

4 April 2022

## FEATURED ARTICLE

### Associations Between the Macular Microvasculatures and Subclinical Atherosclerosis in Patients With Type 2 Diabetes: An Optical Coherence Tomography Angiography Study.

Frontiers in Medicine (Lausanne). 2022 Mar 4. eCollection 2022.  
Yoon J, Kang HJ, Lee JY, Kim JG, Yoon YH, Jung CH, Kim YJ.

**Objective:** To investigate the associations between the macular microvasculature assessed by optical coherence tomography angiography (OCTA) and subclinical atherosclerosis in patients with type 2 diabetes.

**Methods:** We included patients with type 2 diabetes who received comprehensive medical and ophthalmic evaluations, such as carotid ultrasonography and OCTA at a hospital-based diabetic clinic in a consecutive manner. Among them, 254 eyes with neither diabetic macular edema (DME) nor history of ophthalmic treatment from 254 patients were included. The presence of increased carotid intima-media thickness (IMT) ( $>1.0$  mm) or carotid plaque was defined as subclinical atherosclerosis. OCTA characteristics focused on foveal avascular zone (FAZ) related parameters and parafoveal vessel density (VD) were compared in terms of subclinical atherosclerosis, and risk factors for subclinical atherosclerosis were identified using a multivariate logistic regression analysis.

**Results:** Subclinical atherosclerosis was observed in 148 patients (58.3%). The subclinical atherosclerosis group were older ( $p < 0.001$ ), had a greater portion of patients who were men ( $p = 0.001$ ) and who had hypertension ( $p = 0.042$ ), had longer diabetes duration ( $p = 0.014$ ), and lower VD around FAZ ( $p = 0.010$ ), and parafoveal VD (all  $p < 0.05$ ). In the multivariate logistic regression analysis, older age ( $p \leq 0.001$ ), male sex ( $p \leq 0.001$ ), lower VD around FAZ ( $p = 0.043$ ), lower parafoveal VD of both superficial capillary plexus (SCP) ( $p = 0.011$ ), and deep capillary plexus (DCP) ( $p = 0.046$ ) were significant factors for subclinical atherosclerosis.

**Conclusion:** The decrease in VD around FAZ, and the VD loss in parafoveal area of both SCP and DCP were significantly associated with subclinical atherosclerosis in patients with type 2 diabetes, suggesting that common pathogenic mechanisms might predispose to diabetic micro- and macrovascular complications.

DOI: [10.3389/fmed.2022.843176](https://doi.org/10.3389/fmed.2022.843176)

# GENETICS

## Heritability of retinal drusen in the Copenhagen Twin Cohort Eye Study.

Acta Ophthalmology. 2022 Mar 24. Online ahead of print.

Belmouhand M, Rothenbuehler SP, Hjelmberg JB, Dabbah S, Bjerager J, Sander BA, Dalgård C, Larsen M.

**Purpose:** To study age- and sex-adjusted heritability of small hard drusen and early age-related macular degeneration (AMD) in a population-based twin cohort.

**Methods:** This was a single-centre, cross-sectional, classical twin study with ophthalmic examination including refraction, biometry, best-corrected visual acuity assessment, colour and autofluorescence fundus photography, and fundus optical coherence tomography. Grading and categorization of drusen was by diameter and location.

**Results:** The study enrolled 176 same-sex pairs of twins of mean (SD) age 58.6 (9.9) years. The prevalence of the four phenotypes  $\geq 20$  small hard macular drusen (largest diameter  $< 63 \mu\text{m}$ ),  $\geq 20$  small hard extramacular drusen, intermediate drusen ( $63\text{--}125 \mu\text{m}$ ) anywhere, and large drusen ( $> 125 \mu\text{m}$ ) anywhere was 12.4%, 36.4%, 5.8%, and 8.4%, respectively, and the respective heritabilities, adjusted for age and sex, were 78.2% [73.5–82.9], 69.1% [62.3–75.9], 30.1% [4.1–56.1], and 65.6% [26.4–100]. Age trajectory analysis supported a gradual transition to larger numbers of small hard drusen with increasing age. The heritability of  $\geq 20$  small hard drusen was markedly lower than the 99% found in the 40% overlapping twin cohort that was seen 20 years earlier.

**Conclusion:** Numerous ( $\geq 20$ ) small hard drusen and larger drusen that fit the definition of dry AMD were highly heritable. Small hard drusen counts increased with age. Decreasing heritability with increasing age suggests that the impact of behavioural and environmental factors on the development of small hard drusen increases with age.

DOI: [10.1111/aos.15136](https://doi.org/10.1111/aos.15136)

## The Natural History of Leber Congenital Amaurosis and Cone-Rod Dystrophy Associated with Variants in the GUCY2D Gene.

Ophthalmology Retina. 2022 Mar 18. Online ahead of print.

Hahn LC, Georgiou M, Almushattat H, van Schooneveld MJ, de Carvalho ER, Wesseling NL, Ten Brink JB, Florijn RJ, Lissenberg-Witte BI, Strubbe I, van Cauwenbergh C, de Zaeytijd J, Walraedt S, de Baere E, Mukherjee R, McKibbin M, Meester-Smoor MA, Thiadens AAHJ, Al-Khuzaei S, Akyol E, Lotery AJ, van Genderen MM, Norel JO, Ingeborgh van den Born L, Hoyng CB, Klaver CCW, Downes SM, Bergen AA, Leroy BP, Michaelides M, Boon CJF.

**Objective:** To describe the spectrum of Leber congenital amaurosis (LCA) and cone-rod dystrophy (CORD) associated with the GUCY2D gene, and to identify potential clinical endpoints and optimal patient selection for future therapeutic trials. DESIGN: International multicenter retrospective cohort study.

**Subjects:** 82 patients with GUCY2D-associated CORD and LCA from 54 molecularly confirmed families.

**Methods:** Data were gathered by reviewing medical records for medical history, symptoms, best-corrected visual acuity (BCVA), ophthalmoscopy, visual fields, full-field electroretinography and retinal imaging (fundus photography, spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence).

**Main Outcomes Measures:** Age of onset, annual decline of visual acuity, estimated visual impairment per age, genotype-phenotype correlations, anatomic characteristics on funduscopy, and multimodal imaging.

**Results:** Fourteen patients with autosomal recessive LCA and 68 with autosomal dominant CORD were included. The median follow-up time was 5.2 years (interquartile range (IQR), 2.6–8.8) for LCA, and 7.2 years (IQR, 2.2–14.2) for CORD. Generally, LCA presented in the first year of life. The BCVA in LCA ranged from no light perception to 1.00 logMAR, and remained relatively stable during follow-up. Imaging for LCA was limited, but showed little to no structural degeneration. In CORD, progressive vision loss started around the second

decade of life. The annual decline rate of visual acuity was 0.022 logMAR ( $P < 0.001$ ), which did not differ between the c.2513G>A and the c.2512C>T GUCY2D variant ( $P = 0.798$ ). At the age of 40 years the probability of being blind or severely visually impaired was 32%. The integrity of the ellipsoid zone (EZ) and external limiting membrane (ELM) on SD-OCT were correlated significantly with BCVA (Spearman's  $\rho = 0.744$ ,  $P = 0.001$  and  $\rho = 0.712$ ,  $P < 0.001$ , respectively) in CORD.

**Conclusion:** LCA due to variants in GUCY2D results in severe congenital visual impairment with relatively intact macular anatomy on funduscopy and available imaging, suggesting a long preservation of photoreceptors. Despite large variability, GUCY2D-associated CORD generally presented during adolescence with a progressive loss of vision and culminated in severe visual impairment during mid to late-adulthood. The integrity of the ELM and EZ may be suitable structural endpoints for therapeutic studies in GUCY2D-associated CORD.

DOI: [10.1016/j.oret.2022.03.008](https://doi.org/10.1016/j.oret.2022.03.008)

## CASE REPORT

### **Bilateral neovascular age-related macular degeneration: unilateral regression following endophthalmitis with persistent activity in the fellow eye.**

BMJ Case Reports. 2022 Mar 24.

Gaur S, Singh DV, Reddy RR, Sharma A.

A woman in her 70s who was being followed up for neovascular age-related macular degeneration (nAMD) in both eyes for 2 years with recalcitrant choroidal neovascularisation (CNV) and had an episode of acute endophthalmitis in one eye was identified. After treatment of postinjection culture-negative right eye (RE) endophthalmitis with intravitreal vancomycin and tazobactam, the patient had complete regression of treatment-resistant CNV in RE to date with postinfection follow-up of 2 years. In contrast, the fellow eye continued showing activity in the choroidal neovascular membrane that required antivasculature endothelial growth factor injections on a pro re nata basis to date. Prolonged regression of nAMD for 3 years in the affected eye and continued activity in the fellow eye support the hypothesis that inflammation accompanying endophthalmitis or the drugs used for the treatment can have a role in the regression of nAMD.

DOI: [10.1136/bcr-2021-244771](https://doi.org/10.1136/bcr-2021-244771)

## NUTRITION AND LIFESTYLE

### **Dietary Patterns and Their Associations with Intermediate Age-Related Macular Degeneration in a Japanese Population.**

Journal of Clinical Medicine. 2022 Mar 15

Sasaki M, Miyagawa N, Harada S, Tsubota K, Takebayashi T, Nishiwaki Y, Kawasaki R.

This population-based cross-sectional study investigated the influence of dietary patterns on age-related macular degeneration (AMD) in a Japanese population. The Tsuruoka Metabolomics Cohort Study enrolled a general population aged 35-74 years from among participants in annual health check-up programs in Tsuruoka City, Japan. Eating habits were assessed using a food frequency questionnaire. Principal component analysis was used to identify dietary patterns among food items. The association between quartiles of scores for each dietary pattern and intermediate AMD was assessed using multivariate logistic regression models. Of 3433 participants, 415 had intermediate AMD. We identified four principal components comprising the Vegetable-rich pattern, Varied staple food pattern,

Animal-rich pattern, and Seafood-rich pattern. After adjusting for potential confounders, higher Varied staple food diet scores were associated with a lower prevalence of intermediate AMD (fourth vs. first quartile) (OR, 0.63; 95% confidence interval [CI], 0.46-0.86). A significant trend of decreasing ORs for intermediate AMD associated with increasing Varied staple food diet scores was noted ( $p$  for trend = 0.002). There was no significant association between the other dietary patterns and intermediate AMD. In a Japanese population, individuals with a dietary pattern score high in the Varied staple food pattern had a lower prevalence of intermediate AMD.

DOI: [10.3390/jcm11061617](https://doi.org/10.3390/jcm11061617)

## **Low Light Exposure and Physical Activity in Older Adults With and Without Age-Related Macular Degeneration.**

Translational Vision Science Technology. 2022 Mar 2  
Dev MK, Black AA, Cuda D, Wood JM.

**PURPOSE:** To investigate the extent of low light exposure and associated physical activity in older adults with and without age-related macular degeneration (AMD). **METHODS:** Light exposure (lux) and physical activity (counts per minute, CPM) were measured in 28 older adults (14 bilateral AMD and 14 normally sighted controls) using a wrist-worn actigraphy device (Actiwatch) for 7 days and nights. Exposure to low light levels ( $\leq 10$  lux) and physical activity during waking hours were determined, as well as number of brief active periods during sleeping hours (e.g., going to the bathroom). Assessments included visual acuity and the Low Luminance Questionnaire (LLQ). **RESULTS:** No significant differences were found in low light exposure ( $39 \pm 14\%$  vs.  $34 \pm 10\%$ ) or physical activity ( $200 \pm 82$  CPM vs.  $226 \pm 55$  CPM) during waking hours between the AMD and control group. However, the AMD group had more brief active periods during sleeping hours than controls ( $1.8 \pm 1.3$  vs.  $1.1 \pm 0.4$ ;  $P = 0.007$ ). Reduced physical activity under low light levels was significantly associated with lower LLQ scores ( $P = 0.012$ ). **CONCLUSIONS:** Exposure to low light levels and associated physical activity were similar in older adults with and without AMD. This has important implications for older adults with AMD, given the impact of low light levels on visual function and mobility, suggesting the need for including lighting advice in rehabilitation programs for this population. **TRANSLATIONAL RELEVANCE:** Older adults with and without AMD spend over a third of waking hours under low light levels, which are an environmental falls hazard. Findings suggest the need for interventions to improve lighting levels for older adults.

DOI: [10.1167/tvst.11.3.21](https://doi.org/10.1167/tvst.11.3.21)

## **EPIDEMIOLOGY**

### **Incidence, risk factors and outcomes of submacular haemorrhage with loss of vision in neovascular age-related macular degeneration in daily clinical practice: data from the FRB! registry.**

Acta Ophthalmology. 2022 Mar 23. Online ahead of print.

Gabrielle PH, Maitrias S, Nguyen V, Arnold JJ, Squirrell D, Arnould L, Sanchez-Monroy J, Viola F, O'Toole L, Barthelmes D, Creuzot-Garcher C, Gillies M; Fight Retinal Blindness! Study Group.

**PURPOSE:** The main purpose of the study was to report the estimated incidence, cumulative rate, risk factors and outcomes of submacular haemorrhage (SMH) with loss of vision in neovascular age-related macular degeneration (nAMD) receiving intravitreal injections (IVT) of vascular endothelial growth factor (VEGF) inhibitor in routine clinical practice. **METHODS:** Retrospective analysis of treatment-naïve eyes receiving IVTs of VEGF inhibitors (ranibizumab, aflibercept or bevacizumab) for nAMD from 1 January 2010 to 31 December 2020 that were tracked the Fight Retinal Blindness! registry. Estimated

incidence, cumulative rate and hazard ratios (HR) of SMH with loss of vision during treatment were measured using the Poisson regression, Kaplan-Meier survival curves and Cox proportional hazard models. RESULTS: We identified 7642 eyes (6425 patients) with a total of 135 095 IVT over a 10-year period. One hundred five eyes developed SMH with loss of vision with a rate of 1 per 1283 injections (0.08% 95% confidence interval [95% CI] [0.06; 0.09]). The estimated incidence [95% CI] was 4.6 [3.8; 5.7] SMH with loss of vision per year per 1000 treated patients during the study. The cumulative [95% CI] rate of SMH per patient did not increase significantly with each successive injection ( $p = 0.947$ ). SMH cases had a mean VA drop of around 6 lines at diagnosis, which then improved moderately to a 4-line loss at 1 year. CONCLUSIONS: Submacular haemorrhage (SMH) with loss of vision is an uncommon complication that can occur at any time in eyes treated for nAMD in routine clinical practice, with only limited recovery of vision 1 year later.

DOI: [10.1111/aos.15137](https://doi.org/10.1111/aos.15137)

## Characterization of poor visual outcomes of diabetic macular edema: the Fight Retinal Blindness! Project.

Ophthalmology Retina. 2022 Mar 17. Online ahead of print.

Shah J, Nguyen V, Hunt A, Mehta H, Romero-Núñez B, Zarranz-Ventura J, Viola F, Bougamha W, Barnes R, Barthelmes D, Gillies MC, Fraser-Bell S.

**Purpose:** To investigate the incidence, characteristics and baseline predictors of poor visual outcomes in eyes with diabetic macular edema (DME) receiving intravitreal therapy in routine clinical practice. **DESIGN:** Observational study.

**Participants:** Treatment-naïve eyes starting intravitreal therapy for DME between 2014 and 2018 tracked in the Fight Retinal Blindness! registry. We examined two groups with poor visual outcomes: 1) Those with sustained vision loss of >10 letters from baseline without recovery of visual acuity (VA) or 2) Those with VA<55 letters at 2 years. Respective controls were eyes that did not experience poor visual outcomes.

**Methods:** Kaplan-Meier curves analyzed proportion of eyes that experienced poor outcomes. Cox proportional hazards models evaluated potential baseline predictors of poor outcomes. **MAIN OUTCOME MEASURES:** The proportion of eyes that experienced poor visual outcomes within 2 years of treatment initiation and its baseline predictors.

**Results:** The proportion of eyes with sustained VA>10 letter loss was 14% at 2 years while 16% of eyes had VA< 55 letters 2 years after starting intravitreal therapy. Initial treatment with intravitreal corticosteroid was independently associated with higher incidence of >10 letter loss was (Hazard ratio [HR], 3.21; 95% confidence interval [CI], 1.60-6.44; P< 0.01). No improvement in VA 3 months after starting treatment was associated with >10 letter loss (HR, 6.81; 95% CI, 4.11-11.27; P<0.01) and VA<55 letters at 2 years (HR, 4.28; 95% CI, 2.66- 6.89; P<0.01). The other factors related to higher risk of VA<55 letters were older age (HR, 1.02 per year; 95% CI, 1-1.04; P = 0.04) and poor baseline VA (HR, 0.68 per 5 letters; 95% CI, 0.65- 0.72, P<0.001).

**Conclusion:** Fourteen percent of eyes managed with intravitreal therapy in routine clinical care experienced >10 letter loss and 16% had VA<55 letters 2 years after starting treatment for DME. Identification of the incidence and predictors of poor outcomes provides more accurate assessment of the potential benefit from intravitreal therapy.

DOI: [10.1016/j.oret.2022.03.007](https://doi.org/10.1016/j.oret.2022.03.007)

## REVIEW

### Long term retinal morphology and functional associations in treated neovascular age-related macular degeneration: findings from the IVAN trial.

Ophthalmology Retina. 2022 Mar 18. Online ahead of print.

Peto T, Evans RN, Reeves BC, Harding S, Madhusudhan S, Lotery A, Downes S, Balaskas K, Bailey CC, Foss A, Ghanchi F, Yang Y, Phillips D, Rogers CA, Muldrew A, Hamill B, Chakravarthy U.

**Objective/Purpose:** To describe the frequency of long-term morphological features and their relationships with visual function in participants who exited the inhibition of VEGF in age-related choroidal neovascularization (IVAN: ISRCTN92166560) trial.

**Design:** Multicenter cohort study up to 7 years after enrolment.

**Participants:** Patients enrolled in IVAN excluding participants who died or withdrew during the trial. **Methods:** Multimodal fundus images, best corrected (BCVA) and low luminance visual acuity (LLVA) were obtained in a subset of 199 participants who attended a research visit. Clinical sites (n=20) also provided all visual acuity and clinical information from usual care records for 532 participants and submitted most recent color, OCT and other fundus images for 468 participants to a reading center. **Main Outcome Measures:** Assessed from most recent images: intraretinal macular atrophy (ILMA) within the footprint of the neovascular lesion; hyperreflective material (HRM); intraretinal fluid (IRF); subretinal fluid



(SRF); pigment epithelial detachment (PED); disorganization of outer retinal layers (DROL). Cross sectional relationships between morphological features and BCVA/LLVA were estimated.

**Results:** ILMA was present in 31.8% of study eyes at IVAN exit (mean follow-up 1.96 years) and 89.5% at the most recent imaging visit (6.18 years). HRM, IRF, SRF, PED and DROL were present in 78.8%, 47.7%, 7.6%, 94.5% and 55% respectively. In the subset with complete imaging data, in eyes without DROL, BCVA was worst in the thinnest outer fovea tertile (thinnest minus middle and thickest tertiles, -19.7 and -19.5 letters respectively) whereas in eyes with DROL, BCVA was worst in the thickest (thinnest and middle tertiles minus thickest, 12.5 and 12.2 respectively). Regression models showed that presence of ILMA and HRM were independently associated with BCVA (22 letters worse (95% CI 11.2, 32.8,  $p<0.001$ ) and 9.8 letters worse (95% CI 0.1, 19.4,  $p=0.047$ ), respectively). SRF and foveal PED were associated with better BCVA (5.9 letters, 95% CI -7.9, 19.7,  $p<0.399$ ; and 6.4 letters, 95% CI -1.1, 14.0,  $p=0.094$  respectively). The model with LLVA was similar. Sensitivity analysis including the entire eligible cohort yielded similar estimates.

**Conclusions:** Macular atrophy and HRM were common after 7 years of follow-up and strongly associated with visual outcomes.

DOI: [10.1016/j.oret.2022.03.010](https://doi.org/10.1016/j.oret.2022.03.010)