

Background

Changes to the choroidal and retinal vasculature seen in the Alzheimer's Disease (AD) continuum are proposed as a non-invasive, cost-effective CNS proxy for clinical trials. However, these changes are not yet fully explored in individuals with Down Syndrome (DS), the largest genetically predisposed group for AD.

Methods

Optos ultra-widefield (UWF, Optos plc) and OCT-EDI (Heidelberg Engineering GmbH, Germany) was performed on 24 DS before the onset of clinical dementia and 17 cognitively healthy, age- and sex-matched Ctrl. We extracted various vascular parameters to evaluate group differences and their association with cognition using the VAMPIRE software, and series of ImageJ plugins (Creative Computing: Kenneth Sloan). Data wrangling, visualisation and analysis was carried out in R (4.3.2 (2023-10-31 ucrt)). The Cambridge Cognition Examination DS (CAMCOG-DS) was used to assess areas of cognition known to decline with the onset of dementia.

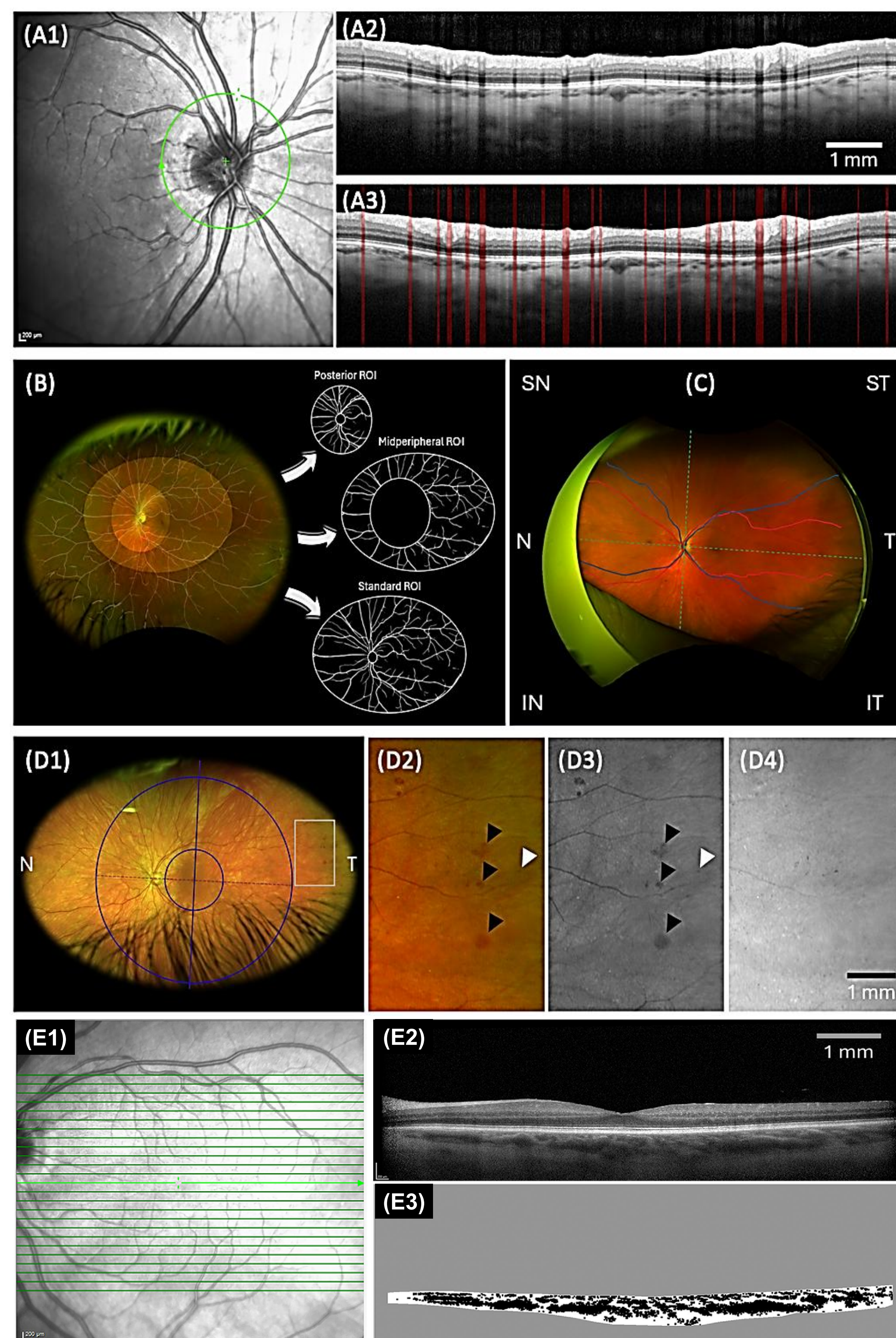


Figure 1. Number of vessels were counted around the optic disk on peripapillary scans (A) using the OCTSEG software (A3). Retinal vasculature was segmented on UWF images using the VAMPIRE software. Fractal dimension (FD) values (Fig1 B) were extracted for posterior pole and midperipheral retina and width gradient (WG) values (Fig1 C) for the entire image (globally) and for the temporal (T) and nasal (N) hemispheres. Vessel calibre values (width intercept) at the optic disk margin was derived from the WG measurements. Peripheral microvascular abnormalities, such as microaneurysms (white arrow) and haemorrhages (black arrow) were graded on UWF images (Fig1 D). OCT volume scans (Fig1 E1-2) were segmented to compute the choroidal vascularity index (CVI) (Fig1 E3), defined as the proportion of the choroidal area occupied by vascular lumens relative to the total choroidal area. CVI was extracted utilising a series of home built ImageJ plugins (Creative Computing: Kenneth Sloan) and values calculated for different sectors of the ETDRS grid.

Cohort characteristics

	N	DS (n=24)	Ctrl (n=17)	P-value
Age	41	39 (7)	36 (9)	.411†
Mean (SD)		27, 53	22, 51	
Range				
Sex	41	9 (37.5)	9 (52.9)	0.326*
Female, n (%)				
Level of ID	19	9 (47.4)	NA	NA
Mild, n (%)		10 (52.6)	NA	
Moderate, n (%)				
	N	DS		
		Mild ID (n=9)	Moderate ID (n=10)	
Age	19‡	37.4 (8.9)	39.5 (6.2)	0.539†
Mean (SD)		27, 53	29, 48	
Range				
CAMCOG-DS	19‡	88 (12)	73 (16)	0.030†
Mean (SD)		60, 100	44, 99	
Range				

Table 1. Continuous variables are presented as mean and range, and categorical variables as counts and percentages. P values were calculated using the Wilcoxon rank sum test for continuous and Pearson's Chi-squared test for categorical variables. Abbreviations: DS, Down syndrome; Ctrl, control; Level ID, Level of intellectual disability; CAMCOG-DS, Cambridge Cognition Examination DS.; SD, standard deviation; *Pearson's Chi-squared test; † Wilcoxon rank sum test; ‡ Three individuals with DS had no CAMCOG-DS available;

Supernumerary blood vessels at the optic disk

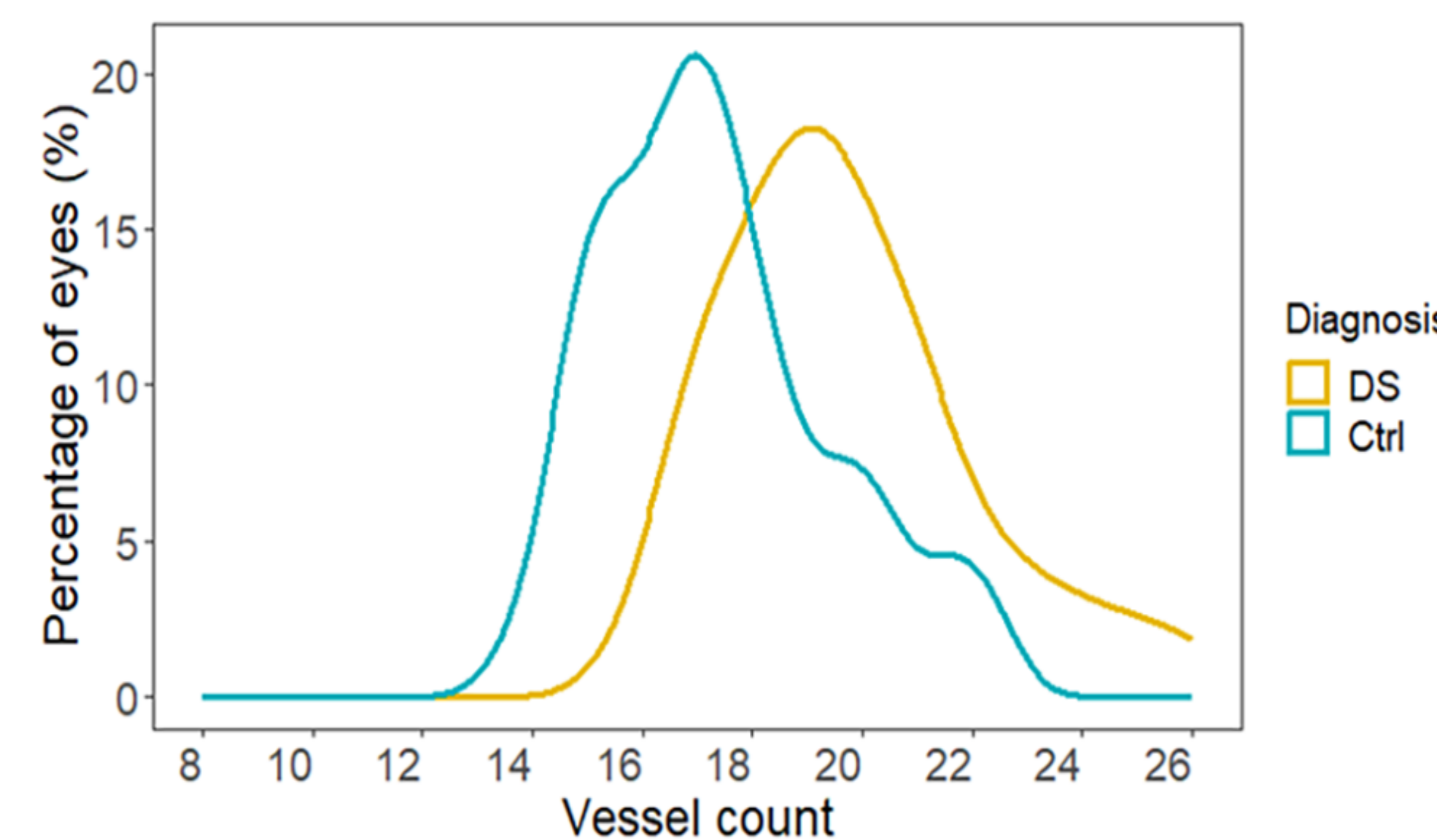


Figure 2. Supernumerary vessels associated to DS ($\beta = 2.53$, $P < 0.001$) counted on peripapillary OCT scans. Average vessel count in DS was 20 ± 2 , with controls only being 17 ± 2 .
Abbreviations: Ctrl, control participants; DS, participants with Down syndrome;

Central increase and peripheral decrease in retinal vessel complexity (fractal dimension)

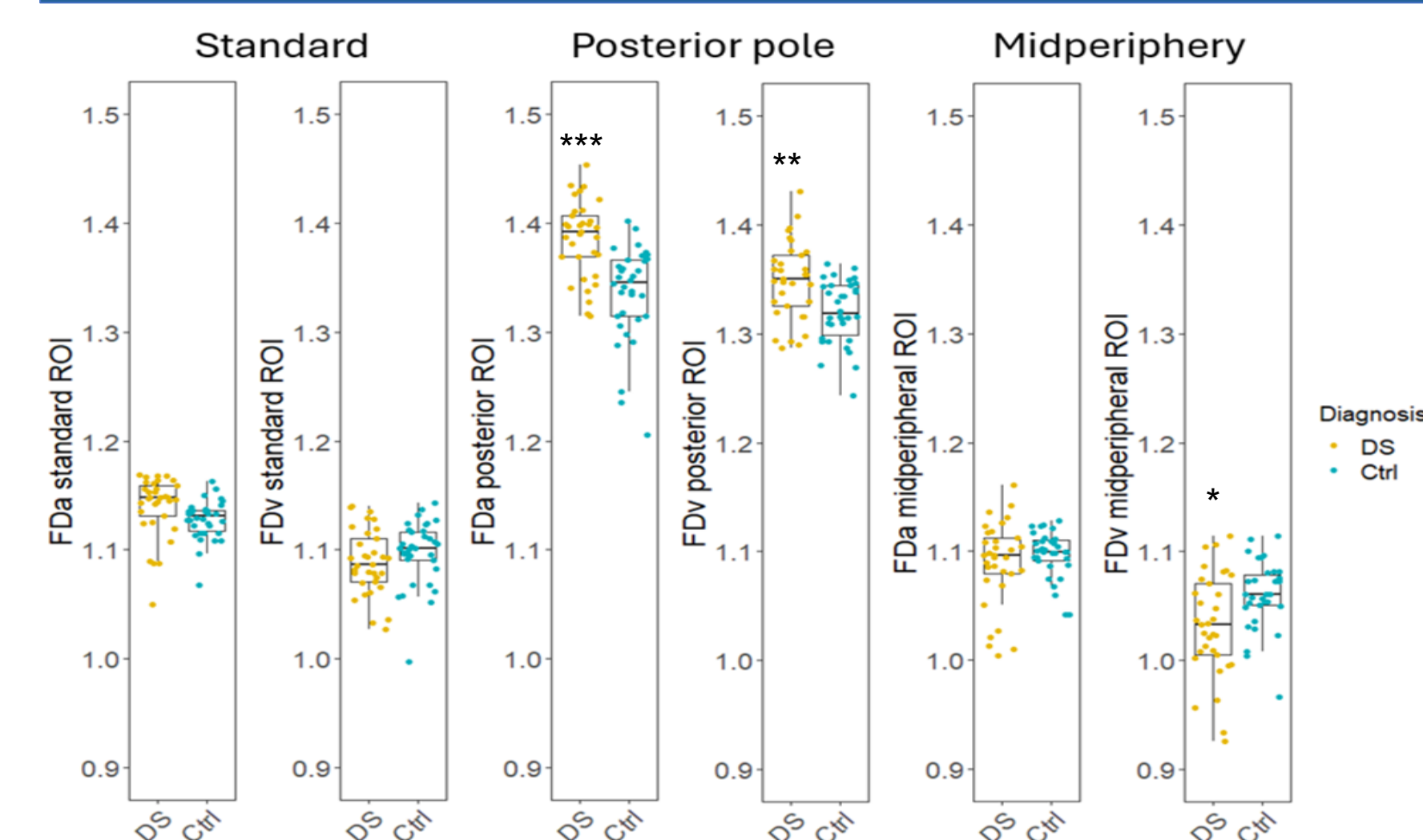


Figure 3. Boxplots with individual data points of fractal dimension for each available eyes. A higher fractal dimension (FD) was observed in the posterior pole (arterioles: $\beta=0.050$, $P<0.001$; venules: $\beta=0.027$, $P=0.01$), and a lower was noted in the midperiphery (venules: $\beta=-0.029$, $P=0.047$) in DS. **Abbreviations:** Ctrl, control; DS, Down syndrome; FDa, arterial fractal dimension; Fdv, venular fractal dimension; ROI, region of interest; ***, $P<0.001$; **, $P<0.01$; *, $P<0.05$

Retinal vascular attenuation (width gradient)

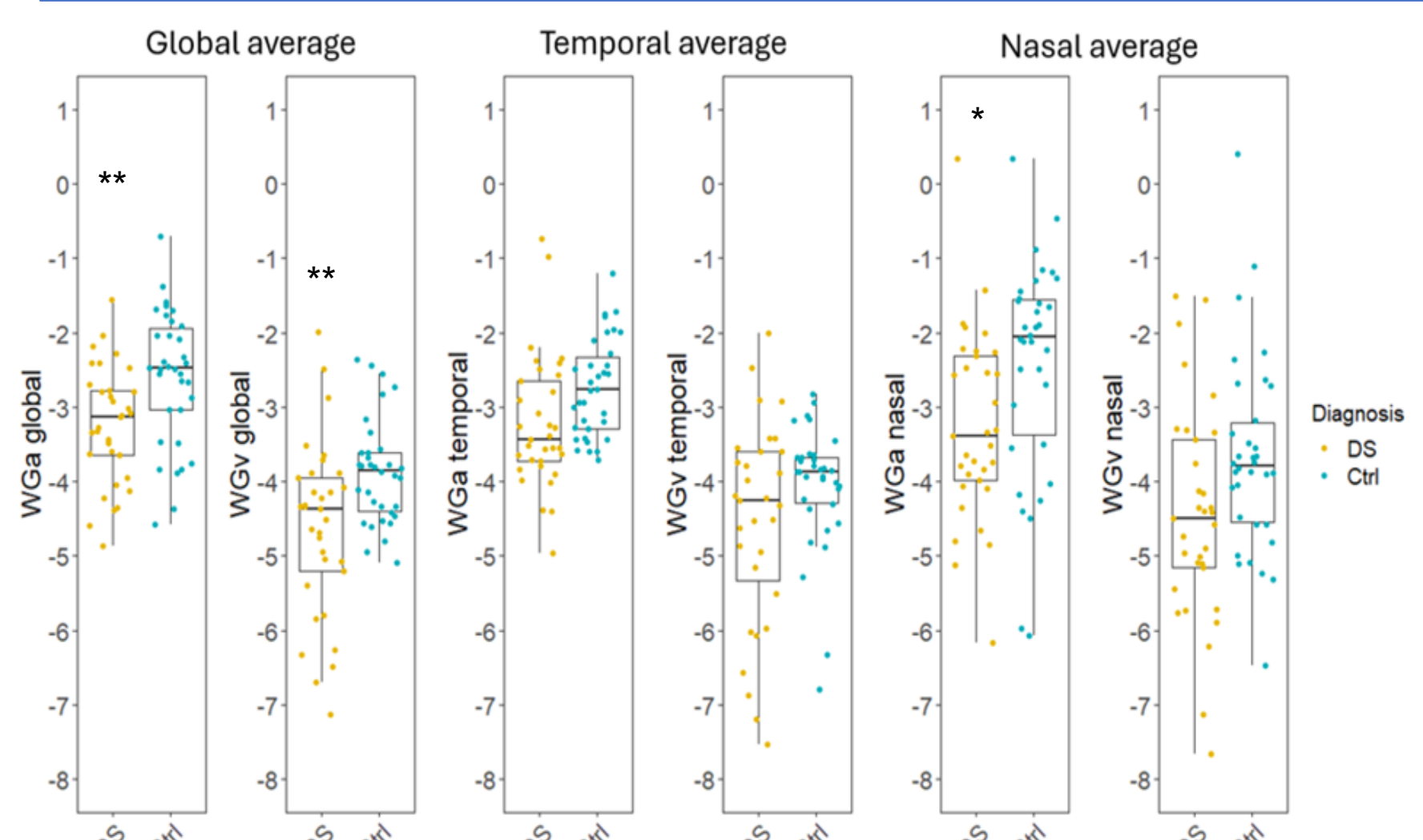


Figure 4. Boxplots with individual data points of width gradient values (micron/mm). Globally vessels thinned more rapidly along their paths in DS (arterioles: $\beta=-0.66$, $P=0.006$; venules: $\beta=-0.75$, $P<0.001$). A greater degree of thinning occurred nasally, specifically in the arterioles ($\beta=-0.86$, $P=0.030$). **Abbreviations:** Ctrl, control; DS, Down syndrome; WGa, arterial width gradient; Wgv, venular width gradient; ***, $P<0.001$; **, $P<0.01$; *, $P<0.05$

Increased retinal vessel calibre at the optic disk (width intercept)

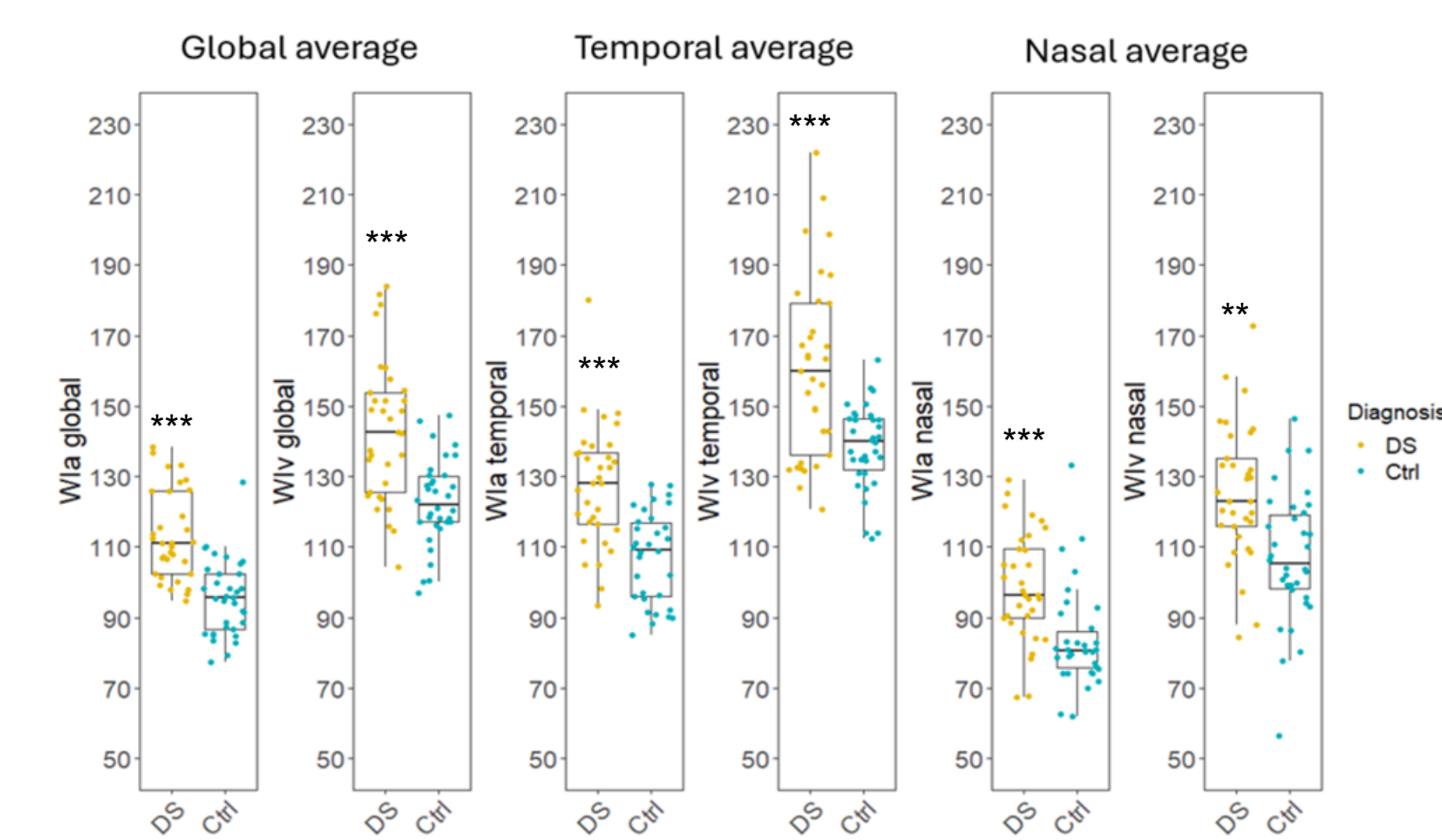


Figure 5. Boxplots with individual data points of vessel calibre (WI) values (micron) for each available eye. An increased vessel calibre was associated to DS regardless the area assessed (arterioles: $\beta: 15.3 - 18.3$; venules: $\beta: 17.6 - 20.5$; $P<0.01$) indicating thicker vessels at the optic disk margin.
Abbreviations: Ctrl, control; DS, Down syndrome; Wla, arterial width intercept; Wlv, venular width intercept; ***, $P<0.001$; **, $P<0.01$; *, $P<0.05$

Higher prevalence of microvascular abnormalities

UWF imaging	DS (n=33)	Ctrl (n=34)	GEE		
	n (%)*		OR	95% CI	P-value†
Microvascular abnormality (YES)	12 (36.4)	3 (8.8)	8.332	1.570, 44.21	0.038
Microaneurysm (YES)	7 (21.2)	2 (5.9)	5.231	0.993, 27.55	0.153
Haemorrhage (YES)	5 (15.2)	1 (2.9)	8.455	0.880, 81.26	0.191

Abbreviations: Ctrl, control; DS, Down syndrome; GEE, generalised estimating equation; CI, confidence intervals

Figure 6. Shows the number of individuals in each cohort presenting with peripheral microvascular abnormalities. Higher odds of having microvascular abnormalities was predicted in the DS group compared to Ctrl.

Choroidal vascularity

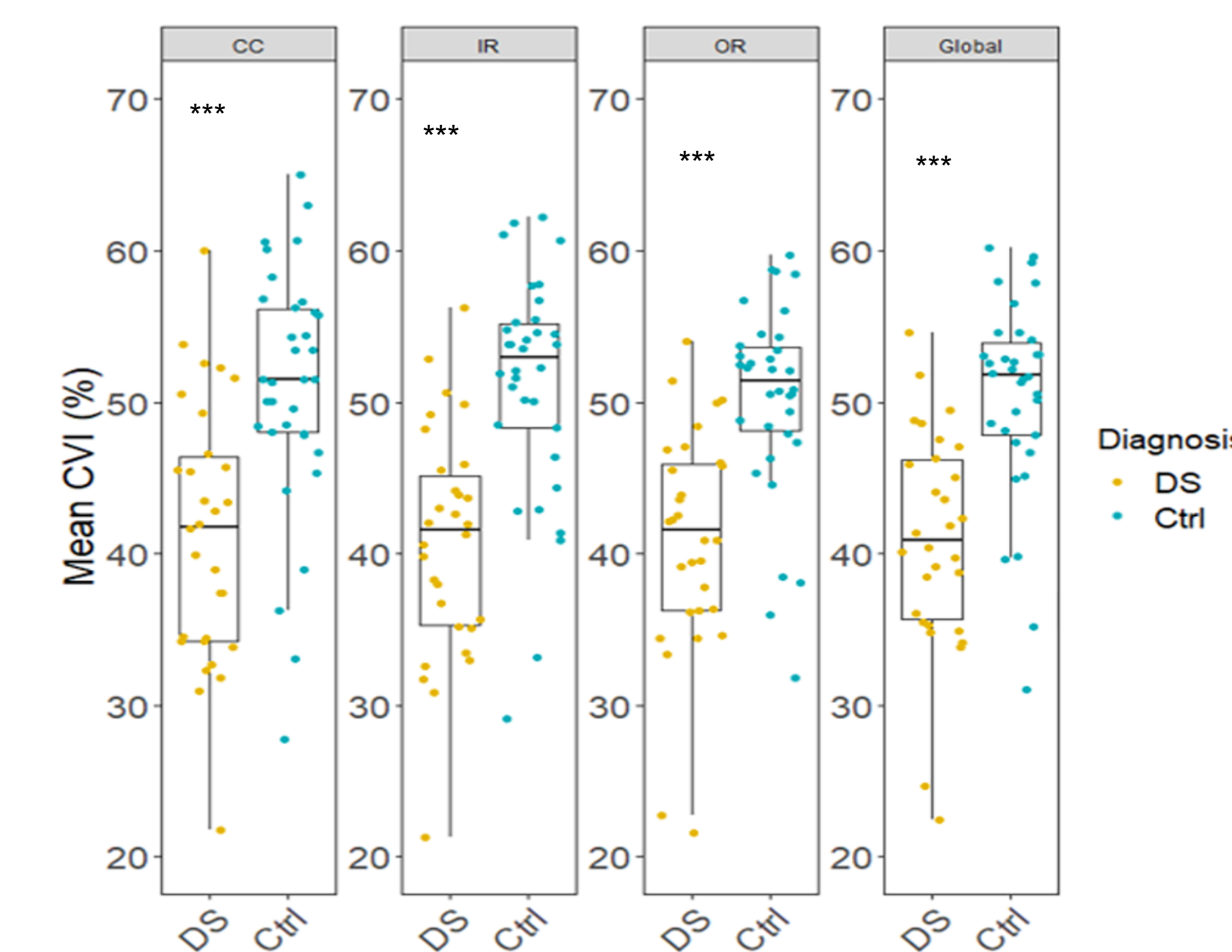


Figure 7. Showing boxplots with individual data points of choroidal vascularity index (CVI) for each available eye. A lower CVI associated to DS across all sectors of the ETDRS grid ($\beta: -9.66 - -8.65$; $P<0.001$).

There was also a positive correlation observed between CAMCOG-DS and CVI in the nasal quadrants of the ETDRS grid (nasal inner: $r=0.480$, $P=0.015$; nasal outer: $r=0.557$, $P=0.004$) (data not presented as figures).

Abbreviations: Ctrl, control; DS, Down syndrome; CC, central circle; inner ring, outer ring; ***, $P<0.001$; **, $P<0.01$; *, $P<0.05$

Conclusion

We found that retinal and choroidal vascular changes are present in DS adults before the clinical onset of AD and might become early surrogates for cerebral vascular abnormalities.