-smoker versus never smoked, Amsler grid use, and AREDS supplementation use). Entering each imaging biomarker as an individual block rather than as a single structural block allowed the unique variance contribution of each imaging factor to be assessed independently. Missing data for disease duration (BSE: N = 23; WSE: N = 19) were imputed using the median of observed values (3 months). Missing responses for Amsler grid use (N = 4), AREDS supplement use (N = 3), and smoking status (N = 2) were imputed with the most frequently observed response; in each case this was the “No” or “Never” category, consistent with the distribution in the wider cohort. VA and SD-OCT biomarker data were not imputed; participants with missing values for these variables were excluded from the retrospective eye model using complete-case analysis. The change in R^2 (ΔR^2) and the associated F-change and p-values are reported at each block to quantify the incremental variance explained. Unstandardised (β) and standardised (Std. β) regression coefficients with 95% confidence intervals (CI) are reported for the final model. Statistical significance was set at $p < 0.05$ (two-tailed). All analyses were conducted in Python 3.14.

Results

A total of 253 eyes from 133 participants were enrolled into the DORADO study between July 2024 and April 2025. Of these, 240 eyes of 120 participants had bilateral iAMD. Thirteen eyes of 13 participants were excluded from the study: 8 eyes were diagnosed with iAMD but did not meet the inclusion criteria, 1 eye was diagnosed with lamella hole, and 4 eyes were deemed healthy.

The mean age of the whole cohort was 75.6 (SD = 9.3) years, with 27.8% aged over 80 years, 63.9% were female and 51.9% were either ex- or current smokers. 27.8% of participants were from postcodes with the two lower deprivation quintiles, 60.9% of participants did not use an Amsler grid and 87.2% were not taking AREDS2 supplements (Table 1). Of the 14 participants (20 eyes) with GA recruited into the DORADO study, 57% (N = 8) were either ex- or current smokers. The most common disease duration was between 1–4 years in 41.5% of eyes with a diagnosis within 5 years for 57.7% (Table 1).

Of the eligible eyes, 44.1% (N = 113) met only 1 eligibility criteria, 35.2% (N = 90) met 2 criteria, 15.6% (N = 40) met 3 criteria, 3.5% (N = 9) met 4 criteria, with 1 eye meeting 5 criteria. The most common criteria were medium drusen with pigmentary abnormalities and large drusen with or without pigmentary abnormalities, which were present in 63.2% (N = 160) of eyes, respectively. Extrafoveal geographic atrophy was present in 7.9% (N = 20) of eyes (Table 1).

Mean BCVA for the cohort was 75.2 (SD = 13.1) ETDRS letters, with a BCVA $\geq$ 75 letters in 69.2% (N = 175) (Table 3). Comparing eyes with bilateral or unilateral inclusion criteria, eyes with bilateral medium and/or large drusen, SDD or GA had on average a 5–10 letter worse VA. In contrast, eyes with bilateral vitelliform lesion or SPED had on average 10 letter better VA (Table 3).

Baseline QoL data were available for 114–119 of the 133 participants. All assessments were significantly non-normally distributed (Shapiro-Wilk $p < 0.001$ for all). The mean NEI-VFQ composite score was 79.1 (SD = 23.9) Higher scores were recorded for colour vision (Mean = 92.2, SD = 24.2), social functioning (Mean = 88.6, SD = 25.4) and dependency (Mean = 86.7, SD = 26.8). The lowest score was in driving, with a mean of 56.6 (SD = 42.8). The MacDQoL mean AWI score – 1.0 (SD = 1.6). In particular, feelings about the future was – 1.9 (SD = 2.8). The mean general-QoL was 1.7 (SD = 1.0) AMD-specific-QoL score was – 0.9 (SD = 1.1). The mean EQ-5D-3L SSI was 0.78 (SD = 0.2) with the number of participants responding 1 (no issues) ranging from 58 to 107 across the 5 health state domains. The mean EQ-5D-3L VAS was 76.5 (SD = 14.5) with 97.4% of participants reporting a score of over 50. The mean total PHQ9 score was 2.9 (SD = 3.5) indicating a greater prevalence of minimal to mild depressive symptom burden across the cohort. Further details can be found in Table 4.

Hierarchical Regression

Block level results are presented in Tables 5 (BSE) and 6 (WSE) with the final model coefficients presented in Tables 7 (BSE) and 8 (WSE).

Block 2 - Visual Acuity. The most consistent single predictor of baseline QoL was VA, explaining significant additional variance over demographic factors alone across all 4 outcomes in both the BSE and WSE models. In the BSE model, VA explained between 6.7–13.7% of additional variance (ΔR^2 range: 0.07–0.14; F-change p-value range: <0.001–0.005). In the WSE model, VA explained between 5.3–12.3% of the additional variance (ΔR^2 range: 0.05–0.12; F-change p-value range: <0.001–0.015). In the final BSE model, higher VA was independently associated with better NEI-VFQ-25 composite score ($\beta = 0.62$, 95% CI 0.15 to 1.09; Std. $\beta = 0.27$, $p = 0.011$), better MacDQoL AWI ($\beta = 0.04$, 95% CI 0.004 to 0.068; Std. $\beta = 0.24$, $p = 0.026$), and lower PHQ9 score ($\beta = -0.11$, 95% CI -0.18 to -0.04; Std. $\beta = -0.33$, $p = 0.003$). Findings were consistent in the WSE model (NEI-VFQ: $\beta = 0.39$, $p = 0.018$; MacDQoL AWI: $\beta = 0.03$, $p = 0.006$; PHQ9: $\beta = -0.06$, $p = 0.009$).

Block 3 – Disease Duration. Disease duration explained significant additional variance in EQ5D3L SSI beyond VA in both the BSE model ($\Delta R^2 = 0.07$; F-change(1,101) = 8.7, $p = 0.004$) and WSE model ($\Delta R^2 = 0.07$, F-change(1,105) = 8.99, $p = 0.003$). In the WSE model, disease duration also explained additional variance in PHQ9 score ($\Delta R^2 = 0.04$, F-change(1,110) = 5.22, $p = 0.024$), and in the BSE model, in NEI-VFQ composite score ($\Delta R^2 = 0.03$, F-change(1,105) = 4.07, $p = 0.046$). In the final adjusted models, longer disease duration was independently associated with lower EQ5D3L SSI in both the BSE ($\beta = -0.01$, 95% CI -0.02 to -0.002, Std. $\beta = -0.26$, $p = 0.023$) and WSE models ($\beta = -0.02$, 95% CI -0.03 to -0.01, Std. $\beta = -0.23$, $p = 0.004$), and with higher PHQ9 in the WSE model ($\beta = 0.23$, 95% CI 0.05 to 0.42, Std. $\beta = 0.23$, $p = 0.014$).

Blocks 4–9 – SD-OCT Biomarkers. No individual SD-OCT biomarker block explained additional variance in NEIVFQ composite, EQ5D3L SSI or PHQ9 scores (all block F-change $p > 0.10$). For MacDQoL AWI, no single biomarker block reached significance in the sequential F-change test in either model (all $p > 0.10$); however, in the final adjusted models, the presence of SDD was independently associated with worse MacDQoL AWI score in

both the BSE model ($\beta = -0.710$, 95% CI -1.373 to -0.047, Std. $\beta = -0.209$, $p = 0.036$) and the WSE model ($\beta = -0.733$, 95% CI -1.396 to -0.070, Std. $\beta = -0.212$, $p = 0.031$), after adjusting for all other structural and behavioural factors. No other OCT biomarker was a significant independent predictor of any QoL outcome in the final models of either eye.

Block 10 – Behavioural and Lifestyle Factors. Behavioural and lifestyle factors explained significant additional variance in NEI-VFQ-25 composite score in both models (BSE:

$\Delta R^2 = 0.16$, F-change(4,95) = 5.70, $p < 0.001$; WSE: $\Delta R^2 = 0.19$, F-change(4,99) = 6.6, $p < 0.001$) and in MacDQoL AWI (BSE: $\Delta R^2 = 0.10$, F-change(4,95) = 3.58, $p = 0.009$; WSE: $\Delta R^2 = 0.12$, F-change(4,99) = 4.12, $p = 0.004$). The behavioural block did not explain significant additional

variance in EQ-5D-3L SSI or PHQ-9 in either model (all $p > 0.30$). Current smoking was the strongest independent predictor of lower NEI-VFQ-25 composite score in both the BSE ($\beta = -41.68$, 95% CI -61.78

to -21.57 , $\text{Std.}\beta = -0.39$, $p < 0.001$) and WSE models ($\beta = -45.17$, 95% CI -64.8 to -25.55 , $\text{Std.}\beta = -0.42$, $p < 0.001$). Ex-smoking was also independently

associated with lower NEI-VFQ-25 in the BSE model ($\beta = -10.25$, 95% CI -19.52 to -0.97 , $\text{Std.}\beta = -0.21$, $p = 0.031$) and showed a trend in the WSE model ($\beta = -7.82$, $p = 0.094$). AREDS supplementation use was independently associated with worse MacDQoL AWI in both models (BSE: $\beta = -1.39$, 95% CI -2.39 to -0.40 , $\text{Std.}\beta = -0.26$, $p = 0.006$; WSE: $\beta = -1.54$, 95% CI -2.51 to -0.58 , $\text{Std.}\beta = -0.28$, $p = 0.002$).

Overall Model Fit. Final model R^2 values ranged from 0.18 to 0.35 (BSE models) and 0.2

to 0.31 (WSE models). Adjusted R^2 values were lower, reflecting the number of predictors relative to sample size, and ranged from 0.06 to 0.25 (BSE) and 0.08 to 0.21 (WSE). The EQ-5D-3L models showed the greatest discrepancy between R^2 and Adj. R^2 , indicating that SD-OCT biomarker blocks added limited independent explanatory power for this outcome beyond VA and disease duration.

Table 1
Baseline characteristics of the DORADO cohort

Participant Level, N	133
Bilateral eligibility, N	120
Age, mean (SD)	75.6 (9.3) years
Age range, years	50.01–93.03
Age categories, N (%)	
- < 70	34 (25.6)
- 71–80	62 (46.6)
- > 80	37 (27.8)
Gender, N (%)	
- Male	48 (36.1)
- Female	85 (63.9)
Smoking Status, N (%)	
- Ex-smoker	60 (45.1)
- Current smoker	9 (6.8)
- Non-smoker	62 (46.6)
- Not answered	2 (1.5)
IMD Score, N (%)	
- Quintile 1	23 (17.3)
- Quintile 2	14 (10.5)
- Quintile 3	15 (11.3)
- Quintile 4	40 (30.1)
- Quintile 5	41 (30.8)
Amsler grid use, N (%)	
- Yes	48 (36.1)
- No	81 (60.9)
- Not answered	4 (3.0)
AREDS2 supplement use, N (%)	

Participant Level, N	133
- Yes	14 (10.5)
- No	116 (87.2)
- Not answered	3 (2.3)
Eye Level, N	253 eyes
Disease duration, N (%)	
- < 1 year	41 (16.2)
- 1–4 years	105 (41.5)
- 5–9 years	54 (21.3)
- > 10 years	27 (10.7)
- Unknown	11 (4.3)
- Missing	15 (5.9)
SD-OCT inclusion criteria, N (%)	
- Medium drusen ($\geq 63\mu\text{m}$ < $125\mu\text{m}$) with pigmentary abnormalities	160 (63.2)
- Large drusen ($\geq 125\mu\text{m}$) with or without pigmentary abnormalities	160 (63.2)
- SDD (pseudo-reticular drusen) with or without pigmentary abnormalities	94 (37.2)
- GA > $175\mu\text{m}$, extrafoveal (not including the foveal dip)	20 (7.9)
- Vitelliform lesions with VA < 62 ETDRS letters (6/18)	13 (5.1)
- Serous PED without neovascularisation	7 (2.8)

*IMD: Index of Multiple Deprivation; AREDS: Age-related Eye Disease Study; SD-OCT: Spectral-domain Optical Coherence Tomography; SDD: Subretinal drusenoid deposits; GA: Geographic atrophy; VA: Visual Acuity; PED: Pigment epithelial detachment.

Table 2
Comparison of study design features across the recent iAMD studies

DORADO	Inclusion criteria - Study eye	Fellow eye characteristics	N	VA	OCT	QoL
	NG82 but with GA > 175µm from the fovea	Any except nAMD under routine care	133	Y	Y	Y
INTERCEPT	Beckman	Any	805	Y	Y	N
MACUSTAR	Beckman	No MNV	168	Y	Y	Y
LEAD	Beckman	Beckman	147	Y	Y	N
LIGHTSIGHT	Presence of drusen and/or non-foveal centre GA with BCVA 50–75	Not stated	91	Y	Y	N

*VA: Visual acuity; OCT: Optical coherence tomography; QoL: Quality of life; GA: Geographic Atrophy; BCVA: Best Corrected Visual Acuity.

Table 4

Mean baseline scores for the 25-item and 39-item NEI-VFQ, MacDQoL and EQ-5D-3L questionnaires and prevalence rates for the PHQ9 questionnaire

NEI-VFQ-25 (n = 118)	Mean (SD)	Median	IQR
- Composite score	79.1 (23.9)	87.8	72.7–94.6
- General health	62.8 (23.7)	65.0	55.0–77.5
- General vision	69.3 (23.7)	80.0	61.3–85.0
- Ocular pain	81.6 (24.9)	87.5	75.0–100.0
- Near activities	75.9 (27.0)	86.3	66.7–95.8
- Distance activities	80.2 (27.1)	91.7	76.0–100.0
- Social functioning	88.6 (25.4)	100.0	91.7–100.0
- Mental health	77.8 (27.2)	90.0	71.3–95.0
- Role difficulties	77.7 (29.0)	93.8	62.5–100.0
- Dependency	86.7 (26.8)	100.0	87.5–100.0
- Driving	56.6 (42.8)	79.2	0.0–91.7
- Colour vision	92.2 (24.2)	100.0	100.0–100.0
- Peripheral vision	83.1 (28.1)	100.0	75.0–100.0
MacDQoL (n = 118)			
- AWI score	-1.0 (1.6)	-0.2	-1.3–0
- General-QoL	1.7 (1.0)	-1	-1–0
- AMD-specific QoL	-0.9 (1.1)	2	1–2
- Household tasks	-1.0 (2.0)	0	-2–0
- Personal affairs	-1.2 (2.3)	0	-2–0
- Shopping	-1.5 (2.5)	0	-2–0
- Working life	-0.3 (1.2)	0	0–0
- Close personal relationships	-0.5 (1.7)	0	0–0
- Family life	-0.9 (2.1)	0	0–0
- Friendships and social life	-0.8 (2.0)	0	0–0
- Physical appearance	-0.7 (1.9)	0	0–0

NEI-VFQ-25 (n = 118)	Mean (SD)	Median	IQR
- Physical ability	-1.2 (2.2)	0	-2–0
- Out and about	-1.3 (2.5)	0	-2–0
- Holidays	-0.8 (1.8)	0	0–0
- Leisure activities	-1.6 (2.5)	0	-2–0
- Self-confidence	-1.0 (2.0)	0	-1–0
- Motivation	-1.0 (2.1)	0	0–0
- Other people's reactions	-0.3 (1.4)	0	0–0
- Feelings about the future	-1.9 (2.8)	0	-3–0
- Finance	-0.2 (1.2)	0	0–0
- Independence	-1.6 (2.8)	0	-3–0
- Do for others	-1.2 (2.4)	0	-1–0
- Mishaps	-1.0 (2.3)	0	0–0
- Enjoyment of meals	-0.4 (1.4)	0	0–0
- Time taken	-1.1 (2.3)	0	-1–0
- Enjoyment of nature	-1.6 (2.8)	0	-2–0
EQ-5D-3L (n = 114)			
- SSI	0.78 (0.2)	0.8	0.7–1.0
- VAS	76.5 (14.5)	80.0	70.0–85.0
PHQ9 (n = 119)			
- Total score	2.9 (3.5)	2	0–4.5
	N	(%)	
PHQ9 (n = 119)			
- Minimal depression	89	(74.8)	
- Mild depression	25	(21.0)	
- Moderate depression	3	(2.5)	
- Moderately severe depression	2	(1.7)	
- Severe depression	0	(0.0)	

**NEI-VFQ-25: 25-item National Eye Institute Visual Functioning Questionnaire (range 0-100); MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range -9 to + 3); General-QoL: range (-3 to + 3); AMD-specific QoL: range (-3 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; VAS: Visual Analogue Scale PHQ9: Public Health Questionnaire 9.*

Table 5
Hierarchical regression summary per block for the BSE

Outcome	Block	K	R ²	Adj. R ²	ΔR ²	F-change	df	p
NEIVFQ25	Block 1 – Demographics	2	0.05	0.04	0.05	3.02	2, 107	0.05
composite	Block 2 - VA	3	0.12	0.10	0.07	8.10	1, 106	0.01
score	Block 3: Disease Duration	4	0.15	0.12	0.03	4.07	1, 105	0.05
	Block 4: Medium Drusen	5	0.16	0.12	0.00	0.36	1, 104	0.55
	Block 5: Large Drusen	6	0.16	0.11	0.00	0.28	1, 103	0.60
	Block 6: SDD	7	0.16	0.10	0.00	0.25	1, 102	0.62
	Block 7: GA	8	0.16	0.10	0.00	0.24	1, 101	0.63
	Block 8: Vitelliform	9	0.19	0.11	0.02	2.94	1, 100	0.09
	Block 9: Serous PED	10	0.19	0.11	0.00	0.26	1, 99	0.61
	Block 10: Behavioural/Lifestyle	14	0.35	0.25	0.16	5.70	4, 95	0.00
MacDQoL AWI score	Block 1: Demographics	2	0.01	-0.01	0.01	0.36	2, 107	0.70
	Block 2: VA	3	0.13	0.10	0.12	14.72	1, 106	0.00
	Block 3: Disease Duration	4	0.13	0.10	0.00	0.40	1, 105	0.53
	Block 4: Medium Drusen	5	0.14	0.10	0.01	1.09	1, 104	0.30
	Block 5: Large Drusen	6	0.17	0.12	0.03	3.11	1, 103	0.08
<i>*NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9</i>								

Outcome	Block	K	R ²	Adj. R ²	ΔR ²	F-change	df	p
	Block 6: SDD	7	0.18	0.13	0.02	2.44	1, 102	0.12
	Block 7: GA	8	0.20	0.14	0.02	2.41	1, 101	0.12
	Block 8: Vitelliform	9	0.21	0.13	0.00	0.19	1, 100	0.66
	Block 9: Serous PED	10	0.21	0.13	0.00	0.43	1, 99	0.51
	Block 10: Behavioural/Lifestyle	14	0.31	0.21	0.10	3.58	4, 95	0.01
EQ5D3L SSI score	Block 1: Demographics	2	0.01	-0.01	0.01	0.49	2, 103	0.61
	Block 2: VA	3	0.09	0.06	0.08	8.57	1, 102	0.00
	Block 3: Disease Duration	4	0.16	0.13	0.07	8.70	1, 101	0.00
	Block 4: Medium Drusen	5	0.16	0.12	0.00	0.34	1, 100	0.56
	Block 5: Large Drusen	6	0.16	0.11	0.00	0.03	1, 99	0.87
	Block 6: SDD	7	0.16	0.11	0.00	0.35	1, 98	0.55
	Block 7: GA	8	0.17	0.10	0.00	0.12	1, 97	0.73
	Block 8: Vitelliform	9	0.17	0.09	0.00	0.34	1, 96	0.56
	Block 9: Serous PED	10	0.17	0.08	0.00	0.03	1, 95	0.85
	Block 10: Behavioural/Lifestyle	14	0.18	0.06	0.01	0.39	4, 91	0.82
PHQ9 score	Block 1: Demographics	2	0.02	0.00	0.02	1.21	2, 108	0.30
<i>*NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9</i>								

Outcome	Block	K	R ²	Adj. R ²	ΔR ²	F- change	df	p
	Block 2: VA	3	0.16	0.14	0.14	17.47	1, 107	0.00
	Block 3: Disease Duration	4	0.18	0.15	0.02	2.68	1, 106	0.10
	Block 4: Medium Drusen	5	0.18	0.14	0.00	0.04	1, 105	0.84
	Block 5: Large Drusen	6	0.18	0.13	0.00	0.19	1, 104	0.66
	Block 6: SDD	7	0.19	0.14	0.01	1.22	1, 103	0.27
	Block 7: GA	8	0.20	0.13	0.00	0.48	1, 102	0.49
	Block 8: Vitelliform	9	0.20	0.12	0.00	0.06	1, 101	0.81
	Block 9: Serous PED	10	0.20	0.12	0.00	0.03	1, 100	0.86
	Block 10: Behavioural/Lifestyle	14	0.23	0.11	0.03	0.94	4, 96	0.44
<i>*NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9</i>								

Table 5
Hierarchical regression summary per block for the WSE

Outcome	Block	K	R ²	Adj. R ²	ΔR ²	F- change	df	p
NEIVFQ25	Block 1 – Demographics	2	0.03	0.01	0.03	1.86	2, 111	0.16
composite	Block 2 - VA	3	0.09	0.06	0.05	6.62	1, 110	0.01
score	Block 3: Disease Duration	4	0.09	0.06	0.01	0.73	1, 109	0.40
	Block 4: Medium Drusen	5	0.10	0.05	0.00	0.34	1, 108	0.56
	Block 5: Large Drusen	6	0.10	0.05	0.00	0.04	1, 107	0.84
	Block 6: SDD	7	0.10	0.04	0.00	0.16	1, 106	0.69
	Block 7: GA	8	0.10	0.03	0.00	0.00	1, 105	0.96
	Block 8: Vitelliform	9	0.10	0.02	0.00	0.23	1, 104	0.64
	Block 9: Serous PED	10	0.11	0.02	0.01	1.00	1, 103	0.32
	Block 10: Behavioural/Lifestyle	14	0.30	0.20	0.19	6.60	4, 99	0.00
MacDQoL AWI score	Block 1: Demographics	2	0.00	-0.01	0.00	0.25	2, 111	0.78
	Block 2: VA	3	0.13	0.10	0.12	15.47	1, 110	0.00
	Block 3: Disease Duration	4	0.13	0.10	0.00	0.39	1, 109	0.53
	Block 4: Medium Drusen	5	0.14	0.10	0.01	1.53	1, 108	0.22
	Block 5: Large Drusen	6	0.15	0.10	0.01	0.77	1, 107	0.38
<i>*NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9</i>								

Outcome	Block	K	R²	Adj. R²	ΔR²	F-change	df	p
	Block 6: SDD	7	0.17	0.11	0.02	2.28	1, 106	0.13
	Block 7: GA	8	0.17	0.11	0.01	0.88	1, 105	0.35
	Block 8: Vitelliform	9	0.18	0.11	0.01	0.88	1, 104	0.35
	Block 9: Serous PED	10	0.19	0.11	0.01	1.27	1, 103	0.26
	Block 10: Behavioural/Lifestyle	14	0.31	0.21	0.12	4.12	4, 99	0.00
EQ5D3L SSI score	Block 1: Demographics	2	0.02	0.00	0.02	0.83	2, 107	0.44
	Block 2: VA	3	0.07	0.04	0.05	6.09	1, 106	0.02
	Block 3: Disease Duration	4	0.14	0.11	0.07	8.99	1, 105	0.00
	Block 4: Medium Drusen	5	0.15	0.11	0.00	0.57	1, 104	0.45
	Block 5: Large Drusen	6	0.15	0.10	0.01	0.76	1, 103	0.39
	Block 6: SDD	7	0.15	0.10	0.00	0.06	1, 102	0.81
	Block 7: GA	8	0.16	0.10	0.01	1.31	1, 101	0.25
	Block 8: Vitelliform	9	0.18	0.11	0.02	2.12	1, 100	0.15
	Block 9: Serous PED	10	0.18	0.10	0.00	0.08	1, 99	0.78
	Block 10: Behavioural/Lifestyle	14	0.20	0.08	0.02	0.45	4, 95	0.77
PHQ9 score	Block 1: Demographics	2	0.02	0.00	0.02	1.15	2, 112	0.32
<i>*NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9</i>								

Outcome	Block	K	R ²	Adj. R ²	ΔR ²	F- change	df	p
	Block 2: VA	3	0.14	0.11	0.12	14.96	1, 111	0.00
	Block 3: Disease Duration	4	0.18	0.15	0.04	5.22	1, 110	0.02
	Block 4: Medium Drusen	5	0.18	0.15	0.01	1.04	1, 109	0.31
	Block 5: Large Drusen	6	0.19	0.14	0.00	0.25	1, 108	0.61
	Block 6: SDD	7	0.19	0.14	0.01	1.12	1, 107	0.29
	Block 7: GA	8	0.21	0.15	0.01	1.78	1, 106	0.18
	Block 8: Vitelliform	9	0.21	0.15	0.01	1.04	1, 105	0.31
	Block 9: Serous PED	10	0.22	0.14	0.00	0.46	1, 104	0.50
	Block 10: Behavioural/Lifestyle	14	0.25	0.15	0.03	1.15	4, 100	0.34
<i>*NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9</i>								

Table 7
Final BSE Model Coefficients

Outcome	Block	Predictor	β	Std. β	CI range	p
NEIVFQ25	Block 1 – Demographics	Age (years)	0.66	0.25	0.15–1.17	0.01
composite		Male sex	5.50	0.11	-3.17–14–17	0.21
score	Block 2 - VA	BSE VA	0.62	0.27	0.15–1.09	0.01
	Block 3: Disease Duration	Disease duration (months)	-0.23	-0.04	-1.51–1.05	0.73
	Block 4: Medium Drusen	Medium drusen	4.42	0.08	-5.29–14.13	0.37
	Block 5: Large Drusen	Large drusen	1.46	0.03	-8.46–11.37	0.77
	Block 6: SDD	SDD	5.81	0.12	-3.82–15.44	0.23
	Block 7: GA	GA	-4.46	-0.05	-20.19 – 11.26	0.57
	Block 8: Vitelliform	Vitelliform	19.69	0.17	-3.05–42.44	0.09
	Block 9: Serous PED	Serous PED	-4.53	-0.02	-49.40–40.34	0.84
	Block 10: Behavioural/Lifestyle	Current smoker*	-41.68	-0.39	-61.78 - -21.57	0.00
		Ex-smoker*	-10.25	-0.21	-19.52 - -0.97	0.03
		Amsler grid use	5.33	0.11	-3.80–14.47	0.25
		AREDS supplement use	-0.19	0.00	-14.65–14.27	0.98
MacDQoL	Block 1: Demographics	Age (years)	-0.01	-0.07	-0.05–0.02	0.49

NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; BSE: Better seeing eye; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; AREDS: Age-Related Eye Disease Studies; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9

Outcome	Block	Predictor	β	Std. β	CI range	p
AWI score		Male sex	-0.13	-0.04	-0.73–0.47	0.66
	Block 2: VA	BSE VA	0.04	0.24	0.00–0.07	0.03
	Block 3: Disease Duration	Disease duration (months)	-0.06	-0.13	-0.14–0.03	0.19
	Block 4: Medium Drusen	Medium drusen	-0.23	-0.07	-0.90–0.44	0.50
	Block 5: Large Drusen	Large drusen	-0.64	-0.18	-1.31–0.04	0.06
	Block 6: SDD	SDD	-0.71	-0.21	-1.37 - -0.05	0.04
	Block 7: GA	GA	-0.66	-0.11	-1.74–0.42	0.23
	Block 8: Vitelliform	Vitelliform	-0.86	-0.11	-2.43–0.70	0.28
	Block 9: Serous PED	Serous PED	1.38	0.08	-1.72–4.47	0.38
	Block 10: Behavioural/Lifestyle	Current smoker*	-0.96	-0.14	-2.22–0.31	0.14
		Ex-smoker*	0.46	0.14	-0.19–1.10	0.16
		Amsler grid use	-0.45	-0.13	-1.08–0.17	0.15
		AREDS supplement use	-1.39	-0.25	-2.39 - -0.40	0.01
EQ5D3L	Block 1: Demographics	Age (years)	0.00	-0.05	-0.01–0.00	0.62
SSI score		Male sex	0.02	0.06	-0.06–0.10	0.58
	Block 2: VA	BSE VA	0.00	0.23	0.00–0.01	0.05
NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; BSE: Better seeing eye; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; AREDS: Age-Related Eye Disease Studies; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9						

Outcome	Block	Predictor	β	Std. β	CI range	p
	Block 3: Disease Duration	Disease duration (months)	-0.01	-0.26	-0.02–0.00	0.02
	Block 4: Medium Drusen	Medium drusen	-0.02	-0.06	-0.11–0.06	0.58
	Block 5: Large Drusen	Large drusen	-0.01	-0.02	-0.10–0.08	0.89
	Block 6: SDD	SDD	-0.02	-0.04	-0.11–0.07	0.69
	Block 7: GA	GA	0.04	0.06	-0.11–0.20	0.59
	Block 8: Vitelliform	Vitelliform	-0.07	-0.08	-0.27–0.14	0.51
	Block 9: Serous PED	Serous PED	-0.03	-0.02	-0.43–0.37	0.88
	Block 10: Behavioural/Lifestyle	Current smoker*	-0.08	-0.09	-0.25–0.10	0.39
		Ex-smoker*	-0.01	-0.03	-0.10–0.07	0.75
		Amsler grid use	-0.03	-0.08	-0.12–0.05	0.44
		AREDS supplement use	0.04	0.07	-0.09–0.17	0.52
PHQ9	Block 1: Demographics	Age (years)	-0.08	-0.21	-0.16–0.00	0.04
score		Male sex	0.33	0.05	-1.03–1.69	0.63
	Block 2: VA	BSE VA	-0.11	-0.33	-0.18 - -0.04	0.00
	Block 3: Disease Duration	Disease duration (months)	0.17	0.18	-0.03–0.36	0.09
	Block 4: Medium Drusen	Medium drusen	-0.42	-0.06	-1.94–1.10	0.58
NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; BSE: Better seeing eye; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; AREDS: Age-Related Eye Disease Studies; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9						

Outcome	Block	Predictor	β	Std. β	CI range	p
	Block 5: Large Drusen	Large drusen	0.14	0.02	-1.39–1.67	0.86
	Block 6: SDD	SDD	0.62	0.09	-0.88–2.13	0.41
	Block 7: GA	GA	0.97	0.08	-1.49–3.44	0.43
	Block 8: Vitelliform	Vitelliform	0.05	0.00	-3.52–3.61	0.98
	Block 9: Serous PED	Serous PED	0.32	0.01	-6.72–7.35	0.93
	Block 10: Behavioural/Lifestyle	Current smoker*	0.44	0.03	-2.43–3.32	0.76
		Ex-smoker*	0.14	0.02	-1.31–1.59	0.85
		Amsler grid use	0.99	0.14	-0.42–2.40	0.17
		AREDS supplement use	1.40	0.12	-0.86–3.65	0.22

NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; BSE: Better seeing eye; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; AREDS: Age-Related Eye Disease Studies; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to +3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9

***reference=never smoked**

Table 8
Final WSE Model Coefficients

Outcome	Block	Predictor	β	Std. β	CI range	p
NEIVFQ25 composite score	Block 1 – Demographics	Age (years)	0.41	0.16	-0.08–0.89	0.10
		Male sex	3.63	0.07	-5.20–12.47	0.42
	Block 2 - VA	WSE VA	0.39	0.24	0.07–0.71	0.02
	Block 3: Disease Duration	Disease duration (months)	0.01	0.00	-1.23–1.24	0.99
	Block 4: Medium Drusen	Medium drusen	0.50	0.01	-8.84–9.85	0.92
	Block 5: Large Drusen	Large drusen	-0.01	0.00	-9.45–9.42	1.00
	Block 6: SDD	SDD	3.34	0.07	-6.44–13.12	0.50
	Block 7: GA	GA	2.24	0.03	-14.24–18.73	0.79
	Block 8: Vitelliform	Vitelliform	6.42	0.06	-12.80–25.63	0.51
	Block 9: Serous PED	Serous PED	5.39	0.04	-17.90–28.68	0.65
	Block 10: Behavioural/Lifestyle	Current smoker*	-45.17	-0.42	-64.80 - -25.54	0.00
		Ex-smoker*	-7.82	-0.16	-17.01–1.37	0.09
		Amsler grid use	4.98	0.10	-3.94–13.90	0.27
		AREDS supplement use	-2.95	-0.04	-17.13–11.23	0.68
MacDQoL	Block 1: Demographics	Age (years)	0.00	-0.01	-0.04–0.03	0.91

NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; WSE: Worst seeing eye; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; AREDS: Age-Related Eye Disease Studies; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9

Outcome	Block	Predictor	β	Std. β	CI range	p
AWI score		Male sex	-0.13	-0.04	-0.73–0.47	0.67
	Block 2: VA	BSE VA	0.03	0.28	0.01–0.05	0.01
	Block 3: Disease Duration	Disease duration (months)	-0.05	-0.10	-0.13–0.04	0.27
	Block 4: Medium Drusen	Medium drusen	-0.37	-0.11	-1.01–0.27	0.25
	Block 5: Large Drusen	Large drusen	-0.36	-0.10	-1.00 - -0.07	0.26
	Block 6: SDD	SDD	-0.73	-0.21	-1.40–0.42	0.03
	Block 7: GA	GA	-0.70	-0.11	-1.82–0.42	0.22
	Block 8: Vitelliform	Vitelliform	-1.03	-0.14	-2.34–0.28	0.12
	Block 9: Serous PED	Serous PED	0.87	0.10	-0.71–2.46	0.28
	Block 10: Behavioural/Lifestyle	Current smoker*	-0.70	-0.10	-1.93–0.54	0.26
	Ex-smoker*	0.67	0.20	0.04–1.30	0.04	
	Amsler grid use	-0.38	-0.11	-0.98–0.23	0.22	
	AREDS supplement use	-1.54	-0.28	-2.51 - -0.58	0.00	
EQ5D3L	Block 1: Demographics	Age (years)	0.00	-0.06	-0.01–0.00	0.56
SSI score		Male sex	0.06	0.14	-0.02–0.14	0.16
	Block 2: VA	BSE VA	0.00	0.18	0.00–0.01	0.09
NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; WSE: Worst seeing eye; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; AREDS: Age-Related Eye Disease Studies; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9						

Outcome	Block	Predictor	β	Std. β	CI range	p
	Block 3: Disease Duration	Disease duration (months)	-0.02	-0.29	-0.03 - -0.01	0.00
	Block 4: Medium Drusen	Medium drusen	-0.03	-0.08	-0.12–0.05	0.46
	Block 5: Large Drusen	Large drusen	0.03	0.08	-0.05–0.12	0.44
	Block 6: SDD	SDD	0.03	0.07	-0.06–0.12	0.52
	Block 7: GA	GA	-0.09	-0.12	-0.25–0.06	0.25
	Block 8: Vitelliform	Vitelliform	-0.13	-0.15	-0.30–0.04	0.14
	Block 9: Serous PED	Serous PED	0.03	0.03	-0.18–0.24	0.80
	Block 10: Behavioural/Lifestyle	Current smoker*	-0.05	-0.05	-0.22–0.13	0.60
		Ex-smoker*	-0.03	-0.07	-0.11–0.06	0.51
		Amsler grid use	-0.04	-0.11	-0.12–0.04	0.28
		AREDS supplement use	0.03	0.05	-0.10–0.16	0.64
PHQ9	Block 1: Demographics	Age (years)	-0.08	-0.22	-0.15 - -0.01	0.03
score		Male sex	0.11	0.01	-1.22–1.43	0.87
	Block 2: VA	BSE VA	-0.06	-0.27	-0.11 - -0.02	0.01
	Block 3: Disease Duration	Disease duration (months)	0.23	0.23	0.05–0.42	0.01
	Block 4: Medium Drusen	Medium drusen	0.74	0.10	-0.67–2.14	0.30
NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0-100); VA: Visual Acuity; WSE: Worst seeing eye; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; AREDS: Age-Related Eye Disease Studies; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to + 3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9						

Outcome	Block	Predictor	β	Std. β	CI range	p
	Block 5: Large Drusen	Large drusen	-0.31	-0.04	-1.71–1.09	0.66
	Block 6: SDD	SDD	0.71	0.10	-0.75–2.17	0.34
	Block 7: GA	GA	1.95	0.15	-0.52–4.42	0.12
	Block 8: Vitelliform	Vitelliform	1.93	0.12	-0.95–4.82	0.19
	Block 9: Serous PED	Serous PED	-1.09	-0.06	-4.58–2.40	0.54
	Block 10: Behavioural/Lifestyle	Current smoker*	0.12	0.01	-2.60–2.84	0.93
		Ex-smoker*	-0.12	-0.02	-1.50–1.26	0.86
		Amsler grid use	0.83	0.12	-0.49–2.15	0.22
		AREDS supplement use	1.87	0.16	-0.25–3.99	0.08

NEIVFQ25: 25-item National Eye Institute Visual Functioning Questionnaire composite score (range 0–100); VA: Visual Acuity; WSE: Worst seeing eye; SDD: Subretinal Drusenoid Deposits; GA: Geographic Atrophy; PED: Pigment Epithelial Detachment; AREDS: Age-Related Eye Disease Studies; MacDQoL: Macular Disease Dependent Quality-of-life; AWI: average weighted impact (range-9 to +3); EQ-5D-3L: EuroQoL 5 dimension 3 level; SSI: Single summary index; PHQ9: Public Health Questionnaire 9

***reference=never smoked**

Discussion

The DORADO report 1 provides a comprehensive description of VA, OCT and QoL baseline characteristics of a cohort of iAMD participants enrolled in a community-based OCT screening programme for the early detection of nAMD. The DORADO cohort is similar to other large datasets, MACUSTAR, LEAD, INTERECPT, INSIGHT, despite slightly different inclusion criteria. The criteria used in DORADO were similar to the international classification (as used in NG82) in that extrafoveal GA was included. Yet, the criteria used in the LEAD, INTERCEPT and MACUSTAR studies were based upon the Beckman criteria where centre-involving GA was excluded (11–15). DORADO therefore also included a small proportion of participants 10.5% (N = 14) that had GA > 175 μ m, not including the fovea in either one or both eyes. The INTERCEPT and MACUSTAR studies however, reported GA in 8.9% and 3.6%, respectively of fellow eyes only at baseline (12, 15). Baseline mean age and gender characteristics are in

line with LEAD (N = 292; mean age = 70.0; 73.3% female), INTERCEPT (N = 805; mean age = 75.8 years; 65% female), MACUSTAR (N = 301; mean age = 71.2 years; 63.1% female) and AREDS2 (N = 4203; median age = 74.0 years; 56.7% female). Mean BCVA was lower than those reported in LEAD (83 letters), INTERCEPT (79.8 letters), and MACUSTAR (79 letters) studies (11, 12, 15). The reasons for this are unclear, as the presence of ocular co-morbidities such as cataract was not collected.

In the DORADO cohort, 8 participants had unilateral GA with a mean BCVA of 79.9. This is higher than the INTERCEPT study, which reported a mean BCVA of 63.4 (SD = 21.3) albeit in a larger sample size of 72 participants (12). By far the majority of individuals had the same imaging features of iAMD in both eyes. However, when participants had unilateral medium and/or large drusen, SDD or GA, compared with these bilaterally, the VA was typically approximately 2-lines better in that eye. This reflects the progressive nature of AMD and that biomarkers may be evident unilaterally early on in the disease.

The causal association between smoking and development of AMD is well documented with an estimated 2- to 3-fold increased risk in smokers compared to non-smokers (16, 17). In the DORADO cohort, 51.9% of participants were either ex- or current smokers, in line with the LEAD and AREDS2 studies which report a prevalence of 47.2% and 55.8%, respectively (11, 14). Moreover, the EUREYE study also reported the association between smoking and GA (16). The DORADO study demonstrates there remains an opportunity to encourage lifestyle modifications to prevent the development of iAMD and GA. The AREDS study also demonstrated over 5 years a 25% reduction in the risk of developing advanced AMD due to oral supplementation with antioxidant vitamins and minerals (18). Despite this, 87.2% (N = 116) of participants in the DORADO cohort diagnosed with iAMD were not taking AREDS2 supplementation. This also presents an opportunity for prevention of advanced AMD. Use of the Amsler chart has been widely recommended to detect early vision changes in people at risk of developing AMD. However, studies have reported low levels of sensitivity, poor accuracy and reliability in its detection of intermediate and advanced AMD in both the first and second eye to develop nAMD. Furthermore, poor patient compliance is well documented and indeed, only approximately one third (N = 48) of the DORADO cohort were regularly using the Amsler grid (8, 19–21).

It is well reported that QoL is negatively impacted by AMD, particularly as the disease advances (6, 22). In the DORADO cohort, baseline mean NEI-VFQ-25 composite score, MacDQoL AWI and AMD-specific scores are in line with previous reports (6, 22) with negative MacDQoL scores indicating the impact of AMD on QoL. The EQ-5D-3L SSI score is 0.8. However, the majority of the cohort experience minimal depression. Across all regression models, VA was the dominant and most consistent predictor of baseline QoL, explaining significant additional variance over demographics in every outcome in both the BSE and WSE models. Higher VA was associated with better NEIVFQ25 composite score, better MacDQoL AWI score and lower PHQ9 in both eyes. Critically, both BSE and WSE VA predicted QoL with comparable effect sizes, reinforcing that bilateral visual function matters to patient wellbeing. Longer disease duration independently predicted lower EQ5D3L SSI scores in both eye models. In the BSE model, it also contributed to NEIVFQ25 composite score, suggesting a worse generic health utility and greater burden with longer disease duration, independent of current VA, may result in a cumulative toll of

living with iAMD that goes beyond what VA alone captures at any single time point. No individual SD-OCT biomarker explained significant additional variance in any outcome model once VA was accounted for. The single exception was SDD, whilst non-significant in the sequential block test, was independently associated with worse MacDQoL AWI scores in the fully adjusted BSE and WSE final models. This may suggest that in iAMD, patient-reported QoL is driven primarily by what the individual can see rather than by the structural features of disease visible on OCT imaging. In both the BSE and WSE models, we see a significant effect of current or ex-smoker status on a worse NEIVFQ25 and MacDQoL score. The use of AREDS2 supplementation was also associated with a negative QoL score.

The strength of the DORADO study is that it provides a comprehensive evaluation of iAMD participants including VA, OCT characteristics, smoking status, Amsler grid use, AREDS supplementation and QoL outcomes in a large UK cohort. It is limited however by the fact that imaging characteristics were not quality controlled by a reading centre. Whilst this may reduce consistency and reliability across the sites, all investigators undertook specific training on imaging characteristics with at least 90% score being required prior to opening to recruitment. A further limitation is that VA was measured using both ETDRS and Snellen charts, with Snellen VA converted to ETDRS score. This may introduce potential measurement bias reducing comparability across sites. Finally, due to the number of classifications of AMD and that studies similar to DORADO studying AMD do not all use the same AMD classification, caution needs to be applied to any cross-study interpretation.

In conclusion, the DORADO report 1 is a comprehensive overview of baseline characteristics of a cohort of iAMD individuals undergoing community-based OCT screening in the UK. In this cohort, QoL is driven primarily by how well patients can see, secondarily by how long they have lived with the disease and, for vision-specific outcomes, substantially by whether they smoke. SD-OCT biomarkers add little independent explanatory power beyond VA.

Declarations

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Conflict of Interest

RP: Received honorarium for advisory board meetings and speaker fees from Abbvie, Allergan, Alimera, Apellis, Bayer, Heidelberg Engineering, Lux Biosciences, Novartis, Notal Vision and Roche; Institutional grants from Novartis Pharmaceuticals UK Ltd and Bayer Pharmaceuticals. **SS:** Member of the Eye editorial board. Institutional research grants and received support for publication from Novartis, Bayer, Allergan/Abbvie and Boehringer Ingelheim; Attended advisory board meetings of Allergan, Apellis, Bayer, Boehringer Ingelheim, Heidelberg Engineering, Novartis, Oxurion, Oculus, Optos, Ophthea and Roche.

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Author Contribution Statement

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Analysis and Interpretation: RPG, AA, RLH, AAS, SS, RM

Obtained Funding: RPG

Overall Responsibility: RPG

Data Availability Statement

The dataset generated and analysed during the current study are available from the corresponding author on reasonable request.

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Table 3

Table 3 is available in the Supplementary Files section.

Supplementary Files

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