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Prevalence and risk factors for age-related macular degeneration in a population-based cohort study of older adults in Northern Ireland using multimodal imaging: NICOLA Study

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ABSTRACT

Purpose To report prevalence and risk factor associations for age-related macular degeneration (AMD) and AMD features from multimodal retinal grading in a multidisciplinary longitudinal population-based study of aging in Northern Ireland.

Study design Population-based longitudinal cohort study.

Methods Retinal imaging at the Norther Ireland Cohort for the Longitudinal Aging Study health assessment included stereo Colour Fundus Photography (CFP) (Canon CX-1, Tokyo, Japan) and Spectral-Domain Optical Coherence Tomography (SD-OCT) ((Heidelberg Retinal Angopgraph (HRA)+OCT; Heidelberg Engineering, Heidelberg, Germany). Medical history and demographic information was obtained during a home interview. Descriptive statistics were used to describe the prevalence of AMD and individual AMD features. Multiple imputation followed by multiple regression modelling was used to explore risk factor associations including relationships with AMD genetic risk score.

Results Retinal images from 3386 participants were available for analysis. Mean age of the sample was 63.4 (SD 9.01, range: 36–99). Population weighted prevalence of AMD using colour grading in those over 55 years was: no drusen: 6 0.4%; drusen <63 µm: 15.9%; drusen 63–125 µm: 13.7%; drusen >125 µm or pigmentary changes: 8.3%; late AMD: 1.6%. Prevalence of AMD features in those over 55 years was: OCT drusen 27.5%, complete outer retinal pigment epithelium and outer retinal atrophy (cRORA) on OCT was 4.3%, reticular drusen 3.2% and subretinal drusenoid deposits 25.7%. The genetic risk score was significantly associated with drusen and cRORA but less so for SDD alone and non-significant for hyperpigmentation or vitelliform lesions.

Conclusions Multimodal imaging-based classification has provided evidence of some divergence of genetic risk associations between classical drusen and SDD. Our findings support an urgent review of current AMD severity classification systems.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Age-related macular degeneration (AMD) is of significant public health concern due to the impact of vision loss on quality of life together with an increasingly aged population. Substantial advances in retinal imaging has furthered our understanding of the condition through the use of optical coherence tomography (OCT) images, yet most epidemiological studies rely solely on colour fundus photographs for assessment.

WHAT THIS STUDY ADDS

⇒ The Norther Ireland Cohort for the Longitudinal Aging Study included multimodal retinal imaging (colour fundus photography, OCT and ultrawide field retinal imaging enabling an unprecedented assessment of AMD including individual retinal features of the condition. The results show disparities between assessments using different imaging modalities highlighting the importance of using multimodal imaging for future studies of prevalence and incidence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports the incorporation of OCT based features into future grading schemes or severity staging systems and the need for longitudinal data on progression of OCT based features to better understand their significance in progression to late-stage disease.

INTRODUCTION

Epidemiological studies of age-related macular degeneration (AMD) have traditionally relied on colour fundus photography (CFP) to identify the characteristics used to classify each eye into disease severity stages. Landmark studies such as the Beaver Dam Eye study,[1] the Rotterdam Eye Study[2] and the Blue Mountain's Eye Study[3] have identified the key phenotypic features and revealed the natural history of progression and associations with risk factors especially age, smoking and genetic risk.[4–7] Although studies showed the importance of drusen size and hyperpigmentation in influencing the risk of progression, the role of other colour-defined features such as reticular pseudodrusen[8] (RPD; a characteristic form of extracellular drusenoid

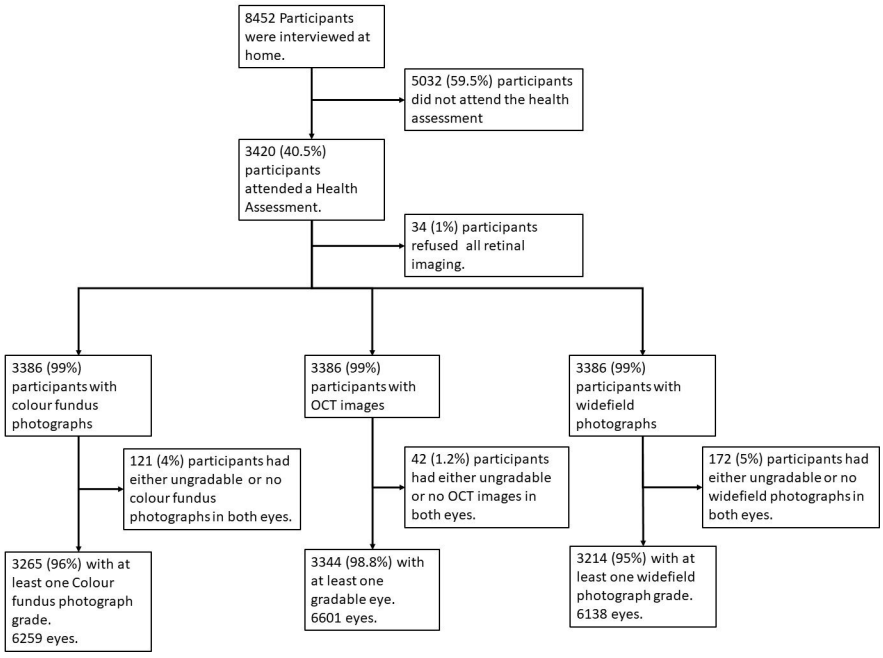

Figure 1 Flow chart showing participant pathway in wave 1 of the NICOLA Study. NICOLA, Northern Ireland Cohort for the Longitudinal Study of Aging.

deposits) and small drusen remains controversial. This is mainly because colour grading can overestimate presence of small drusen[9] and underestimate presence of RPD.[10] Optical Coherence tomography (OCT permits the distinction of nodular (classic) drusen from RPD through characterisation of layer location.

The establishment of a new population-based longitudinal study of ageing in Northern Ireland (The Northern Ireland Cohort for the Longitudinal Study of Aging (NICOLA)) offered an opportunity to assess the retina using multimodal retinal imaging (CFP, OCT, ultrawide field imaging (UWFII)) approach, define previously unexplored phenotypes from an epidemiological perspective and study risk factor associations with an extended range of markers of systemic health.

METHODS

NICOLA Study overview

The NICOLA is a multidisciplinary prospective population-based cohort study. Wave 1 of the study commenced in December 2013 and ended in April 2018. In total, 8452 persons completed the home-based computer-assisted personal interview. Of these, 3420 (40.5%) attended for the health assessment, which consisted of anthropometric, cardiac, respiratory, cognitive and ophthalmic tests (figure 1).

Details on image acquisition, image grading, physical data collection, self-report, blood-based biomarkers, genetic analysis, outcome categorisation and covariate selection can be found in the online supplemental methods.

Statistical analysis

All statistical analysis was conducted using R (V.3.6.0).[11]

Prevalence analysis

Prevalence of AMD was estimated, weighting records by the population distribution of age and sex as recorded in the 2011 Census for Northern Ireland. For the eye level analysis, the frequency, prevalence and 95% CIs for each AMD feature was calculated. To facilitate comparison with prior studies,[12] estimates are provided by age category and with a separate estimate for participants aged 55 years and above.

Imputation and risk factor association

Missing risk factor values were imputed using multivariate imputation by chained equations (MICE) using the *R* package *mice* (V.3.8.0),[13] which yielded a set of five datasets in which the missing values had been imputed probabilistically. The regression models outlined further were fitted using each of the imputed datasets, and estimates were pooled across imputations. A single estimate was generated for each parameter of interest that encompassed the additional uncertainty introduced by imputation. Further details of the imputation procedure are given in online supplemental methods.

Associations between AMD features and risk factors were explored using logistic regression. A series of regressions were fitted for each AMD feature with the feature as the response variable. First, a set of univariate models was fitted, the sole predictor in each being one of the candidate risk factors. A second set was adjusted with the addition of age (linear and quadratic terms) and sex. Risk factors receiving some statistical support in the age-adjusted andsex-adjusted models ($p<0.1$) were included in a multivariable model. Finally, a saturated model including all risk factors was fitted. Where an AMD feature was particularly rare, inclusion of all the selected variables occasionally resulted in unstable estimates or a failure of multivariable or saturated models to converge. In these instances, problematic combinations of predictors were identified, and models were refitted after removing these risk factors. For the analysis of person-level AMD risk factors (dichotomised AMD stage), an additional model was fitted excluding the Genetic Risk Score (GRS) to explore the extent to which associations with other risk factors differed in the absence of the GRS.

Table 1 Prevalence by stage of Beckman clinical classification for AMD % (95% CI) by age

Unweighted							Weighted				
Age (years)	Number at risk	0	1	2	3	4	0	1	2	3	4
All ≥55	2690	61.1 (59.2 to 63.0)	16.6 (15.2 to 18.1)	13.8 (12.5 to 15.1)	7.5 (6.6 to 8.6)	1.0 (0.6 to 1.4)	60.4 (58.3 to 62.6)	15.9 (14.5 to 17.5)	13.7 (12.3 to 15.2)	8.3 (7.1 to 9.8)	1.6 (0.9 to 2.6)
<55	575	63.1 (59.0 to 67.1)	23.7 (20.2 to 27.3)	9.4 (7.1 to 12.1)	3.8 (2.4 to 5.7)	0.0	62.7 (58.5 to 66.7)	23.7 (20.2 to 27.5)	9.6 (7.3 to 12.4)	4.0 (2.5 to 6.0)	0.0
55–64	1257	64.6 (61.9 to 67.2)	18.5 (16.3 to 20.7)	12.2 (10.4 to 14.1)	4.7 (3.6 to 6.0)	0.1 (0.0 to 0.4)	64.5 (61.8 to 67.2)	18.6 (16.4 to 20.8)	12.1 (10.3 to 14.0)	4.8 (3.7 to 6.1)	0.1 (0.0 to 0.4)
65–74	1061	59.3 (56.3 to 62.3)	16.0 (13.9 to 18.4)	14.9 (12.8 to 17.2)	8.8 (7.1 to 10.6)	1.0 (0.5 to 1.8)	59.0 (55.9 to 62.0)	16.1 (13.9 to 18.4)	15.2 (13.1 to 17.5)	8.7 (7.1 to 10.6)	1.0 (0.5 to 1.8)
75–84	325	54.8 (49.2 to 60.3)	12.3 (8.9 to 16.4)	16.9 (13.0 to 21.5)	13.2 (9.7 to 17.4)	2.8 (1.3 to 5.2)	55.6 (49.9 to 61.2)	11.3 (8.1 to 15.2)	17.3 (13.2 to 22.0)	13.0 (9.5 to 17.2)	2.8 (1.2 to 5.3)
≥85	47	53.2 (38.1 to 67.9)	10.6 (3.5 to 23.1)	8.5 (2.4 to 20.4)	17.0 (7.6 to 30.8)	10.6 (3.5 to 23.1)	54.3 (36.7 to 71.1)	10.9 (2.9 to 26.1)	7.1 (1.4 to 19.9)	16.9 (6.4 to 33.3)	10.9 (2.9 to 26.1)

Table 1 shows the prevalence of AMD severity stages based on the Beckman clinical classification using the worse eye (person level). Unweighted and weighted estimates are shown. Data were weighted by age and gender using the 2011 Census for Northern Ireland.
AMD, age-related macular degeneration.

RESULTS

Cohort characteristics

Of the 3420 participants who attended the health assessment, retinal imaging was performed in 3386 (99%) (figure 1). Images were available for colour 6259 eyes (92%), OCT 6601 (96%) and UWFI 6138 (89%). Images were ungradable in approximately 121 (4%) (colour), 42 (1%) (OCT) and 172 (5%) (UWFI) eyes. The number of individuals for whom both eyes were gradable was: colour 2994 (88%), OCT 3257 (95%) and UWFI 2934 (85%). More than 85% of participants had gradable images from both eye on all three imaging modalities. Online supplemental table 1 shows proportions of participants with ungradable images by imaging modality. The mean (SD) age of participants with gradable colour images was 63.5 (8.9) years (online supplemental table 1), and over 99.9% were Caucasian.

Prevalence by Beckman stage

The prevalence of stage 0 and stage 1 (representing no features of AMD or small hard drusen only) declined from 62.7% and 23.7% to 54.3 % and 10.9%, respectively (table 1). For stage 2, the prevalence rose steadily from 9.6% to 17.3% in those in age band 75–84 but was 7.1% in the oldest age band. For participants in stage 3, the prevalence increased from 4.0% to 16.9%. Stage 4 representing the most advanced cases of AMD was rare in the two younger age bands, was infrequent in the age groups between 65 and 84 and occurred at 10.9% in the oldest age group. Prevalence rates were similar across sexes (online supplemental table 2).

Prevalence by graded features

The prevalence of features of AMD based on colour or OCT grading is shown in table 2.

With colour detection, the prevalence of focal hyperpigmentation increased from 1.0% to 9.6% with age. Small drusen <63 µm rose from 7.9% in the youngest to 22.9% in those older than 85 years. The prevalence of drusen >125 µm rose steadily from 1.3% to 9.6% doubling by each age category, but the oldest two age bands were similar. RPD frequencies were similar for the two youngest age bands but showed steady rises in the three oldest age categories. On OCT images, subretinal drusenoid deposit (SDD) were observed frequently on OCT in all age bands compared with RPD on colour. These differentials were striking 18.0% on OCT versus 1.1% on colour in the youngest age category and 53.6% versus 12.0% in those >85 years. The prevalence of geographic atrophy (GA) was low on colour and only seen in the two oldest age bands at 0.5% and 1.2%. This contrasted with the higher proportions of cRORA on OCT, which rose from 2.5% from those under 55 year to 16.5% in those aged 85 years and above. The prevalence of all the graded features was not significantly different between men and women (online supplemental table 3).

Prevalence of AMD features on UWFI colour imaging

The prevalence of hard and soft drusen and hyperpigmentation in UWFI colour images by age groups are shown in table 3.

Small hard drusen were highly prevalent in the central (62.8%), mid (86.8%) and far periphery (75.8%) of the fundus with the highest prevalences seen in the midregion, but no significant differences were seen with age and sex (sex data not shown). The prevalence of soft drusen rose monotonically with age in the central fundus, with similar rises in the mid and far periphery. Hyperpigmentation increased with age in all three regions, but the prevalence by age group and rise with increasing age group was most marked in the far periphery. Table 4 shows the relationship between Beckman stage and the UWFI grades. The UWFI-based prevalence of soft drusen in central, mid and far regions rose with increasing Beckman stage.

The prevalence of hard drusen in all UWFI regions was similar across all Beckman stages. The prevalence of hyperpigmentation increased with increasing Beckman stage.

Genetic risk score (GRS)

The GRS ranged from −3.0 to 5.1 (SD 1.1) and was normally distributed. In controls (Beckman 0,1), the mean GRS was 0.4 (SD 1.1). For cases (Beckman 2,3,4), the GRS was higher 0.7 (SD 1.2) (online supplemental table 4). Mean GRS (SD) for AMD features detected on colour were hyperpigmentation: 0.4 (1.2), drusen (any size): 0.6 (1.2), drusen ≥63 µm: 0.7 (1.2), drusen >125 µm: 1.0 (1.4), reticular drusen: 1.0 (1.2) and geographic atrophy: 1.6 (0.8). The mean GRS for AMD features detected on OCT were classic drusen 0.8 (1.2), SDD 0.7 (1.2), SDD only 0.5 (1.1), cRORA 0.8 (1.3), CNV 1.4 (1.1) and vitelliform lesion 0.1 (1.1).

Risk factor associations

Comparison between stage 0 or 1 versus stages 2, 3 and 4 (online supplemental table 4) showed that only the GRS (OR 1.25, 95% CI 1.15 to 1.35, p<0.001) and serumHigh Density Lipoprotein (HDL) remained highly statistically significant in the fully adjusted model. Self-reported chronic lung disease (OR 1.71, 95% CI 1.11 to 2.64, p=0.014), Parkinson's disease (OR 5.10, 95% CI 1.39 to 18.74, p=0.014) and the category of elevated hypertension (OR 1.44, 95% CI 1.06 to 1.96, p=0.020) just reached significance in the fully adjusted model. The association with high-sensitivity C-Reactive Protein (hsCRP) was higher in the model with GRS removed (OR 1.09, 95% CI 1.00 to 1.19,

Table 2 Prevalence of AMD features by age category (eye-level analysis, unweighted)

Colour/*en face* grading							Multimodal grading (Infra-red and OCT)						
Age (years)	Number at risk	Hyperpigmentation	Drusen (any size)	Drusen ≥63 µm	Drusen ≥125 µm	Reticular Drusen	GA	Number at risk	Drusen (any size)	SDD	cRORA	CNV	Vitelliform
All ≥55	5128	2.0 (1.5, 2.4)	28.9 (27.4 to 30.4)	14.5 (13.4 to 15.7)	3.9 (3.3 to 4.5)	3.2 (2.7 to 3.9)	0.3 (0.2 to 0.6)	5450	27.5 (26.1 to 29.0)	25.7 (24.3 to 27.1)	4.3 (3.7 to 5.0)	0.3 (0.2 to 0.5)	0.3 (0.2, 0.6)
<55	1131	1.0 (0.5, 1.7)	26.0 (23.0 to 29.2)	7.9 (6.1 to 9.9)	1.3 (0.7 to 2.4)	1.3 (0.6 to 2.5)	0.0	1151	16.3 (13.9 to 19.0)	13.0 (10.9 to 15.4)	2.5 (1.5 to 3.9)	0.0	0.0
55–64	2447	1.0 (0.6, 1.6)	24.7 (22.7 to 26.8)	10.2 (8.8 to 11.6)	1.9 (1.4 to 2.6)	1.1 (0.7 to 1.7)	0.0	2534	20.4 (18.5 to 22.3)	18.3 (16.6 to 20.1)	2.9 (2.2 to 3.7)	0.0 (0.0 to 0.2)	0.0 (0.0, 0.2)
65–74	2003	2.4 (1.7, 3.3)	30.6 (28.2 to 33.1)	16.4 (14.5 to 18.5)	4.7 (3.6 to 6.0)	3.8 (2.8 to 5.1)	0.5 (0.2 to 1.1)	2144	29.5 (27.1 to 31.9)	27.3 (25.1 to 29.6)	4.7 (3.7 to 5.8)	0.2 (0.1 to 0.7)	0.6 (0.2, 1.1)
75–84	595	3.2 (1.8, 5.2)	38.8 (33.9 to 43.9)	24.7 (20.5 to 29.4)	8.2 (5.7 to 11.4)	8.6 (5.9 to 11.9)	1.2 (0.4 to 2.6)	675	44.3 (39.5 to 49.2)	44.1 (39.5 to 48.9)	6.8 (4.7 to 9.5)	0.8 (0.3 to 1.9)	0.6 (0.1, 2.1)
≥85	83	9.6 (3.4, 20.5)	39.8 (26.8 to 53.9)	22.9 (12.1 to 37.1)	9.6 (3.4 to 20.5)	12.0 (4.0 to 26.0)	0.0	97	54.6 (40.9 to 67.9)	53.6 (40.1 to 66.8)	16.5 (8.2 to 28.2)	6.0 (2.0 to 13.5)	2.1 (0.0, 11.1)

Table 2 shows the prevalence of AMD features on en face and multimodal grading (non-weighted) (eye level). The all category is restricted to those over 55 years to enable comparison with other studies who restrict definition of AMD to this age category.
AMD, age-related macular degeneration; CNV, choroidal neovascular membrane; cRORA, complete retinal pigment epithelium and outer retinal atrophy; GA, geographic atrophy; OCT, optical coherence tomography; SDD, subretinal drusenoid deposit.

p=0.045) than when it was included (OR 1.08, 95% CI 0.99 to 1.18, p=0.065).

Risk factor associations with individual features detected by colour grading are shown in online supplemental table 5. The GRS was consistently associated with classical drusen and RPD. The OR for classical drusen <63 µm was 1.24 (1.13 to 1.37) and increased to 1.52 (1.27 to 1.81) for drusen >125 µm. The OR for RPD was 1.47 (1.23 to 1.75). There was no significant association for GRS and hyperpigmentation. The presence of a thickened choroid was significantly associated with drusen of any size.

Online supplemental table 6 shows the risk factor associations with individual grading features based on OCT. A consistent and highly significant association was seen between the GRS and classical drusen with an OR of 1.33 (95% CI 1.24 to 1.43, p<0.001). Eyes with SDD with classical drusen also had a statistically significant association OR 1.35 (95% CI 1.26 to 1.44, p<0.001). For eyes with SDD without classical drusen, the association with the GRS lost significance 1.15 (95% CI 1.02 to 1.28, p=0.017), but the direction of risk remained unchanged. The OR for cRORA was statistically significant p=0.003 at 1.26 (95% CI 1.08 to 1.46). Classical drusen were significantly associated with thick choroid OR 1.84 (95% CI 1.42 to 2.37, p<0.001) and RPD with thin choroid with an OR of 1.69 (95% CI 1.27 to 2.23, p<0.001).

DISCUSSION

NICOLA Study ascertained the prevalence of features of early AMD through traditional colour imaging and extended this to include UWFI and SD-OCT, permitting us to distinguish between participants based on individual characteristics. We showed clear and steady almost monotonic age-related rises in the prevalence of Beckman stages 2 and 3 representing early and intermediate AMD, respectively (table 1). These findings are in accord with prior epidemiological studies.[2 3]

In the eye- level analysis, differences by age group in the frequencies of drusen were seen on comparing features detected by colour versus OCT. Notably, on colour, the prevalence of drusen (any size) was higher than that seen on OCT in the younger age groups, and although it rose with age, the increase was shallow. On OCT, the prevalence of any drusen, which was around 16% in the youngest age band, rose steadily to 54% in the oldest age band. These colour versus OCT discrepancies mainly occurred in the detection of drusen <63 µM. Our data suggest that small drusen were more likely to be graded as present in younger age groups and likely represented an over calling of this feature by the graders.[9 14] By contrast, small drusen when present were more likely to be missed on colour grading in the older age groups in whom there is a higher prevalence of lens opacities with resultant degradation of image quality interfering with the detection process.

We observed good correspondence for prevalence of drusen >125 µM on comparing detection by colour or by OCT. We demonstrated poor agreement for the prevalence RPD comparing detecting by *en face* technologies versus its OCT correlate of SDD, a finding that is in keeping with previous studies.[10 15 16] We expected that the OCT correlate of pseudo drusen, SDDs would be detected at higher frequency than that reported by *en face* imaging, but the magnitude of the difference was surprising. Even though the prevalence on en face imaging of RPD was marginally lower in NICOLA Study at 3.2% than the Rotterdam study (4.9%) or that reported from another UK cohort (5.06%),[17] it was still much higher than that of a large

Table 3 Prevalence of hard drusen, soft drusen and hyperpigmentation on ultrawide field retinal images (weighted)

Age (years)	Number at risk	Centre	Mid	Far	Full
Hard drusen					
All ≥55	5023	62.8 (61.0 to 64.7)	86.8 (85.4 to 88.1)	75.6 (74.0 to 77.2)	94.6 (93.7 to 95.4)
<55	1115	58.6 (55.4 to 61.7)	85.2 (82.7 to 87.4)	76.9 (74.1 to 79.6)	94.4 (92.6 to 95.8)
55–64	2392	57.0 (54.8 to 59.2)	86.4 (84.8 to 87.9)	77.2 (75.2 to 79.0)	94.9 (93.8 to 95.8)
65–74	1971	64.6 (62.2 to 67.0)	87.8 (86.2 to 89.3)	77.0 (74.8 to 79.0)	94.7 (93.6 to 95.7)
75–84	585	69.8 (65.2 to 74.0)	88.2 (84.9 to 91.0)	72.6 (68.2 to 76.6)	94.9 (92.8 to 96.6)
≥85	75	70.8 (52.3 to 85.2)	80.4 (64.3 to 91.4)	68.2 (52.7 to 81.2)	91.2 (80.3 to 97.2)
Soft Drusen					
All≥55	5023	5.6 (4.6 to 6.9)	3.2 (2.6 to 3.9)	3.7 (3.1 to 4.5)	8.6 (7.4 to 10.0)
<55	1115	0.8 (0.3 to 1.7)	0.6 (0.2 to 1.3)	2.2 (1.2 to 3.5)	2.8 (1.7 to 4.2)
55–64	2392	2.3 (1.7 to 3.1)	2.1 (1.5 to 2.8)	3.4 (2.5 to 4.4)	5.5 (4.4 to 6.7)
65–74	1971	6.5 (5.2 to 8.0)	4.3 (3.2 to 5.5)	4.7 (3.6 to 6.0)	10.0 (8.4 to 11.8)
75–84	585	10.0 (7.1 to 13.5)	4.5 (2.6 to 7.1)	4.2 (2.4 to 7.0)	12.8 (9.6 to 16.7)
≥85	75	10.2 (1.9 to 27.9)	1.3 (0.1 to 4.9)	0.0	10.2 (1.9 to 27.9)
Hyperpigmentation					
All≥55	5023	2.0 (1.4 to 2.9)	8.5 (7.1 to 10.2)	12.5 (10.9 to 14.2)	14.5 (12.8 to 16.4)
<55	1115	0.8 (0.3 to 1.7)	2.1 (1.2 to 3.3)	3.2 (2.1 to 4.6)	4.6 (3.2 to 6.2)
55–64	2392	0.9 (0.5 to 1.5)	3.9 (3.0 to 4.9)	6.1 (5.0 to 7.4)	7.6 (6.3 to 9.0)
65–74	1971	1.9 (1.3 to 2.7)	8.9 (7.4 to 10.5)	13.5 (11.7 to 15.5)	15.5 (13.5 to 17.6)
75–84	585	3.1 (1.6 to 5.6)	11.0 (8.0 to 14.6)	19.0 (15.2 to 23.4)	20.9 (16.8 to 25.4)
≥85	75	6.8 (1.5 to 18.4)	27.9 (13.4 to 46.8)	27.8 (13.3 to 46.9)	34.7 (17.9 to 54.7)

Table 3 shows the prevalence of hard, soft drusen and hyperpigmentation on ultrawide field retinal images (weighted) (eye level). Unweighted and weighted estimates are shown. Data were weighted by age and gender using the 2011 Census for Northern Ireland. The all category is restricted to those over 55 years to enable comparison with other studies who restrict definition of AMD to this age category.

community-based cohort study in Australia[18] (0.41%). Studies that have either used OCT alone or in conjunction with other imaging modalities have generally reported high prevalence rates of SDD. Alienor found the prevalence of SDD to be 13.4% using multimodal imaging[19] in contrast to the Alstar study who reported a prevalence of 32% in their clinic based enrolment cohort[20] using multimodal imaging. In NICOLA Study, we found the prevalence to be 25.7% in those aged 55 years and older. We contend that NICOLA Study offers better representation of the true population prevalence of SDD in older adults as its community-based sampling strategy is less likely to be biased in the direction of persons with other ocular morbidities that are common in clinic-based samples.

As with other epidemiological studies, the prevalence of large areas of atrophy visible on colour images representing GA was low, precluding generation of robust estimates of prevalence and risk factor associations for this late stage of AMD. Nonetheless, we were able to characterise in detail the presence of cRORA, an OCT based definition of focal atrophy in the outer retina,[21] using SD-OCT, and indeed NICOLA is the first epidemiological

Table 4 Comparison of Beckman stages graded on colour with presence of hard drusen, soft drusen or hyperpigmentation on UWF

	Beckman classification	Number at risk	Centre % (95% CI)	Mid % (95% CI)	Far % (95% CI)
Hard drusen	0	4131	58.4 (56.8 to 60.0)	86.0 (84.9 to 87.2)	75.8 (74.3 to 77.2)
	1	836	67.5 (64.0 to 70.8)	88.2 (85.7 to 90.3)	78.1 (75.1 to 80.9)
	2	545	68.6 (64.4 to 72.6)	90.3 (87.2 to 92.9)	85.0 (81.5 to 88.0)
	3	277	69.7 (63.9 to 75.1)	88.1 (83.4 to 91.8)	79.1 (73.0 to 84.3)
	4	31	54.8 (32.8 to 75.5)	71.0 (50.3 to 86.8)	67.7 (48.0 to 83.7)
	Ungradable	318	57.2 (51.5 to 62.8)	83.3 (78.7 to 87.3)	63.2 (57.1 to 69.0)
Soft drusen	0	4131	1.5 (1.1 to 1.9)	1.9 (1.5 to 2.5)	2.9 (2.3 to 3.5)
	1	836	2.9 (1.8 to 4.4)	2.8 (1.8 to 4.1)	4.7 (3.2 to 6.5)
	2	545	11.6 (8.7 to 15.0)	5.3 (3.5 to 7.8)	7.0 (4.8 to 9.8)
	3	277	28.5 (22.3 to 35.4)	6.5 (3.7 to 10.4)	4.3 (1.9 to 8.3)
	4	31	38.7 (18.8 to 61.9)	25.8 (9.3 to 49.7)	25.8 (9.3 to 49.7)
	Ungradable	318	6.3 (3.7 to 9.9)	2.5 (1.0 to 5.3)	1.9 (0.7 to 4.1)
Hyperpigmentation	0	4131	1.0 (0.7 to 1.4)	5.5 (4.7 to 6.4)	9.0 (8.0 to 10.1)
	1	836	0.6 (0.2 to 1.4)	5.9 (4.3 to 7.8)	8.0 (6.1 to 10.3)
	2	545	2.0 (0.9 to 3.8)	9.0 (6.4 to 12.2)	12.3 (9.3 to 15.8)
	3	277	9.0 (5.7 to 13.5)	9.0 (5.6 to 13.5)	13.7 (9.6 to 18.8)
	4	31	16.1 (5.3 to 34.1)	16.1 (5.0 to 35.0)	19.4 (6.9 to 38.9)
	Ungradable	318	0.9 (0.2 to 2.7)	5.7 (3.3 to 9.0)	9.4 (6.3 to 13.4)

UWF, ultrawide field.

study to record its prevalence. The proportion of eyes exhibiting cRORA even in the younger age groups was around 2.5%, and this rose steadily with age allowing us to provide robust estimates by age band for focal outer retinal atrophy. This information will be particularly useful for sample size calculations when developing protocols for GA interventional trials. In this context, we recognise that while it is presently unknown if cRORA is a robust precursor of geographic atrophy, longitudinal case series[22] and data from clinical trials[23] that have enrolled participants with early AMD who have progressed to GA strongly support this view.

Peripheral retinal changes have been reported in several clinical AMD cohorts[24 25] and one other population-based study.[26] The prevalence in the periphery of small hard drusen, soft drusen and pigmentary irregularities in the UWFI images in the NICOLA population were in accord with the high rates of abnormalities reported in these prior studies. It was notable that increasing Beckman severity stages was mirrored by increases in soft drusen and hyperpigmentation in the central, mid and far periphery. By contrast, the prevalence of hard drusen was similar in the central mid and far periphery across all Beckman severity stages suggesting that these are a ubiquitous finding. Histological studies however dispute these findings and show that the pathology visible in the periphery is not the same as that in the macula.[27] Widefield OCT images should be prioritised in future studies as these may help resolve these disparities in clinical cohorts.

Various risk factors for intermediate and late AMD have been identified in longitudinal epidemiological studies[28] and clinical cohorts.[29 30] The fully adjusted multivariate regression model revealed that age and the GRS were the only highly statistically significant associations with the Beckman severity stage person-level classification. Associations between AMD and chronic lung disease is relatively novel though has recently been reported from a populatio-based retrospective study in Taiwan[31] so deserves further exploration. Some factors such as physical activity that were significant in univariate are likely to be highly collinear with age, hence the drop from age-adjusted models. The ORs and risk estimates for the GRS and Beckman stages of intermediate and late AMD are in accord those of the eye-risk consortium, which recently reported a similar mean GRS from their large, pooled analysis of cross-sectional data from the European Eye Epidemiology Consortium.[32]

In the AMD feature-level analysis, the GRS was strongly associated with classical drusen, on separating eyes with SDD from eyes with both SDD and classical drusen, the association with the GRS lost significance despite previous studies showing a significant association between SDD and the two major AMD risk loci independent of drusen presence (ARMS2 positively associated and CFH Y402H negatively associated).[33] We also observed that GRS was not significantly associated with hyperpigmentation when this feature present in the absence of drusen. This is not surprising since focal hyperpigmentation on its own can represent pathology such as past inflammation.

All types of drusen were associated with a thicker choroid, which is in keeping with many previous studies,[34–36] whereas those with SDD alone had a significantly thinner choroid. A detailed study of the relationship between choroidal thickness, choroidal vascularity index (CVI) and SDD presence by Keenan *et al*[35] reported a biphasic alteration in choroidal dimensions across the disease spectrum with those with large drusen showing increased choroidal thickness and increased CVI, whereas the same parameters in those with advanced AMD in the fellow eye were no different to controls. Those with just SDD had significantly thinner choroid and reduced CVI.[35] Keenan *et al* propose CVI as a potential biomarker of ageing given its significant and negative correlation with age, and our data on SDD alone suggest that it too may be more reflective of ubiquitous ageing rather than AMD per se. It is also interesting to note SDD alone also had a lower GRS than the other drusen related features though still significantly associated in keeping with recent genetic studies showing significant associations with the major AMD susceptibility loci.[37]

Limitations

Our study suffers from several limitations. First, the response rate for those who attended the health assessment was moderate, but we implemented appropriate weighting strategies to mitigate the effects of such bias. Nonetheless, when weighted and unweighted prevalence estimates were compared (table 1), the differences were minor suggesting that the cohort demographic structure closely matched that of the general population. Second, we investigated a large number of potential risk factors a process that can increase the risk of false positive results. We therefore took a highly conservative approach in the creation of the multivariable models and interpreted the findings in terms of effect size and biological plausibility rather than explicit p value cut-offs. Third, we did not grade for intraretinal hyper-reflective foci an OCT feature, which is now considered a biomarker of deteriorating retinal pigment epithelium (RPE) health and a predictor for progression to late AMD.[38]

CONCLUSIONS

This study provides further insight into the prevalence and risk factors of AMD and AMD features using multiple imaging modalities. Interestingly, the correlation between the Beckman classification and our findings from UWF imaging provide evidence that on a pragmatic level that the former continues to have validity. It highlights the benefits of using a multimodal approach in future epidemiological studies but also the challenges in interpretating findings that can be compared with previous colour only studies. New severity stage systems that incorporate AMD-based OCT features are urgently needed.

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Contributors Conceived and designed the study: REH, UC, TP, ISY and FK.Analysed the data: DMW, LS and AJM. Acquisition of data: BH, KAM, LS and TP. Administrative, technical or material support: AJM, LS, JW, MAT, SC, BM, ISY and FK. Wrote the paper: RH. Critically revised the manuscript: DMW, NBQ, KAM, BH, LS, AJM, JW, MAT, SC, BM, ISY, FK, TP and UC. RH and DMW had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. UC is guarantor. Statistical analyses were performed by DMW.

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REFERENCES

1 Klein R, Klein BE, Moss SE. Diabetes, hyperglycemia, and age-related maculopathy. The Beaver dam eye study. *Ophthalmology* 1992;99:1527–34.
2 Vingerling JR, Dielemans I, Hofman A, *et al*. The prevalence of age-related maculopathy in the Rotterdam study. *Ophthalmology* 1995;102:205–10.
3 Mitchell P, Smith W, Attebo K, *et al*. Prevalence of age-related maculopathy in Australia. the blue Mountains eye study. *Ophthalmology* 1995;102:1450–60.
4 Buitendijk GHS, Rochtchina E, Myers C, *et al*. Prediction of age-related macular degeneration in the general population: the three continent AMD Consortium. *Ophthalmology* 2013;120:2644–55.
5 Joachim N, Colijn JM, Kifley A, *et al*. Five-Year progression of unilateral age-related macular degeneration to bilateral involvement: the three continent AMD Consortium report. *Br J Ophthalmol* 2017;101:1185–92.
6 Joachim N, Kifley A, Colijn JM, *et al*. Joint contribution of genetic susceptibility and modifiable factors to the progression of age-related macular degeneration over 10 years: the three continent AMD Consortium report. *Ophthalmol Retina* 2018;2:684–93.
7 Saunier V, Merle BMJ, Delyfer M-N, *et al*. Incidence of and risk factors associated with age-related macular degeneration: four-year follow-up from the ALIENOR study. *JAMA Ophthalmol* 2018;136:473–81.
8 Mimoun G, Soubrane G, Coscas G. [Macular drusen]. *J Fr Ophtalmol* 1990;13:511–30.
9 Graham KW, Chakravarthy U, Hogg RE, *et al*. Identifying features of early and late age-related macular degeneration: a comparison of multicolor versus traditional color fundus photography. *Retina* 2018;38:1751–8.
10 Hogg RE, Silva R, Staurenghi G, *et al*. Clinical characteristics of reticular pseudodrusen in the fellow eye of patients with unilateral neovascular age-related macular degeneration. *Ophthalmology* 2014;121:1748–55.
11 Team RC. R: a language and environment for statistical computing. Vienna, Austria R Foundation for Statistical Computing; 2019.
12 Colijn JM, Buitendijk GHS, Prokofyeva E, *et al*. Prevalence of age-related macular degeneration in Europe: the past and the future. *Ophthalmology* 2017;124:1753–63.
13 Buuren Svan, Groothuis-Oudshoorn K. mice : Multivariate Imputation by Chained Equations in *R*. *J Stat Softw* 2011;45:1–67.
14 Farinha C, Cachulo ML, Coimbra R, *et al*. Age-Related Macular Degeneration Staging by Color Fundus Photography vs. Multimodal Imaging-Epidemiological Implications (*The Coimbra Eye Study-Report 6*). *J Clin Med* 2020;9. doi:10.3390/jcm9051329. [Epub ahead of print: 02 05 2020].
15 Wu Z, Ayton LN, Luu CD, *et al*. Reticular Pseudodrusen in intermediate age-related macular degeneration: prevalence, detection, clinical, environmental, and genetic associations. *Invest Ophthalmol Vis Sci* 2016;57:1310–6.
16 De Bats F, Mathis T, Mauget-Faÿsse M, *et al*. Prevalence of reticular PSEUDODRUSEN in age-related macular degeneration using multimodal imaging. *Retina* 2016;36:46–52.
17 Wilde C, Poostchi A, Mehta RL, *et al*. Prevalence of reticular pseudodrusen in an elderly UK Caucasian population-The Bridlington eye assessment project (BEAP): a cross-sectional study (2002-2006). *Eye* 2018;32:1130–7.
18 Finger RP, Chong E, McGuinness MB, *et al*. Reticular Pseudodrusen and their association with age-related macular degeneration: the Melbourne Collaborative cohort study. *Ophthalmology* 2016;123:599–608.
19 Chan H, Cougnard-Grégoire A, Delyfer M-N, *et al*. Multimodal imaging of reticular Pseudodrusen in a population-based setting: the Alienor study. *Invest Ophthalmol Vis Sci* 2016;57:3058–65.
20 Zarubina AV, Neely DC, Clark ME, *et al*. Prevalence of Subretinal Drusenoid Deposits in Older Persons with and without Age-Related Macular Degeneration, by Multimodal Imaging. *Ophthalmology* 2016;123:1090–100.
21 Sadda SR, Guymer R, Holz FG, *et al*. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology* 2018;125:537–48.
22 Jaffe GJ, Chakravarthy U, Freund KB, *et al*. Imaging features associated with progression to geographic atrophy in age-related macular degeneration: classification of atrophy meeting report 5. *Ophthalmol Retina* 2021;5:855-867.
23 Guymer RH, Wu Z, Hodgson LAB, *et al*. Subthreshold nanosecond laser intervention in age-related macular degeneration: the LEAD randomized controlled clinical trial. *Ophthalmology* 2019;126:829–38.
24 , Domalpally A, Clemons TE, *et al*, Writing Committee for the OPTOS PEripheral RetinA (OPERA) study (Ancillary Study of Age-Related Eye Disease Study 2). Peripheral Retinal Changes Associated with Age-Related Macular Degeneration in the Age-Related Eye Disease Study 2: Age-Related Eye Disease Study 2 Report Number 12 by the Age-Related Eye Disease Study 2 Optos PEripheral RetinA (OPERA) Study Research Group. *Ophthalmology* 2017;124:479–87.
25 Tan CS, Heussen F, Sadda SR. Peripheral autofluorescence and clinical findings in neovascular and non-neovascular age-related macular degeneration. *Ophthalmology* 2013;120:1271–7.
26 Lengyel I, Csutak A, Florea D, *et al*. A population-based ultra-widefield digital image grading study for age-related macular Degeneration-Like lesions at the peripheral retina. *Ophthalmology* 2015;122:1340–7.
27 Rudolf M, Clark ME, Chimento MF, *et al*. Prevalence and morphology of druse types in the macula and periphery of eyes with age-related maculopathy. *Invest Ophthalmol Vis Sci* 2008;49:1200–9.
28 Joachim N, Mitchell P, Kifley A, *et al*. Incidence and progression of geographic atrophy: observations from a population-based cohort. *Ophthalmology* 2013;120:2042–50.
29 Grunwald JE, Daniel E, Huang J, *et al*. Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2014;121:150–61.
30 Wu Z, Luu CD, Hodgson LAB, *et al*. Prospective longitudinal evaluation of nascent geographic atrophy in age-related macular degeneration. *Ophthalmol Retina* 2020;4:568–75.
31 Bair P-J, Hsia N-Y, Lin C-L, *et al*. Population-Based retrospective cohort study on risk of age-related macular degeneration in people with chronic obstructive pulmonary disease. *Sci Rep* 2021;11:15079.
32 Colijn JM, Meester-Smoor M, Verzijden T, *et al*. Genetic risk, lifestyle, and age-related macular degeneration in Europe: the EYE-RISK Consortium. *Ophthalmology* 2021;128:1039-1049.
33 Lin LY, Zhou Q, Hagstrom S, *et al*. Association of single-nucleotide polymorphisms in age-related macular degeneration with Pseudodrusen: secondary analysis of data from the comparison of AMD treatments trials. *JAMA Ophthalmol* 2018;136:682–8.
34 Lee J, Kim M, Lee CS, *et al*. Drusen subtypes and choroidal characteristics in Asian eyes with typical neovascular age-related macular degeneration. *Retina* 2020;40:490–8.
35 Keenan TD, Klein B, Agron E. Choroidal thickness and vascularity vary with disease severity and subretinal drusenoid deposit presence in Nonadvanced age-related macular degeneration. *Retina*2019 (published Online First: 2019/01/22).
36 Velaga SB, Nittala MG, Vupparaboina KK, *et al*. Choroidal vascularity index and choroidal thickness in eyes with reticular Pseudodrusen. *Retina* 2020;40:612–7.
37 Domalpally A, Agrón E, Pak JW, *et al*. Prevalence, risk, and genetic association of reticular Pseudodrusen in age-related macular degeneration: age-related eye disease study 2 report 21. *Ophthalmology* 2019;126:1659–66.
38 Nassisi M, Lei J, Abdelfattah NS, *et al*. Oct risk factors for development of late age-related macular degeneration in the fellow eyes of patients enrolled in the harbor study. *Ophthalmology* 2019;126:1667–74.