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Reticular Pseudodrusen on the Risk of Progression in Intermediate Age-Related Macular Degeneration

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ABSTRACT

Purpose: To examine the association between reticular pseudodrusen (RPD) and progression to late age-related macular degeneration (AMD) in individuals with intermediate AMD.

Design: Prospective cohort study.

Methods: 280 eyes from 140 participants with bilateral large drusen underwent multimodal imaging (MMI), including optical coherence tomography (OCT), near-infrared reflectance (NIR), fundus autofluorescence and color fundus photography (CFP), at 6-monthly intervals up over a 36-month follow-up period. The presence of RPD per eye was determined based on either a combined MMI criteria, as well as based on each individual imaging modality, and their extent measured on combined OCT and NIR imaging. The association between the presence of RPD on different imaging modalities, and their extent, with the development of late AMD (including OCT-defined atrophy) was evaluated.

Results: The presence of RPD on MMI, or any of its individual modalities at baseline, was not significantly associated with an increased rate of developing late AMD, with or without adjusting for risk factors for AMD progression (age, drusen volume on OCT, and pigmentary abnormalities on CFP; all $P \geq 0.205$). The extent of RPD present was also not significantly associated with an increased rate of developing late AMD, with or without adjustment for risk factors for AMD progression (both $P \geq 0.522$).

Conclusions: In this cohort with bilateral large drusen, the presence of RPD was not significantly associated with an increased risk of developing late AMD. Additional longitudinal studies in all stages of AMD are needed to understand the implications of RPD on vision loss in this condition.

INTRODUCTION

In the early stages of age-related macular degeneration (AMD), the presence of large drusen and pigmentary abnormalities are recognized as crucial risk factors for the subsequent development of late complications of AMD including atrophy and neovascularization.[1] However, prediction models based on the presence of these features can only correctly predict less than half of those who subsequently develop late AMD at a 5% false-positive rate.[2-4] This highlights the need to identify other key disease features in the early stages of AMD that are associated with an increased risk of progression, to improve risk stratification.

Reticular pseudodrusen (RPD), or subretinal drusenoid deposits (SDDs), are distinct lesions found above the retinal pigment epithelium (RPE).[5] RPD were first described over three decades ago as a network of interlacing drusen-like deposits seen more clearly with blue light.[6] It is now recognized that these subretinal lesions, visible on optical coherence tomography (OCT) imaging,[7] can also appear as more discrete lesions, and less commonly as confluent lesions, on color fundus photographs (CFPs).[8, 9] However, they are missed when assessing CFPs in more than half to three-quarters of eyes with OCT-defined RPD,[10-12] and more effectively detected using other *en face* imaging modalities such as near-infrared reflectance (NIR) and fundus autofluorescence (FAF).[10, 11, 13]

Several previous studies, including our own, have reported that the presence of RPD in the non-late, fellow AMD eyes of individuals with unilateral neovascular AMD (nAMD) is associated with an increased risk of developing any late AMD[14-19] or geographic atrophy (GA) only.[11, 20] However, one of these studies no longer found a significant association with an increased risk of disease progression over a longer 5-year follow-up period.[21] Two population-based studies, based upon RPD identified on CFPs, also reported that eyes with RPD showed a higher likelihood of developing late AMD over time.[22, 23] However, AMD severity at the eye- and person-level (e.g., based on the maximum drusen size, presence of pigmentary abnormalities, and presence of late AMD in the fellow eye, being key risk factors for progression[1]) was not accounted for in these studies. Furthermore, the use of CFPs would have likely resulted in a large proportion of the eyes with RPD being missed.[10-12]

More recently, an ancillary study of the Age-Related Eye Disease Study 2 (AREDS2) reported that the presence of RPD as detected on fundus autofluorescence (FAF) imaging was associated with a 2.6-fold increased risk of developing late AMD over a 1-year period in 646 individuals with bilateral drusen (with a total drusen area larger than the area in a 354μm diameter circle).[24] However, another ancillary study of the AREDS2 did not find a significant association between the presence of OCT-defined RPD and an increased risk of new-onset GA in eyes with large drusen from 265 participants with or without late AMD in the fellow eye.[25] Two other smaller studies, one also evaluating non-late AMD eyes of individuals with or without late AMD in the fellow eye[26] and one evaluating individuals with intermediate AMD,[27] also did not observe a significant association between the presence of RPD and an increased risk of late AMD development.

Clearly, the current evidence available for the role of RPD as a risk factor for progression to vision-threatening late AMD in individuals with the early stages of AMD is mixed and inconclusive, yet many assume their presence as a significant risk factor. It is thus paramount that we obtain further evidence about the prognostic significance of RPD in AMD progression, which will also play a key role in further understanding the potential disease mechanisms underlying RPD formation. This study thus sought to examine whether the presence of RPD, detected on multimodal imaging (MMI), is associated with an increased risk of progression to late AMD in a cohort of individuals with intermediate AMD, all with bilateral large drusen at baseline. It further seeks to examine whether associations with disease progression differ based on the imaging modality used to determine the presence of RPD, as well as whether the association differs based on the extent of RPD present as determined on combined NIR and OCT imaging.

METHODS

This study included participants randomized to the sham treatment arm of the Laser Intervention in the Early Stages of AMD (LEAD) study (clinicaltrials.gov identifier, NCT01790802).[28] Participants were seen at five sites in Australia and one site in Northern Ireland, and the list of investigators at each site are included in the Supplementary Material. Institutional board approval was obtained at

each site, and this study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and with the tenets of the Declaration of Helsinki. All participants provided written informed consent before enrollment in this study.

Participants

At baseline, all participants were required to be ≥50 years of age and have at least one large druse (>125μm) within 1500μm of the fovea (in radius) in both eyes (and thus meet the definition of intermediate AMD[1]). Participants were also required to have a best-corrected visual acuity of 20/40 or better, and not have MMI-defined late AMD (defined below) in either eye at baseline. Participants with any other ocular or systemic conditions that could also affect the assessment of the retina were excluded.

In this study, late AMD was defined using MMI as the presence of either: (i) neovascular AMD, characterized by lesions on fluorescein and/or indocyanine green angiography or a retinal hemorrhage associated with fluid on OCT imaging; (ii) geographic atrophy on CFP, based on a sharply delineated area of partial or complete RPE depigmentation that results in an increased visibility of the underlying choroidal vessels, which was roughly round or oval in shape and ≥175μm in diameter and within 3000μm of the fovea (in radius); (iii) OCT-defined atrophic changes of nascent geographic atrophy (nGA),[29, 30] based on the presence of subsidence of the outer plexiform layer and inner nuclear layer, and/or presence of a hyporeflective wedge-shaped band within Henle's fiber layer, or more progressed OCT atrophic lesions that do not meet the definition of GA (e.g., nGA that was associated with a zone of choroidal signal hypertransmission that was associated with attenuation or disruption of the RPE band that was ≥250 μm[31]).

The participants were reviewed at 6-monthly intervals up to 36-months to determine the development of late AMD over time. Participants were seen at an additional visit outside of their scheduled regular visits if they developed new ocular symptoms. In this study, only participants that were seen at ≥1 visits after baseline were included.

Multimodal Imaging

All participants underwent OCT, NIR, and FAF imaging on the Spectralis HRA+OCT (Heidelberg Engineering; Heidelberg, Germany) using a standardized protocol. OCT volume scans of the central 20 x 20º region were obtained, consisting of 49 B-scans and each with 25 frames averaged. NIR and FAF images covered the central 30 x 30º region, with a minimum resolution of 768 x 768 pixels, with 25 frames averaged for each image. Foveal-centered CFPs were also obtained using site-specific fundus cameras that had a minimum resolution of 2000 x 2000 pixels. These four imaging modalities are thus described as multimodal imaging (MMI).

Image Grading and Processing

The presence of RPD on each imaging modality and combined MMI was determined by a senior grader (K.Z.A.) and senior medical retina clinician (R.H.G.). An MMI definition of RPD required the results of OCT imaging and at least two *en face* imaging modalities (NIR, FAF, or CFP) to be gradable, and RPD was otherwise considered ungradable. RPD were deemed definitely present on MMI if: (i) there were ≥5 definite RPD present on ≥2 B-scans on OCT imaging, and RPD were definitely present or questionable on ≥1 *en face* modality (based on the presence of a characteristic group or groups of RPD lesions on these *en face* modalities), or (ii) RPD were definitely present on ≥2 *en face* modalities. RPD were deemed absent on MMI if there were not ≥5 definite RPD on ≥2 B-scans on OCT imaging, and absent on all *en face* modalities or questionable on only one *en face* modality. RPD were otherwise deemed questionable if they were neither considered definitely present or absent.

In eyes deemed to have OCT- and MMI-defined RPD, another senior grader (L.A.B.H.) used NIR and OCT imaging simultaneously to quantify the area of RPD present in the central 20 x 20º region. This was performed by manually outlining areas with groups of hyporeflective lesions with or without a central hyper- or iso-reflective core on NIR imaging that correspond to definite RPD on OCT B-scans; an example is shown in Figure 1.

CFPs were also graded for the presence of AMD pigmentary abnormalities by a senior grader. Drusen volume in the central 20 x 20º region from the OCT volume scan was determined using convolutional neural network-based retinal layer segmentation of each B-scan using a

method described previously.[32] The investigators that performed this OCT image analysis to calculated drusen volume are listed in the Supplemental Material.

Statistical Analysis
The endpoints evaluated in this study were the development of all MMI-defined late AMD or atrophic AMD, and participants who were lost to follow-up or died during the study were censored at their last assessment. Otherwise, participants were censored at the 36-month visit if they were seen over the entire follow-up and did not develop late AMD. The associations between RPD parameters – including the definite presence of RPD on each individual modality or based on MMI, as well as square root-transformed RPD area – and the time to develop the endpoints were evaluated using Cox proportional hazard models. As both eyes from each participant were included in the analyses, we fitted the Cox model with shared frailty (assuming a gamma distribution). Univariable Cox models were first used to evaluate each parameter before they were then evaluated in a multivariable model including baseline age, cube root-transformed drusen volume[33] and presence of pigmentary abnormalities as confounders. These analyses were performed on STATA, software version 16.1 (StataCorp, College Station, Texas, USA).

RESULTS:
This study included 280 eyes from 140 participants who were on average 70 ± 8 years old (range, 51 to 89 years old) and predominantly female (77%); further details about the characteristics of the participants in this study (including ethnicity and smoking history), and specifically for those with and without MMI-defined RPD in either eye, are presented in Table 1. Details about the best-corrected visual acuity, drusen volume and presence of pigmentary abnormalities in this cohort, and separately for the eyes with and without MMI-defined RPD, are also presented in Table 1. MMI-defined definite RPD were detected in a total of 65 (23%) eyes from 37 (26%) participants, and they were bilateral in 28 (76%) of the participants. Table 2 further describes the proportion of eyes detected as having RPD based on each imaging modality, presented separately, dependent upon their RPD status as determined by our MMI-definition. It highlights, for example, that RPD were deemed to be present on CFP in only 30 (46%) eyes when deemed to be present using MMI. It also highlights how there were no eyes where RPD was deemed to be present only on two *en face* imaging modalities and not on OCT imaging (one of the criteria for MMI-defined definite RPD), since all 65 (100%) eyes with MMI-defined RPD had definite RPD on OCT imaging. Amongst the 65 eyes with MMI-defined RPD, the median area with RPD was 13.4 mm^2 (interquartile range = 7.4 to 23.9 mm^2).

A total of 134 (96%) participants were seen up to the 36-month follow-up visit, and 48 (17%) eyes developed MMI-defined late AMD over the follow-up period. There were 40 (14%) and 8 (3%) eyes that developed atrophic and nAMD respectively, as their first late AMD endpoint. As such, we did not examine the nAMD endpoint separately due to its limited number.

Association Between RPD at Baseline and Late AMD Development
The presence of RPD at baseline, either as defined on MMI or as seen as definitely present on any one of its individual modalities (OCT, NIR, FAF, or CFP), was not associated with a difference in the time-to-develop any MMI-defined late AMD or atrophic AMD in univariable analyses ($P \geq 0.205$), or in a multivariable model including age, cube-root drusen volume and pigmentary abnormalities as confounders ($P \geq 0.165$; Table 3). The square root area of RPD present was also not significantly associated with a difference in the time to develop any MMI-defined late AMD or atrophic AMD in univariable ($P \geq 0.687$) or multivariable analyses ($P \geq 0.249$).

Additional analyses were performed for the endpoint of late AMD as traditionally defined based on the presence of nAMD or GA. In these analyses, there were no significant associations between the presence or area of RPD at baseline and this traditional late AMD endpoint ($P \geq 0.723$ in univariable analyses and $P \geq 0.458$ in multivariable analyses), except for CFP-defined RPD where these analyses could not be performed as none (0%) out of the 30 eyes with CFP-defined RPD developed this late AMD endpoint (compared to 16 [6%] out of 250 eyes without CFP-defined RPD that developed this late AMD endpoint).

Association Between Conventional Risk Factors and Progression to MMI-Defined Late AMD

For comparison, larger cube-root drusen volume on OCT imaging and presence of pigmentary abnormalities on CFP at baseline were both significantly associated with an increased rate of progression to all MMI-defined late AMD or all atrophic AMD in univariable analyses ($P < 0.001$ for all comparisons), but not higher baseline age ($P \geq 0.214$; Table 4). However, all three parameters were significantly associated with all MMI-defined late AMD and atrophic AMD endpoints when considered together in multivariable analyses ($P \leq 0.002$ for both; Table 4).

In addition, both drusen volume and presence of pigmentary abnormalities ($P \leq 0.001$), but not baseline age ($P = 0.117$), were significantly associated with the endpoint of late AMD as traditionally defined based on the presence of nAMD or GA in univariable analyses. However, only the presence of pigmentary abnormalities ($P = 0.003$) was significantly associated with progression to this traditional endpoint of late AMD, but not baseline age or drusen volume ($P \leq 0.142$).

DISCUSSION

This study demonstrated that in our cohort of individuals with bilateral large drusen, followed with MMI every 6 months for up to 3 years, neither the presence of RPD defined on MMI at baseline, nor any one of the individual imaging modalities, nor their baseline extent defined on combined NIR and OCT imaging, was associated with an increased risk of progression to MMI-defined late AMD in both univariable and multivariable analyses. These findings were observed in the same cohort where drusen volume and presence of pigmentary abnormalities were both significantly associated with disease progression, being parameters that are well-established in previous studies as risk factors for progression.[1, 34-39]

Our observation of a lack of a significant association between RPD and an increased risk of progression to late AMD was found both when late AMD was defined based upon the traditionally defined endpoint of nAMD or GA, and when using a broader definition of MMI-defined late AMD that also included nGA[29, 30] in the definition of OCT-defined atrophy. This absence of a significant association was also seen when late AMD was defined based on the presence of complete RPE and outer retinal atrophy (cRORA) on OCT imaging,[31] in addition to traditionally defined endpoints of GA and nAMD (*data not shown*)

This is the first study to our knowledge that has examined the association between RPD as detected using MMI or OCT imaging and late AMD progression in a clearly defined cohort of individuals with intermediate or non-late AMD, adjusting for known risk factors for AMD progression. Nonetheless, these findings are supported by those reported from a study of individuals with intermediate AMD in the Colorado AMD Registry ($n = 109$ individuals), which defined RPD using FAF, NIR, and OCT imaging.[27] However, adjustments for conventional risk factors for late AMD development were not performed in that study. Our findings that the presence of RPD was not associated with an increased risk of developing late AMD are also supported by those reported in a subset of the AREDS2 participants in the ancillary spectral-domain OCT (A2A SD-OCT) study ($n = 265$ eyes),[20] from the Molecular Diagnostic of AMD (MODIAMD) study ($n = 91$ eyes).[26] However, note that the A2A SD-OCT and MODIAMD studies examined one eye with non-late AMD from individuals with or without late AMD in the fellow eye, so it did not specifically examine a cohort of individuals solely with the early stages of AMD.

However, this lack of evidence to support the notion that the presence of RPD is a risk factor for late AMD development is not consistent with the findings from a different subset of AREDS2 participants in the autofluorescence ancillary study ($n = 646$).[24] In that study, individuals with bilateral drusen (with a total area larger than the area in a 354μm diameter circle) and coexistent FAF-defined RPD had a 2.6-fold higher likelihood of developing late AMD over a 1-year period compared to those without RPD.[24] Using a similar grading criteria of FAF-defined RPD in our study as the AREDS2 autofluorescence ancillary study, we still did not observe a significant association between RPD defined with this imaging modality and an increased risk of progression (nor when defining RPD based on CFP, NIR or OCT alone).

Our findings are also not consistent with two previous population-based studies that suggested that CFP-defined RPD is associated with an increased risk of progression.[22, 23] However, it is now recognized that CFPs would miss a large proportion of eyes with RPD.[10-12] Furthermore, both of these previous population-based studies did not account for important conventional risk factors for late AMD development, such as the extent of drusen present (or even the presence of large [>125μm] drusen alone[1]) and the presence of pigmentary abnormalities in a

multivariable model when evaluating if RPD is an independent risk factor for progression.[22, 23] For instance, the finding by Joachim *et al*[23] that RPD is associated with a 14-fold increased risk of developing GA over a 15-year period is made in comparison to those with no or small (hard) drusen only. Their study also reported that the presence of soft indistinct drusen was associated with a 29-fold increased risk of progression compared to the presence of no or small (hard) drusen. It is thus not known from these population-based studies whether RPD would be independently associated with an increased risk of progression in those with the early stages of AMD, after accounting for the conventional AMD risk factors.[1]

It is possible that RPD is a risk factor for progression, even in early stages of AMD, but is a feature with a small effect size (compared to risk factors such as pigmentary abnormalities, whose presence was associated with a >4.5-fold increased risk of progression in this study). If so, this would make it difficult to detect an association between RPD and disease progression unless this was examined in a large cohort. However, the effective sample size of this cohort (after accounting for the inter-eye correlations within an individual) would have provided ≥80% power to detect a risk factor that was associated with a ≥2.5-fold increased risk of developing late AMD based on a one-sided alpha of 0.05. This study was thus sufficiently powered to detect an effect size of the same magnitude as reported in the AREDS2 autofluorescence ancillary study, where individuals with FAF-defined RPD were found to have a 2.6-fold increased risk of developing late AMD.[24] It is also possible that our findings are attributed to our requirement for ≥5 lesions on ≥2 B-scans on OCT imaging to define its presence. However, we did not observe a significant association between the presence of any definite RPD (i.e., ≥1 lesions on the entire OCT volume scan) and an increased risk of progression to late AMD ($P \geq 0.201$; *data not shown*). Nonetheless, more definitive evidence about the prognostic significance of RPD in the early stages of AMD could be obtained through the inclusion of further well-designed longitudinal studies (especially those that account for the key, conventional risk factors of AMD progression, including drusen extent and presence of pigmentary abnormalities) and meta-analysis of the collective findings.

Our study is unable to comment on the prognostic significance of RPD in the fellow eye of individuals with late AMD in one eye. Several previous studies, including our own, have reported an association between RPD and an increased risk of developing late AMD[14-19] or geographic atrophy (GA) only[11, 20] in the non-late, fellow AMD eyes of individuals with unilateral nAMD. Note however that in one of these studies, longer-term follow-up of individuals no longer revealed a significant association between RPD and an increased risk of disease progression.[21]

RPD has been observed to be more commonly present in individuals with late AMD compared to those with the early stages of AMD,[40] with one study reporting that RPD are present in up 94% of eyes with GA.[41] This perhaps gives the impression that RPD has driven AMD progression, accounting for a widely held perception that RPD are a significant risk factor for progression to late AMD. It is possible that a distinct pathophysiological process, such as local hypoxia from vascular compromise,[42] not only drives AMD progression, but also leads to the development of RPD. This would thus account for the higher prevalence of RPD in those with late AMD compared to those with the earlier stages of AMD, without RPD itself being a significant risk factor for AMD progression.

The field has not yet agreed upon a standardized approach for defining the presence of RPD in an eye, such as what imaging modalities should be used, or the number or extent of RPD that should be present. Different clinical observations about RPD may thus arise from the use of differing definitions of their presence in an eye. We thus examined whether the presence of RPD on different imaging modalities, or whether the extent of RPD present on combined OCT and NIR imaging, had an impact on AMD progression, but we did not find either to be a significant factor in our cohort.

Understanding RPD and their role in vision loss in AMD remains important, even if there is not a significant association between their presence and disease progression in the early stages of AMD. We recently reported in a *post hoc* analysis that the presence of RPD was a potentially significant treatment effect modifier in the Laser Intervention in the Early Stages of AMD (LEAD) Study.[28, 43] Namely, those without coexistent RPD showed a four-fold reduction in the rate of progression to late AMD with novel subthreshold nanosecond laser treatment, whilst those with coexistent RPD showed a more than two-fold increase in the rate of developing late AMD, in individuals with bilateral large drusen.[28] As such, those with both drusen and RPD appear to represent a distinct AMD phenotype and may require different tailored interventions. Furthermore,

the association between the presence of RPD with greater impairments in dark adaptation in AMD[44-47] underscores their clinical significance as a feature that may reflect a greater level of visual impairment experienced under low luminance conditions.

The strengths of this study include the comprehensive characterization of RPD on four imaging modalities and measurement of its spatial extent. Another strength is its evaluation of RPD in a multivariable model that included important predictors of AMD progression, including drusen volume measured on OCT imaging[34-38] and presence of pigmentary abnormalities on CFP,[1, 39] both of which we confirmed as significant predictors of late AMD development. The rigorous six-monthly follow-up over 3 years in this study also allowed us to evaluate the rate of progression over time, rather than the probability of progression at a fixed follow-up time point only. However, limitations of this study include its sample size, inclusion of a single grader for quantifying RPD area, and the predominance of atrophic AMD as the endpoints, which meant that it was not possible to perform a sufficiently robust assessment of whether RPD was associated with an increased risk of neovascular AMD development. However, studies to date that have reported an association between RPD with an increased risk of late AMD development have generally reported a larger proportion of eyes that developed atrophic AMD compared to neovascular AMD.[24, 48] Another limitation is the lack of an assessment of outer retinal atrophy,[31] which has been reported to occur with the regression of RPD over time.[49] Such an assessment could be robustly achieved in future studies through the automated quantification of photoreceptor degeneration[50] and thickness on OCT imaging.

In conclusion, we observed in this cohort of individuals with bilateral large drusen that the presence of RPD, as detected on MMI or any of its individual modalities, and the spatial extent of RPD, was not associated with an increased rate of progression to late AMD (either as traditionally defined, or when including OCT-defined atrophy). Further longitudinal studies are still needed to understand the implications of the presence of RPD on vision loss when detected in eyes with AMD.

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FIGURE(S)

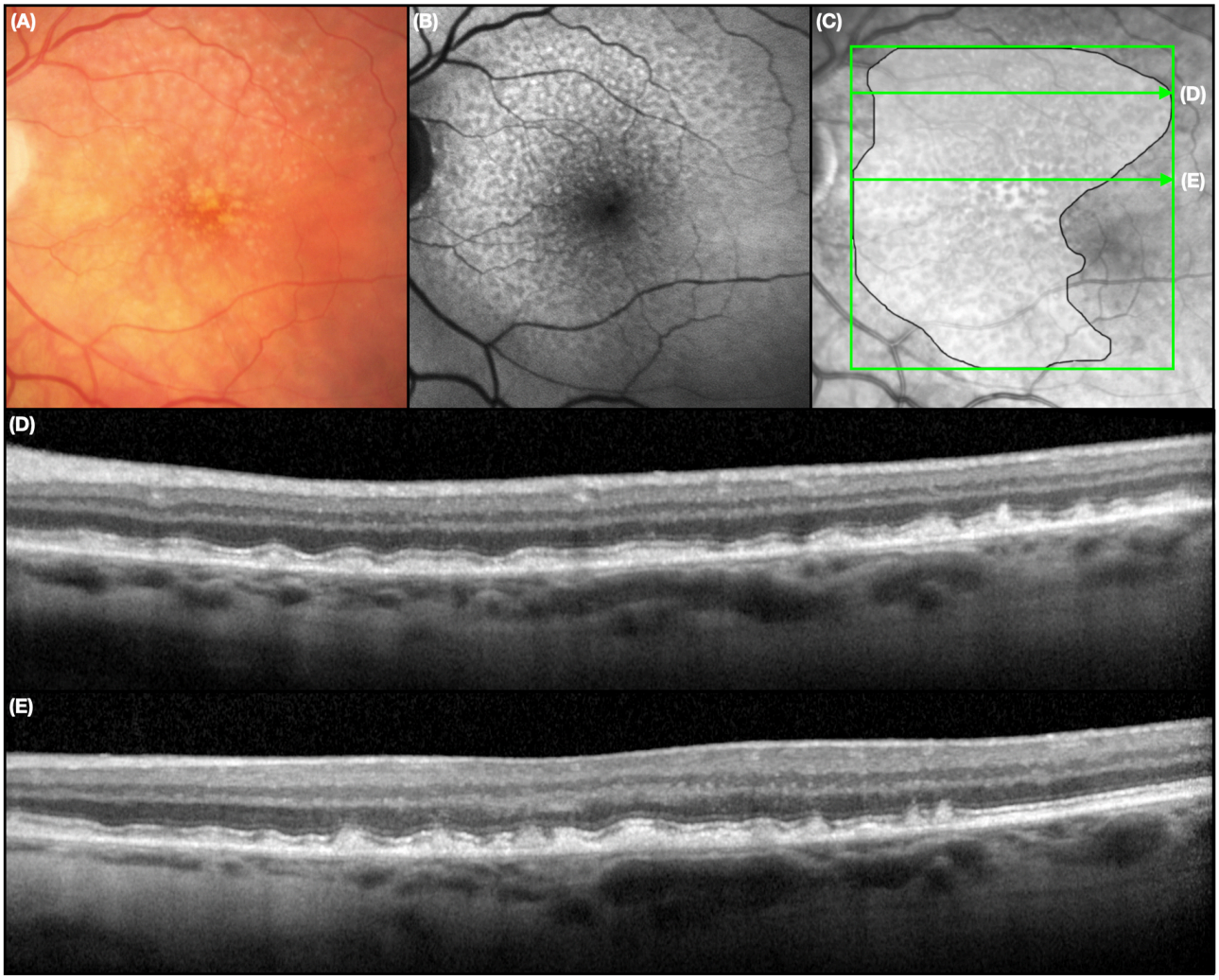


Figure 1: Multimodal imaging of reticular pseudodrusen (RPD), including (**A**) color fundus photography, (**B**) fundus autofluorescence, (**C**) near-infrared reflectance (NIR), and (**D**, **E**) optical coherence tomography (OCT; volume scan taken within the region outlined by the green square in [**C**] and specific B-scans shown taken through the regions outlined by the green arrows in [**C**]). The extent of RPD present on combined NIR and OCT imaging is outlined in [**C**] with a light blue overlay.

Table 1: Characteristics of participants and eyes included in this study

		Definite Presence of RPD*	
	Total Population	**Yes**	**No**
Individual-Level Parameters			
Age (years)	70 ± 8	74 ± 6	68 ± 8
Gender (female), no. (%)	108 (77)	29 (78)	79 (77)
Ethnicity (white), no. (%)	123 (88)	35 (95)	88 (85)
Smoking History (past or current), no. (%)	66 (47)	15 (41)	51 (50)
Completed 36-month follow-up (yes), no. (%)	134 (96)	34 (92)	100 (97)
Eye-Level Parameters			
BCVA (number of letters)	85 (81 to 89)	84 (80 to 87)	85 (82 to 89)
Drusen Volume (mm^3)	0.04 (0.02 to 0.09)	0.05 (0.02 to 0.09)	0.04 (0.02 to 0.09)
Pigmentary Abnormalities (definitely present), no. (%)	82 (29)	12 (18)	70 (33)

Notes: RPD = reticular pseudodrusen; BCVA = best-corrected visual acuity, measured using the Early Treatment Diabetic Retinopathy Study protocol; * = as defined on multimodal imaging, and based on the presence in either eye for the individual-level parameters; all data presented as mean ± standard deviation or median (interquartile range) unless otherwise stated.

Table 2: Presence of reticular pseudodrusen (RPD) on individual imaging modalities in eyes with and without definite RPD as defined on multimodal imaging (MMI; see Methods for full definition)

	RPD on MMI	
RPD Definitely Present On	**Definitely Present** *n* = 65 eyes (%)	**Absent / Questionable** *n* = 215 eyes (%)
OCT	65 (100)	4 (2)
FAF	55 (85)	3 (1)
NIR	52 (80)	2 (1)
CFP	30 (46)	0 (0)

Notes: All values shown as number (percentage); OCT = optical coherence tomography (defined when ≥5 definite RPD are detected on ≥2 B-scans); FAF = fundus autofluorescence; NIR = near-infrared reflectance; CFP = color fundus photography;

Table 3: Association between reticular pseudodrusen (RPD) at baseline and progression to all multimodal imaging-defined late or all atrophic AMD endpoints

	All Late AMD			All Atrophic AMD Only		
Parameters	**HR**	**95% CI**	***P*-Value**	**HR**	**95% CI**	***P*-Value**
Univariable Analysis						
RPD on MMI (definitely present)	1.11	0.38 to 3.18	0.852	1.27	0.39 to 4.13	0.692
RPD on OCT (definitely present)	1.25	0.44 to 3.50	0.677	1.51	0.47 to 4.77	0.487
RPD on NIR (definitely present)	1.21	0.42 to 3.50	0.724	1.30	0.41 to 4.11	0.655
RPD on FAF (definitely present)	1.19	0.42 to 3.41	0.744	1.31	0.41 to 4.16	0.653
RPD on CFP (definitely present)	0.32	0.05 to 1.88	0.205	0.38	0.06 to 2.55	0.321
RPD Area† (per 1.0 mm increase)	1.04	0.79 to 1.36	0.789	1.06	0.79 to 1.43	0.687
Multivariable Analyses#						
RPD on MMI (definitely present)	1.00	0.43 to 2.33	0.997	1.26	0.51 to 3.12	0.616
RPD on OCT (definitely present)	0.90	0.41 to 2.00	0.800	1.13	0.48 to 2.69	0.774
RPD on NIR (definitely present)	1.54	0.67 to 3.57	0.313	1.86	0.77 to 4.49	0.165
RPD on FAF (definitely present)	0.99	0.43 to 2.28	0.974	1.14	0.47 to 2.79	0.773
RPD on CFP (definitely present)	0.62	0.13 to 2.96	0.548	1.02	0.20 to 5.10	0.981
RPD Area† (per 1.0 mm increase)	1.08	0.86 to 1.34	0.522	1.14	0.91 to 1.45	0.249

Notes: HR = hazard ratio; CI = confidence interval; MMI = multimodal imaging (see Methods for full definition); OCT = optical coherence tomography (defined when ≥5 definite RPD are detected on ≥2 B-scans); NIR = near-infrared reflectance; FAF = fundus autofluorescence; CFP = color fundus photography; * = significant at $P < 0.05$; † = square root transformed; # = multivariable models evaluating each RPD parameter including age, cube-root drusen volume and pigmentary abnormalities.

Table 4: Association between age-related macular degeneration (AMD) features at baseline and progression to all multimodal imaging-defined late or atrophic AMD endpoints

	All Late AMD			All Atrophic AMD Only		
Parameters	**HR**	**95% CI**	***P*-Value**	**HR**	**95% CI**	***P*-Value**
Univariable Analysis						
Age (per decade)	1.42	0.82 to 2.45	0.214	1.40	0.75 to 2.61	0.290
Drusen Volume† (per 0.1 mm increase)	3.34	2.26 to 4.95	< 0.001*	3.43	2.27 to 5.17	< 0.001*
Pigmentary Abnormalities (definitely present)	9.44	4.42 to 20.14	< 0.001*	14.97	6.01 to 37.26	< 0.001*
Multivariable Analysis#						
Age (per decade)	1.93	1.31 to 2.84	0.001	1.98	1.28 to 3.04	0.002
Drusen Volume† (per 0.1 mm increase)	2.21	1.65 to 2.95	< 0.001*	2.32	1.68 to 3.21	< 0.001*
Pigmentary Abnormalities (definitely present)	4.55	2.16 to 9.59	< 0.001*	6.56	2.70 to 15.96	< 0.001*

Notes: HR = hazard ratio; CI = confidence interval; * = significant at $P < 0.05$; # = a single multivariable model including all three parameters listed; † = cube root transformed.

SUPPLEMENTARY MATERIAL

Appendix A: LEAD Study Group

Data safety monitoring committee:

S Al-Qureshi (chair), L Busija, and I Constable

Medical monitor:

D Louis

Endpoint adjudication committee:

CA Harper, S Wickremasinghe, P van Wijngaarden, and L Lim

Australian sites:

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International site:

Northern Ireland (Belfast Health and Social Care Trust): U Chakravarthy (principal investigator), L Kelly, K Gillvray, M Williams, G Casalino, G Mangoris, R Das, T Peto, L Toth, M Quinn, R Denham, NJ Lavery, G Sterrett, V Silvestri, G Young, K Graham, J Keenan, L Doyle, T Douglas, D Burns, P Wright, and L Scullion

Appendix B: Investigators Responsible for the Optical Coherence Tomography Imaging Analysis to Calculate Drusen Volume

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