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Retinal vasculometric characteristics and their associations with polymyalgia rheumatica and giant cell arteritis in a prospective cohort: EPIC-Norfolk Eye Study

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Ethical approval information: The study was approved by the Norfolk Local Research Ethics Committee. Participants consented to the study and access to their records was granted. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

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Dear Editor

Both polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) have been associated with an increased future risk of cardiovascular disease (1). However, it remains uncertain whether this is a consequence of inflammatory disease or relates to a common underlying mechanism. Retinal vascular images are a sensitive measures of vascular health, which are emerging as important biomarkers of future cardiovascular risk with changes affecting arterioles and venules (2). In this study, we assess whether vasculometric features associated with CVD are detectable prior to the onset of PMR and GCA.

We analysed data from initially healthy subjects enrolled in the EPIC-Norfolk Study, a prospective population-based cohort which enrolled participants between the years 1993 to 1997 (3, 4). Digital photographs of the retinal fundus were taken of 8,112 participants between 2004 and 2011 using a TRC-NW6S non-mydriatic retinal camera and IMAGEnet Telemedicine System (Topcon Corporation, Tokyo, Japan) with a 10 megapixel Nikon D80 camera (Nikon Corporation, Tokyo, Japan). Retinal vessel widths were measured using the QUARTZ (QUantitative Analysis of Retinal vessel Topology and siZe) programme (5). The fully automated algorithm uses an ensemble classifier of bagged decision trees to allocate vessels into arterioles and venules at 80% probability and calculates summary measures for each participant with an averaged measure between right and left eyes.

Cases of PMR and GCA were identified by three methods: (i) free text questionnaire responses at enrolment, and thereafter, 18 months, 3, 10 and 13 years; (ii) linkage to hospital electronic discharge summaries containing ICD codes (iii) linkage to key word searches (*polymyalgia or rheumatica or giant or arteritis)* of out-patient clinic letters. To be identified as PMR or GCA, participants were required to have received at least two prescriptions for oral glucocorticoids within six months following their diagnosis. This approach follows classification methodology validated in the Clinical Practice Research Datalink (CPRD) (6). Cases were excluded from analysis if the diagnosis in the case record was refuted or changed within the first six months. Case assignment was carried out independently by two rheumatologists (MY, RW). Only incident cases with retinal images captured before their PMR or GCA diagnosis were included.

Amongst 5,532 participants who had retinal images analysable by QUARTZ, we identified 30 cases of incident PMR (median age at diagnosis: 74.8 years, range [60.5, 87.0]; mean ESR at diagnosis: 48 mm/hr; 70.0% female) and an additional 16 cases of GCA (median age at diagnosis: 75.0 years, range [62.1, 84.0]; mean ESR at diagnosis: 80 mm/hr; 81.3% female). Vasculometric measures of those subsequently developing PMR (Table1), showed wider venules compared to controls (5.5 microns increased width 95% CI 1.7 to 9.3, p=0.004), which remained significant after adjustment for age at time of retinal image capture, and sex (4.4 microns wider, 95% CI 0.7 to 8.2, p=0.021). Some who were diagnosed with disease did not meet the classification criteria. A stronger association was present when the analysis was limited to those cases which fulfilled current classification criteria sets. Although, on average those subsequently developing GCA had wider venules compared to controls (93 microns vs 91.1 microns) the difference failed to reach statistical difference. There was no association between arteriolar measures for either PMR or GCA.

Using a novel retinal marker in a longitudinal population-based setting, this analysis shows that participants who developed PMR already had wider retinal venules prior to the onset of their inflammatory disease. The data are limited by the relatively small number of cases with incident disease and need to be replicated in other settings. They nevertheless lend weight to the hypothesis that vascular changes precede the onset of PMR.

Table 1. Retinal vasculometric characteristics and their association to diagnoses of PMR and GCA

	Incident cases†	Incident cases meeting classification sets	Control n=5,477
PMR (n)	30	24	
Venular width (µm) and SD	96.6 SD 12.5	100.0 SD 11.3	91.1 SD 10.6 from 5,036 controls
Difference in venular width (µm) (95% CI) 80% probability*	5.5 (1.7, 9.3) p=0.005	8.9 (4.7, 13.2) p=<0.001	
Adjusted for age at time of retinal photograph capture and sex	4.4 (0.7, 8.2) p=0.021	7.8 (3.6, 12.0) p=<0.001	
Arteriolar width (µm) and SD	75.6 SD 7.6	76.9 SD 7.8	75.0 SD 6.3 from 5,037 controls
Difference in arteriolar width (µm) (95% CI) 80% probability*	0.7 (-1.6, 2.9) p=0.575	0.6 (-1.6, 2.9) p=0.57	
Adjusted for age at time of retinal photograph capture and sex	1.0 (-1.2, 3.3) p=0.366	1.1 (-1.1, 3.4) p=0.32	
GCA (n)	16	13	
Venular width (µm) and SD	93.0 SD 9.4	93.7 SD 10.3	91.1 SD 10.6 from 5,036 controls
Difference in venular width (µm) (95% CI) 80% probability*	1.9 (-3.3, 7.1) p=0.47	2.6 (-3.2, 8.4) p=0.38	
Adjusted for age at time of retinal photograph capture and sex	1.1 (-4.1, 6.2) p=0.68	1.5 (-4.2, 7.2) p=0.60	
Arteriolar width (µm) and SD	74.4 SD 5.9	73.8 SD 6.0	75.0 SD 6.3 from 5,037 controls
Differences in arteriolar width (µm) (95% CI) 80% probability*	-0.6 (-3.6, 2.5) p=0.73	-1.2 (-4.7, 2.2) p=0.48	
Adjusted for age at time of retinal photograph capture and sex	-0.03 (-3.1, 3.0) p=0.98	-0.7 (-4.1, 2.7) p=0.70	

SD – standard deviation. * probability of vascular segment type (arteriole or venule) weighted by segment length, 95% CI – 95% confidence interval †incident cases – median time period 2.9 years between retinal image capture and subsequent diagnosis with >75% having an interval of greater than 1 year.

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Ethical approval

The study complies with the Declaration of Helsinki. The Norwich District Health Authority Ethics Committee approved the study and all participants gave written informed consent.

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