

**Online-only materials included in the supplement:**

**Supplementary Table 1:** Details of the clinical diagnoses for the group labelled 'Other' arranged by frequency.

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**Supplementary Table 12:** Definitions of morphologic macular abnormalities (MMAs) based on optical coherence tomography (OCT) appearance.

**Supplementary Table 3:** Proportion of visual symptomatology reported based on the type of MMAs.

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**Supplementary Table 4:** Frequency of the overall morphologic macular abnormalities (MMAs), and the four most common categories, in relation to age in patients with MS.

**Supplementary Table 25:** Age-matched prevalence estimates of ERM in this study (overall and in the multiple sclerosis subgroup) compared to population-based estimates obtained from the Visual Impairment project

**Supplementary Figure 1 title:** Progression of an epiretinal membrane (ERM) over a 4 year period

**Supplementary Table 1:** Details of the clinical diagnoses for the group labelled 'Other' arranged by frequency.

<u>Diagnosis (Other); n (%)</u>	<u>Overall (n=388)</u>	<u>MNM group (n=321)</u>	<u>MMAs group (n=67)</u>
- <u>Unknown or lost to follow-up</u>	<u>135 (34.8)</u>	<u>113 (35.2)</u>	<u>22 (32.8)</u>
- <u>Probable MS</u>	<u>95 (24.5)</u>	<u>81 (25.2)</u>	<u>14 (20.9)</u>
- <u>Motor neuron disease</u>	<u>27 (7.0)</u>	<u>19 (5.9)</u>	<u>8 (11.9)</u>
- <u>Spondylosis with or without myelopathy</u>	<u>17 (4.4)</u>	<u>13 (4.1)</u>	<u>4 (6.0)</u>
- <u>SLE or Sjogren's disease with CNS involvement</u>	<u>12 (3.1)</u>	<u>11 (3.4)</u>	<u>1 (1.5)</u>
- <u>Migraine headache</u>	<u>12 (3.1)</u>	<u>11 (3.4)</u>	<u>1 (1.5)</u>
- <u>Leukoariosis</u>	<u>11 (2.8)</u>	<u>8 (2.5)</u>	<u>3 (4.5)</u>
- <u>Stroke</u>	<u>9 (2.3)</u>	<u>8 (2.5)</u>	<u>1 (1.5)</u>
- <u>CNS vasculitis</u>	<u>7 (1.8)</u>	<u>4 (1.3)</u>	<u>3 (4.5)</u>
- <u>Infectious myelopathy</u>	<u>6 (1.6)</u>	<u>3 (0.9)</u>	<u>3 (4.5)</u>
- <u>Epilepsy</u>	<u>6 (1.6)</u>	<u>6 (1.9)</u>	<u>=</u>
- <u>ADEM</u>	<u>5 (1.3)</u>	<u>5 (1.6)</u>	<u>=</u>
- <u>Possible CRION</u>	<u>4 (1.0)</u>	<u>3 (0.9)</u>	<u>1 (1.5)</u>
- <u>Leukodystrophy</u>	<u>4 (1.0)</u>	<u>4 (1.3)</u>	<u>=</u>
- <u>Hereditary spastic paraparesis</u>	<u>3 (0.8)</u>	<u>2 (0.6)</u>	<u>1 (1.5)</u>
- <u>Radiologically isolated syndrome</u>	<u>3 (0.8)</u>	<u>2 (0.6)</u>	<u>1 (1.5)</u>

- <u>Syringomyelia</u>	<u>3 (0.8)</u>	<u>3 (0.9)</u>	=
- <u>Non-arteretic ischemic optic neuropathy</u>	<u>3 (0.8)</u>	<u>3 (0.9)</u>	=
- <u>Spinal dural arteriovenous fistula</u>	<u>2 (0.5)</u>	<u>2 (0.6)</u>	=
- <u>Postviral cerebellitis</u>	<u>2 (0.5)</u>	<u>2 (0.6)</u>	=
- <u>Rosai-Dorfman syndrome</u>	<u>2 (0.5)</u>	<u>1 (0.3)</u>	<u>1 (1.5)</u>
- <u>Vascular malformation</u>	<u>2 (0.5)</u>	<u>2 (0.6)</u>	=
- <u>Normal pressure hydrocephalus</u>	<u>2 (0.5)</u>	<u>2 (0.6)</u>	=
- <u>Vitamin B12 deficiency</u>	<u>2 (0.5)</u>	<u>1 (0.3)</u>	<u>1 (1.5)</u>
- <u>Hereditary ataxia</u>	<u>2 (0.5)</u>	<u>2 (0.6)</u>	=
- <u>Idiopathic intracranial hypertension</u>	<u>2 (0.5)</u>	<u>2 (0.6)</u>	=
- <u>Stiff person syndrome</u>	<u>2 (0.5)</u>	<u>1 (0.3)</u>	<u>1 (1.5)</u>
- <u>Intracranial hypotension</u>	<u>2 (0.5)</u>	<u>1 (0.3)</u>	<u>1 (1.5)</u>
- <u>Peripheral neuropathy</u>	<u>2 (0.5)</u>	<u>2 (0.6)</u>	=
- <u>Traumatic spinal cord injury</u>	<u>1 (0.3)</u>	<u>1 (0.3)</u>	=
- <u>Primary CNS lymphoma</u>	<u>1 (0.3)</u>	<u>1 (0.3)</u>	=
- <u>Astrocytoma</u>	<u>1 (0.3)</u>	<u>1 (0.3)</u>	=
- <u>Antiphospholipid syndrome</u>	<u>1 (0.3)</u>	<u>1 (0.3)</u>	=

Abbreviations: ADEM = acute disseminated encephalomyelitis; CNS = central nervous system; CRION = Chronic relapsing inflammatory optic neuropathy; MS = multiple sclerosis; SLE = systemic lupus erythematosus.

**Supplementary Table 12:** Definitions of morphologic macular abnormalities (MMAs) based on optical coherence tomography (OCT) appearance.

MMAs	Description of the OCT Abnormality
Epiretinal membrane (ERM)	A band of high reflectivity across the anterior surface of the macula that displays obvious separation from the retina, although separation may be focal or minimal. Often creates an irregular surface contour or distorts the inner retinal surface <sup>35</sup>
<del>Microcystoid macular pathology (MMP)</del> <del>Microcystoid macular edema (MME)</del>	Cystoid, lacunar areas of hyporefectivity with clear boundaries, evident on at least 2 contiguous B-scans, or visible in a comparable region of the INL or ONL on at least 2 separate acquisitions <sup>3-5</sup>
Drusen	A separation of retinal pigment epithelium from Bruch's membrane or thickening of the retinal pigment epithelium <sup>35</sup>
Pigment epithelial detachment (PED)	Hyporefective area, similar to subretinal fluid, below the retinal pigment epithelium and above Bruch's membrane <sup>35</sup>
Retinal pigment epithelial atrophy (geographic atrophy)	A clear degradation of the reflectivity and thickness of the retinal pigment epithelium layer, or a complete absence of retinal pigment epithelium or contour break <sup>35</sup>
Central serous chorioretinopathy (CSC)	Accumulation of serous fluid between the photoreceptor outer segments and the RPE in combination with monofocal or multifocal changes in the RPE <sup>36</sup>
Vitreomacular traction	Vitreous adhesion to central macula with demonstrable changes by OCT but no full thickness tissue dehiscence; may include the following: tissue cavitation, cystoid changes in macula, loss of foveal contour, elevation of fovea above RPE <sup>37</sup>
Foveal pseudocyst (FP)	Cystoid space occupying the foveal region together with incomplete perifoveal posterior hyaloid detachment or other signs of vitreomacular traction <sup>38,39</sup>

Small full-thickness macular hole (FTMH)	A small break in the macula ( $\leq 250$ $\mu\text{m}$ ), may be round or have a flap adherent to vitreous; operculum may or may not be present <sup>37</sup>
Medium FTMH	Hole $>250$ but $\leq 400$ $\mu\text{m}$ ; may be round or have a flap adherent to vitreous; operculum may or may not be present <sup>37</sup>
Large FTMH	Hole $>400$ $\mu\text{m}$ ; vitreous may or may not be fully separated from macula <sup>37</sup>
Lamellar macular hole (LMH)	Irregular foveal contour associated with a defect in the inner fovea and intra-retinal splitting (typically between the OPL and the ONL) in the setting of an intact photoreceptor layer <sup>37,39</sup>
Macular Pseudohole	Steep macular contour to the central fovea, invaginated or heaped foveal edges, and a concomitant ERM with central opening (no loss of retinal tissue) <sup>37,39</sup>

**Abbreviations:** FTMH = full-thickness macular hole; INL = inner nuclear layer; MMAs = morphologic macular abnormalities; ONL = outer nuclear layer; OPL = outer plexiform layer; RPE = retinal pigment epithelium; OCT = optical coherence tomography.

**Supplementary Table 3: Proportion of visual symptomatology reported based on the type of MMAs\*.**

<u>Visual symptomatology</u>	<u>Drusen</u>	<u>ERM</u>	<u>PED</u>	<u>MMP†</u>	<u>Foveal cystoid changes</u>	<u>Geographic atrophy/other advanced forms of AMD</u>	<u>CSC</u>	<u>VMT</u>	<u>LMH</u>
<u>Asymptomatic</u>	<u>68 (54.4)</u>	<u>67 (55.8)</u>	<u>19 (55.9)</u>	<u>8 (24.2)</u>	<u>10 (90.9)</u>	<u>3 (33.3)</u>	<u>3 (37.5)</u>	<u>4 (66.7)</u>	<u>2 (40.0)</u>
<u>Reported visual symptoms</u>	<u>52 (41.6)</u>	<u>52 (43.3)</u>	<u>14 (41.2)</u>	<u>25 (75.8)</u>	<u>1 (9.1)</u>	<u>6 (66.7)</u>	<u>5 (62.5)</u>	<u>2 (33.3)</u>	<u>3 (60.0)</u>
<u>Missing or unknown</u>	<u>5 (4.0)</u>	<u>1 (0.8)</u>	<u>1 (2.9)</u>	<u>=</u>	<u>=</u>	<u>=</u>	<u>=</u>	<u>=</u>	<u>=</u>

\* Data is presented as n (%), where n is the number of eyes and the percentage refers to the column total.

†Patients with MMP were statistically more likely to report visual symptomatology in the affected eyes (Fisher’s exact test; p = 0.002).

**Abbreviations:** AMD = age-related macular degeneration; CSC = central serous chorioretinopathy; ERM = epiretinal membrane; LMH = lamellar macular hole; MMAs = morphologic macular abnormalities; MMP = microcystoid macular pathology; PED = pigment epithelial detachment; VMT = vitreomacular traction.

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**Supplementary Table 4:** Frequency of the overall MMAs, and the four most common categories, in relation to age in patients with MS\*.

<u>OCT abnormality</u>	<u>Odds ratio per 5-year increase in age in all MS (95% CI)</u>	<u>p-value</u>	<u>Odds ratio per 5-year increase in age in RRMS (95% CI)</u>	<u>p-value</u>	<u>Odds ratio per 5-year increase in age in progressive MS† (95% CI)</u>	<u>p-value</u>	<u>RRMS vs progressive MS, p-value</u>
<u>MMAs overall</u>	<u>1.76 (1.43-2.18)</u>	<u>0.002</u>	<u>1.65 (1.34-2.04)</u>	<u>0.008</u>	<u>2.43 (0.85-6.97)</u>	<u>0.099</u>	<u>0.281</u>
<u>Drusen</u>	<u>-2.04 (-1.36-3.07)</u>	<u>0.001</u>	<u>-1.64 (-1.13-2.36)</u>	<u>0.009</u>	<u>-4.68 (-0.40-54.8)</u>	<u>0.219</u>	<u>0.243</u>
<u>ERM</u>	<u>-4.29 (-1.85-9.92)</u>	<u>0.001</u>	<u>-4.56 (-1.89-10.97)</u>	<u>0.001</u>	<u>-2.25 (-0.01-35.7)</u>	<u>0.229</u>	<u>0.796</u>
<u>PED</u>	<u>-1.15 (-0.86-1.53)</u>	<u>0.340</u>	<u>-1.17 (-0.86-1.59)</u>	<u>0.311</u>	<u>-1.86 (-0.31-11.3)</u>	<u>0.50</u>	<u>0.377</u>
<u>MMP</u>	<u>-0.89 (-0.72-1.11)</u>	<u>0.309</u>	<u>-0.85 (-0.67-1.08)</u>	<u>0.180</u>	<u>-0.78 (-0.40-1.53)</u>	<u>0.466</u>	<u>0.039</u>

\* All models utilized multilevel logistic regression to account for within-subject inter eye correlation and were adjusted for sex and race.

† This includes patients with primary and secondary progressive MS.

**Abbreviations:** CI = confidence interval; ERM = epiretinal membrane; MMAs = morphologic macular abnormalities; MMP = microcystoid macular pathology; MS = multiple sclerosis; OCT = optical coherence tomography; PED = pigment epithelial detachment; RRMS = relapsing-remitting multiple sclerosis.

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**Supplementary Table 25:** Age-matched prevalence estimates of ERM in this study (overall and in the multiple sclerosis subgroup) compared to population-based estimates obtained from the Visual Impairment project

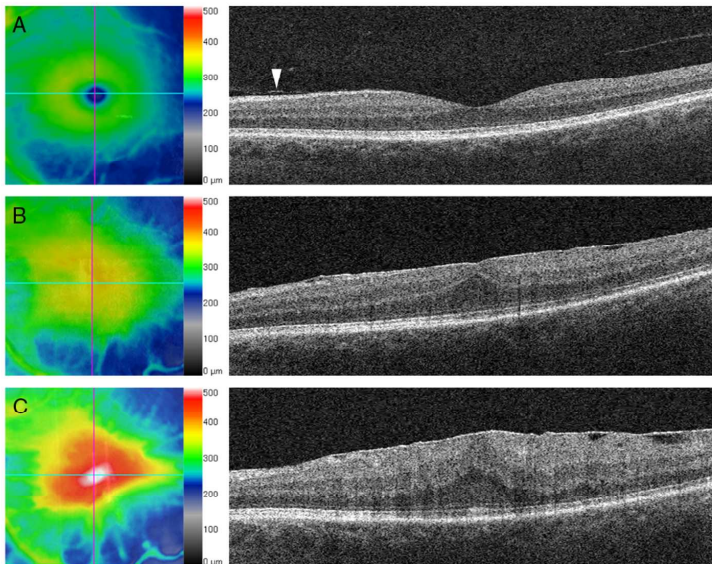
Age, yrs	ERM prevalence, % (No. at Risk; 95% CI) <sup>1</sup>		
	<i>Overall cohort</i>	<i>MS subgroup</i>	<i>Population-based estimates</i>
<b>&lt;40</b>	0.5 (556; 0.2-1.7)	0.3 (340; 0.04-2.1)	- (0)
<b>40-49</b>	4.5 (423; 2.9-6.9) *	4.9 (243; 2.8-8.5) *	0.5 (1176; 0.2-1.1)
<b>50-59</b>	6.3 (303; 4.0-9.6) *	6.1 (164; 3.3-11.0)	2.6 (1248; 1.8-3.6)
<b>60-69</b>	21.1 (142; 15.1-28.7) *	25.4 (63; 16.0-37.9) *	9.4 (1079; 7.7-11.3)
<b>70-79</b>	33.3 (18; 14.4-60.0)	33.3 (3; 0.1-99.7)	15.1 (637; 12.4-18.1)
<b>80+</b>	66.7 (3; 0.3-100.0)	- (0)	11.3 (173; 7.2-17.3)

<sup>1</sup> Population-based estimate data extracted from McCarty et al<sup>17</sup>.

\* Denotes a significantly higher prevalence rate compared to general population estimates.

**Abbreviations:** CI = confidence interval; ERM = epiretinal membrane; MS = multiple sclerosis.

**Supplementary Figure 1 title:** Progression of an epiretinal membrane (ERM) over a 4 year period



**Supplementary Figure 1 legend:** ILM-RPE thickness maps and corresponding OCT images of the left eye of a 60 year old female diagnosed with secondary progressive MS presenting to the clinic for routine follow-up. **Row A**, baseline imaging revealed a partially visualized, globally adherent ERM in the nasal hemi-macula (arrowhead). **Row B**, progression of the ERM over a 2 year interval with increased thickness, extension to the temporal hemi-macula, and signs of mild macular traction (flattening of foveal contour). Patient was referred to ophthalmology and offered ERM peeling and pars plana vitrectomy but elected to undergo careful observation instead. **Row C**, appearance of the ERM at the 4 year time point shows extensive macular traction, pucker, and increased central retinal thickness, a marker associated with poor outcomes in patients with ERM<sup>34</sup>. The patient's corrected Snellen visual acuity dropped from a premorbid level of 20/20 to 20/30 at 4 years of follow-up.

**Abbreviations:** ERM = epiretinal membrane; ILM = inner limiting membrane; MS = multiple sclerosis; OCT = optical coherence tomography; RPE = retinal pigment epithelium.