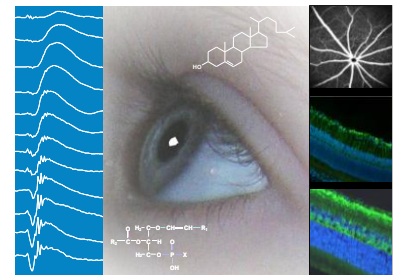


Nutrition and prevention of aging and pathology of the retina

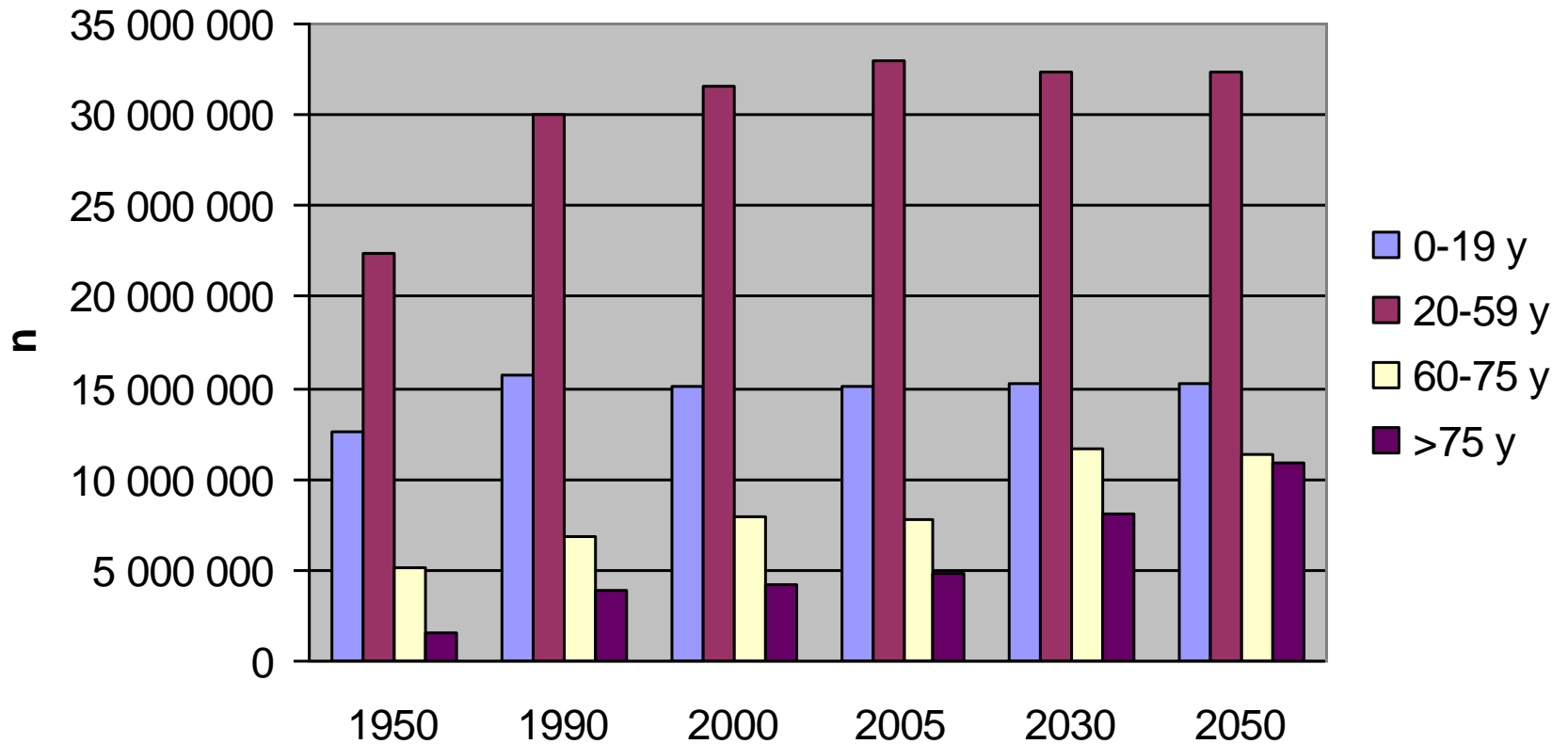
From concept to clinical application

Lionel Bretillon



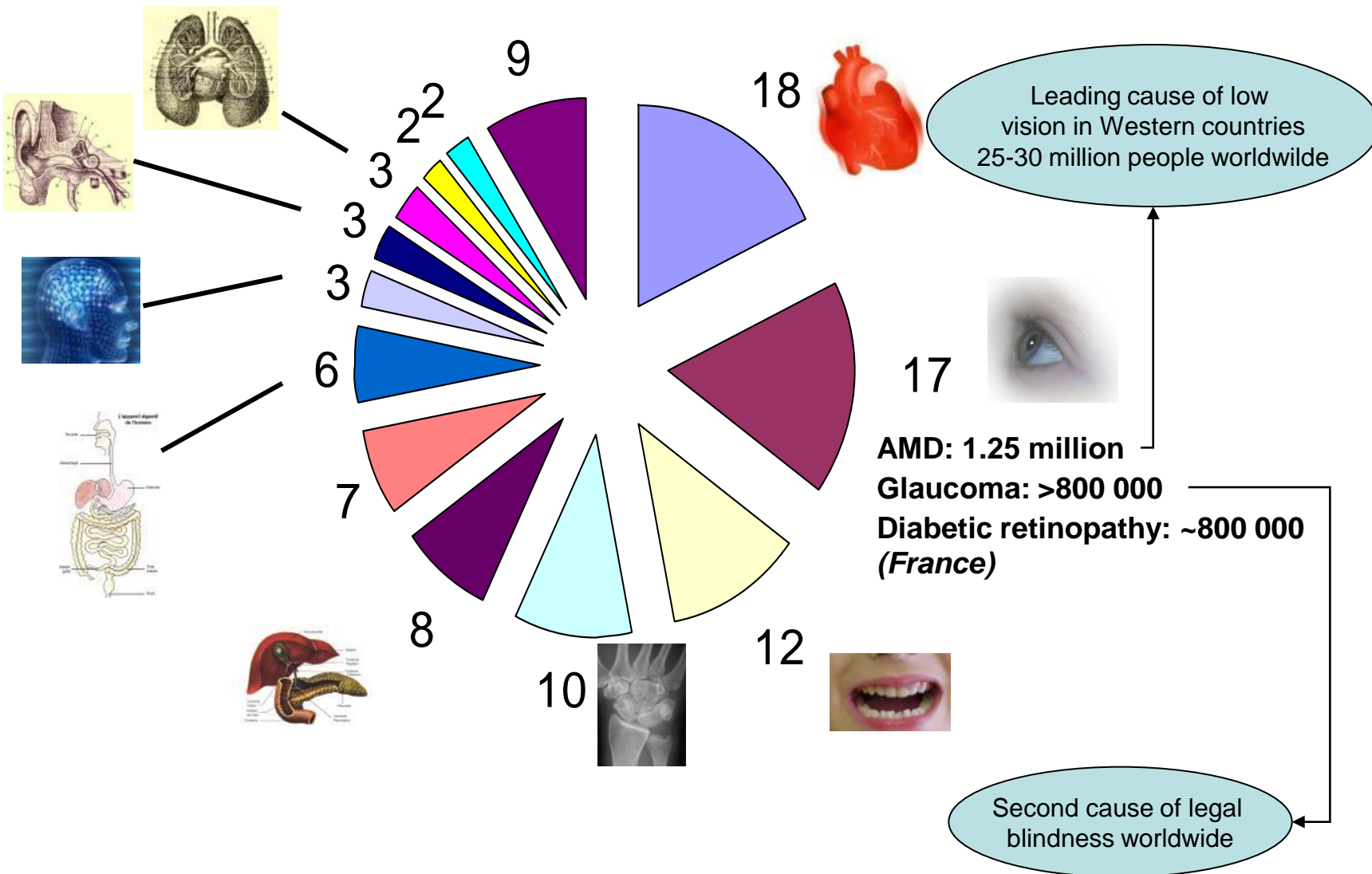
Eye & Nutrition Research Group
Dijon, FRANCE

Demographic data in France

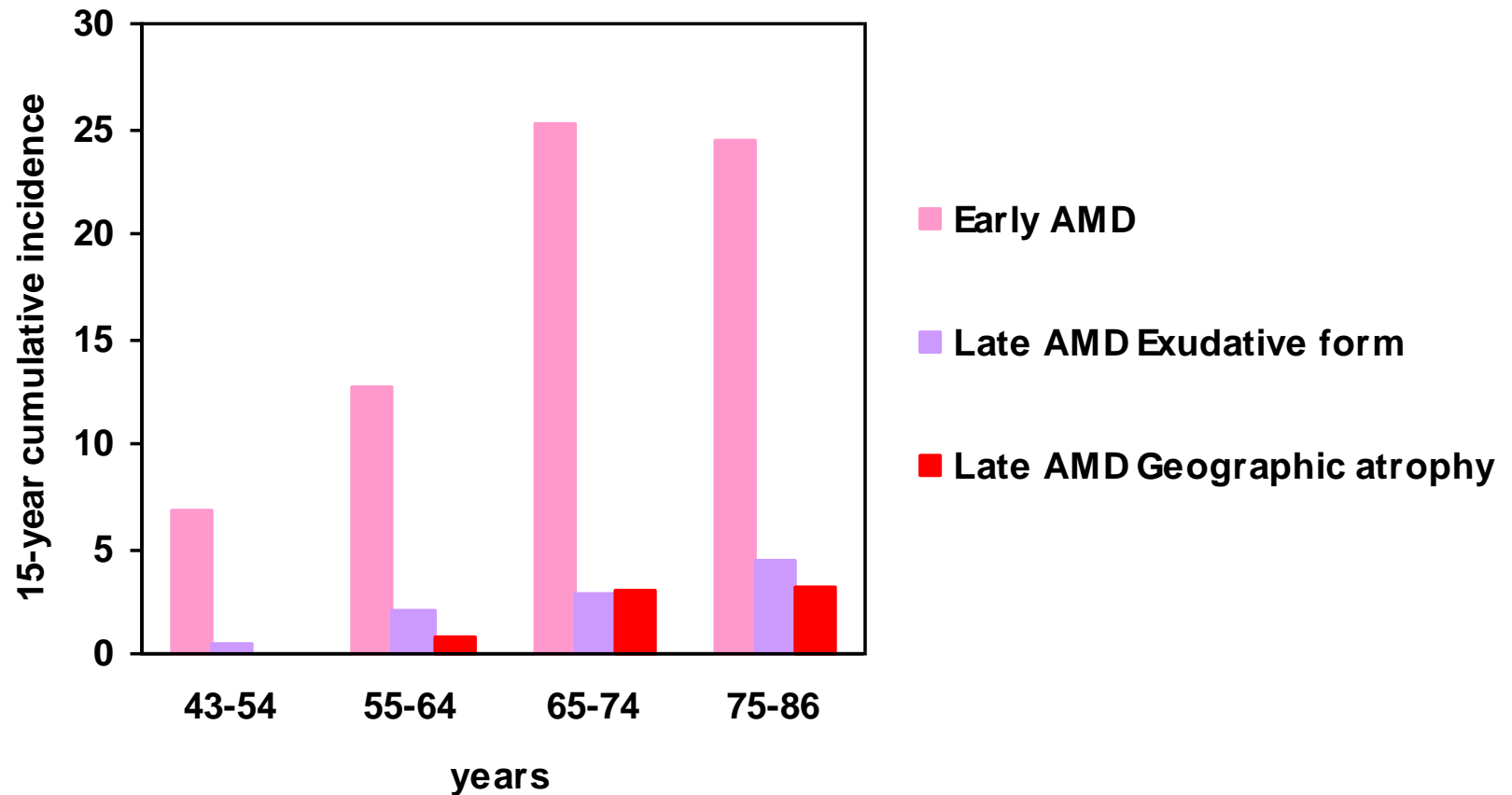


Population 2050 vs 2000 >60y: x2
>75y: x3
>85y: x5

Prevalence of pathologies after 65 years of age

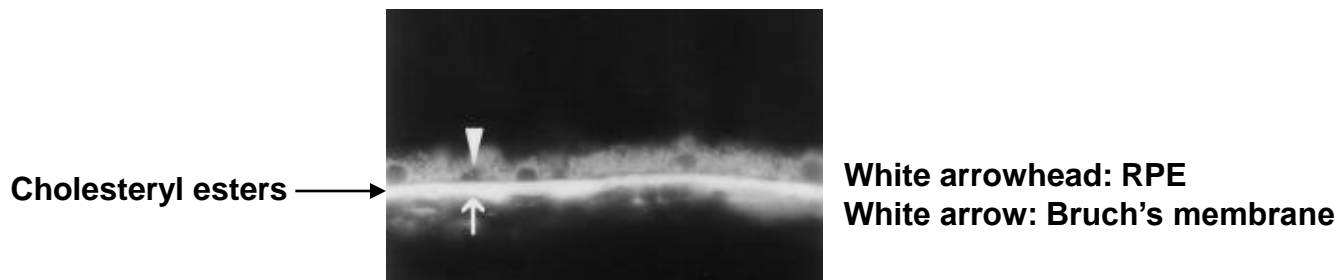
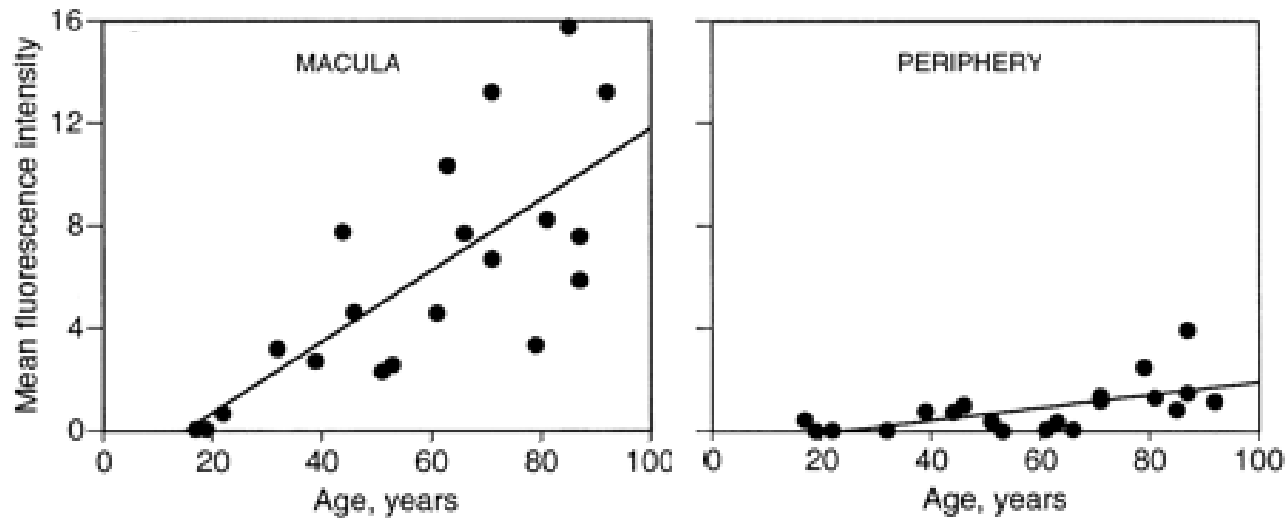


Aging is the main risk factor for AMD



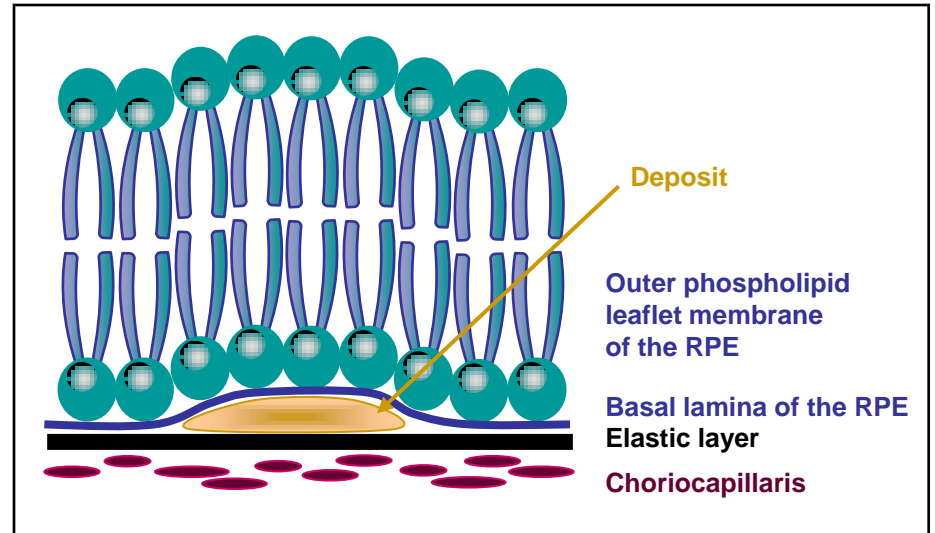
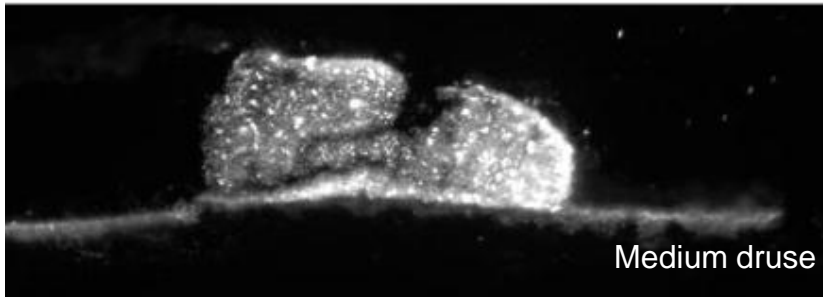
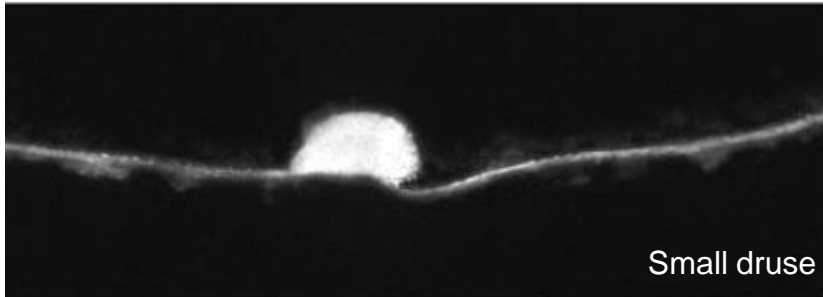
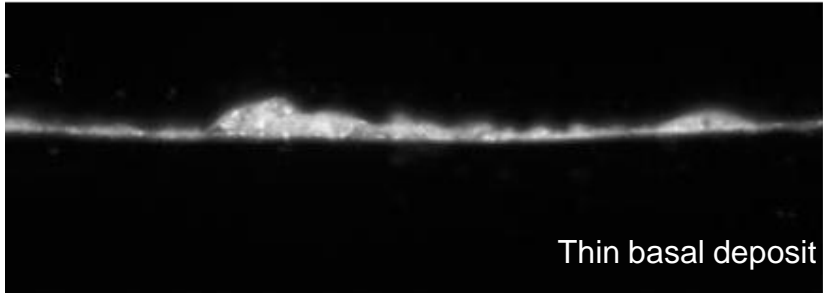
Data from the Beaver Dam Eye Study
Klein *et al.* 2007 *Ophthalmology*

Accumulation of cholesteryl esters, cellular debris, lipofuscin is characteristic to normal aging of the retina



Section of human eye labelled with filipin to reveal cholesteryl esters after extraction of free cholesterol and hydrolysis of the fatty acid residue from CE (fluorescence imaging: excitation 346nm, barrier 460nm)

and age-related maculopathies

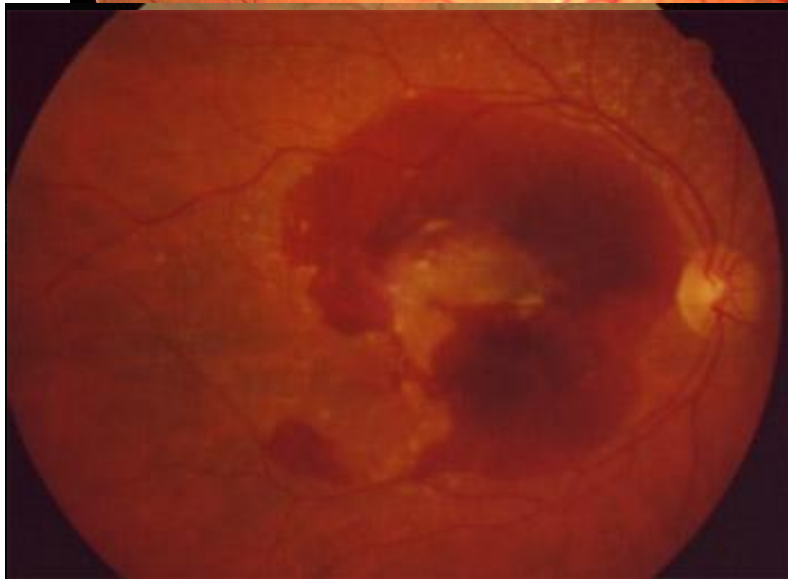
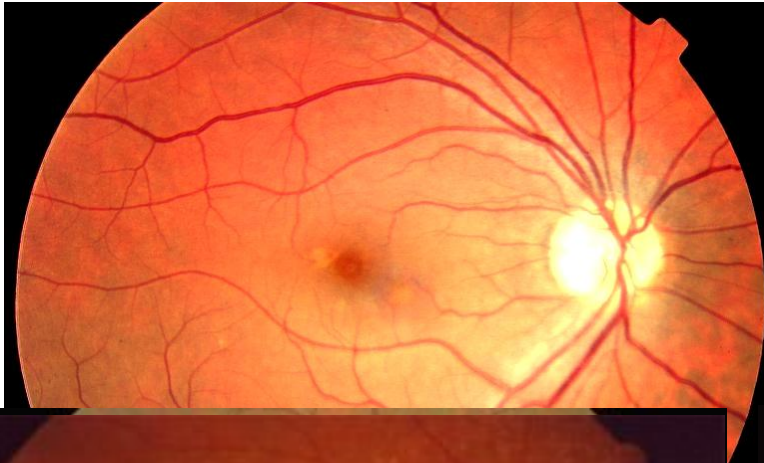


Sections of human eyes labelled with filipin to reveal cholesteryl esters after extraction of free cholesterol and hydrolysis of the fatty acid residue from CE (fluorescence imaging: excitation 346nm, barrier 460nm)

Malek *et al.* 2003 *Am. J. Pathol.* 162:413-25



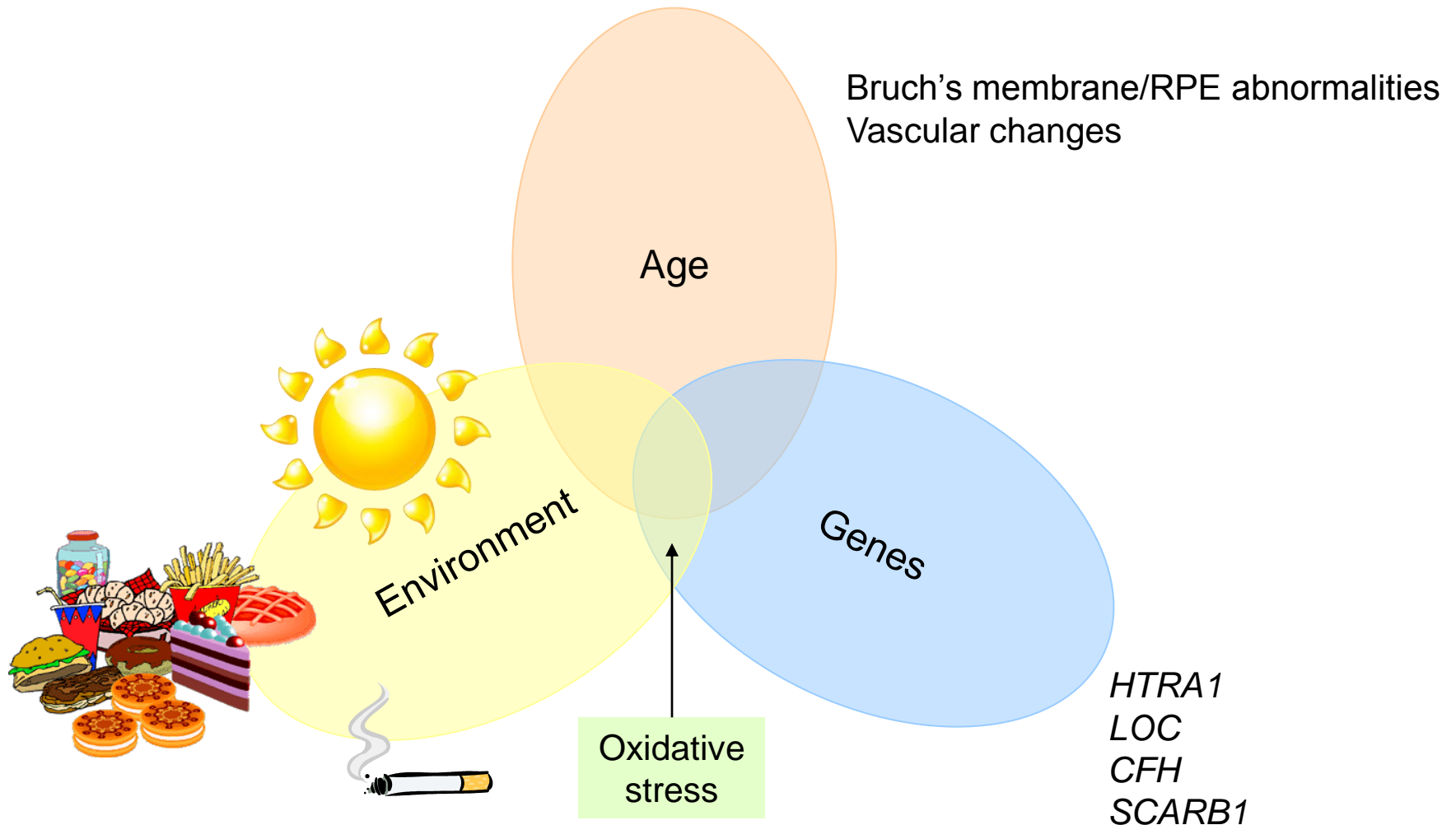
From age-related maculopathies to severe forms of AMD



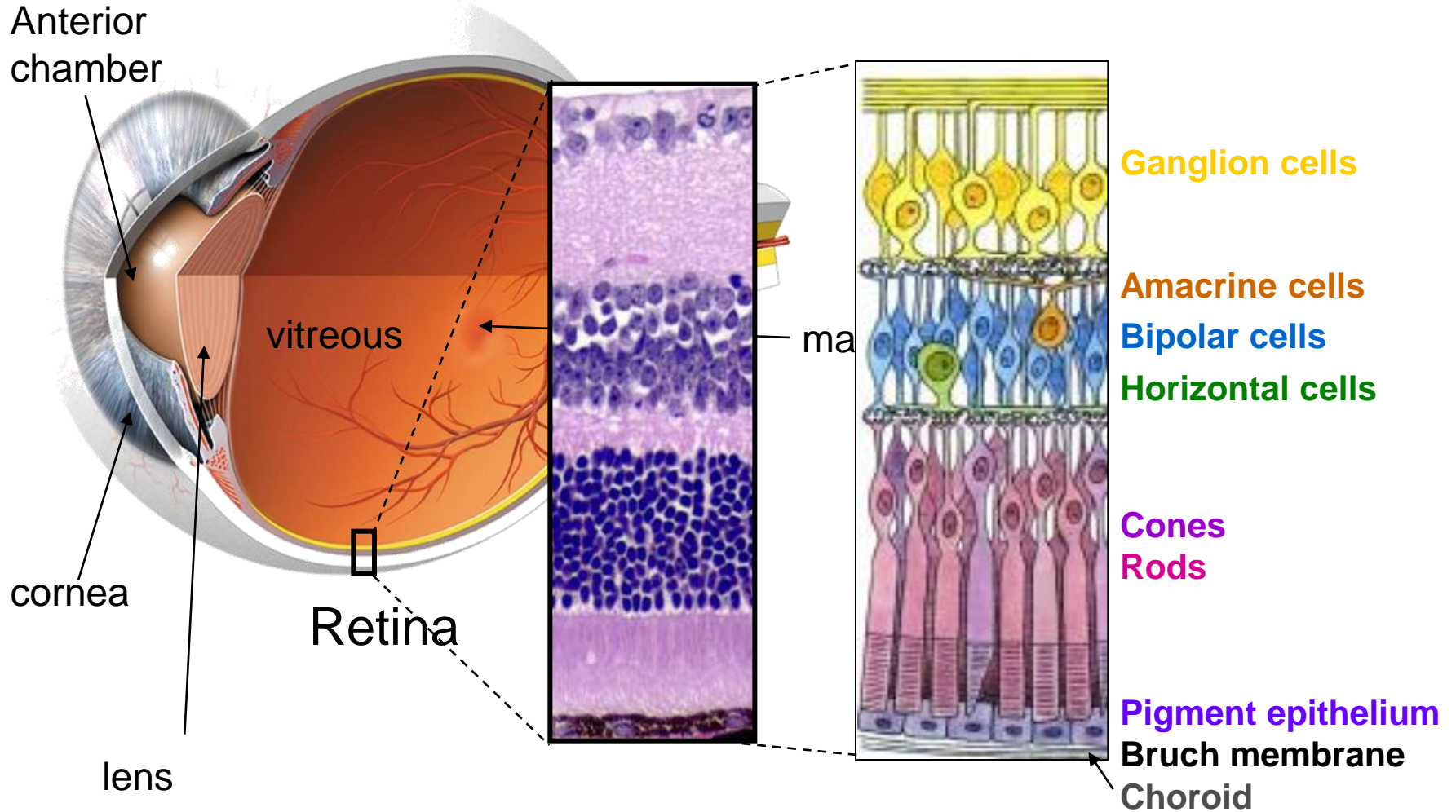
- Pigment abnormalities in 1 or 2 eyes
- Geographic atrophy
- Neovascularization

4 stages: from maculopathy to AMD

AMD: a multifactorial aging disease



Structural organization of the retina



The retina: an ideal environment for oxidative stress

- O₂ consumption by the retina is much greater than by any other tissue,
- The retina is subject to high levels of cumulative irradiation,
- Photoreceptor outer segment membranes are rich in polyunsaturated fatty acids, which are readily oxidized and which can initiate cytotoxic chain-reactions,
- The retina and RPE contain photosensitizers (rhodopsin, lipofuscin),
- The process of phagocytosis by the RPE is itself an oxidative stress and results in the generation of reactive oxygen species.

May dietary compounds prevent the retina from aging and the development of AMD ?

Anti-oxidants (vit C, vit E, β -carotene) do not prevent from AMD, but do in combination with Zinc

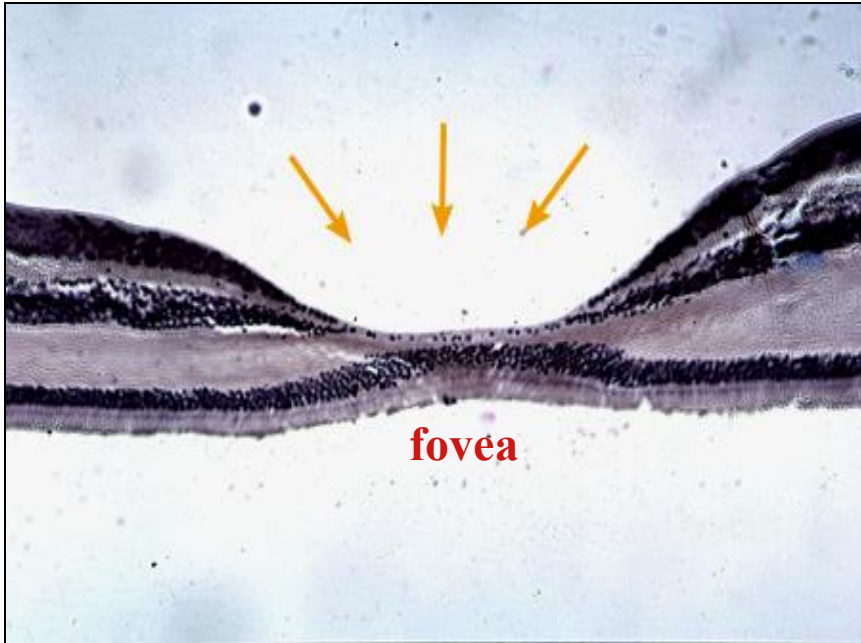
Treatment	Participants in AMD Categories 2, 3, and 4 (n = 3609)		Participants in AMD Categories 3 and 4 (n = 2556)	
	OR (99% CI)	PValue	OR (99% CI)	PValue
Antioxidants vs no antioxidants	0.87 (0.70–1.09)	.12	0.83 (0.66–1.06)	.05
Zinc vs no zinc	0.82 (0.66–1.03)	.02	0.79 (0.62–0.99)	.009
Antioxidants vs placebo	0.80 (0.59–1.09)	.07	0.76 (0.55–1.05)	.03
Adjusted	0.77 (0.56–1.05)	.03 [†]	0.76 (0.54–1.05)	.03 [†]
Zinc vs placebo	0.75 (0.55–1.03)	.02	0.71 (0.52–0.99)	.008
Adjusted	0.71 (0.51–0.98)	.005 [†]	0.70 (0.50–0.97)	.005 [†]
Antioxidants + zinc vs placebo	0.72 (0.52–0.98)	.007	0.66 (0.47–0.91)	.001
Adjusted	0.68 (0.49–0.93)	.002 [†]	0.66 (0.47–0.93)	.001 [†]
Total No. of participants with events	803		775	

[†] Adjusted for age, sex, race, AMD category, and baseline smoking status.

Omega-3: protective factors

		Early AMD	Late AMD
		Odd-ratio	
Lipids		1.54	2.90
Omega 6	Linoleic acid (LA)	1.49	2.00
Omega 3	Total omega 3		0.61
	Linolenic acid		0.61 (low LA)
	EPA		0.44 (Geogr. atrophy)
	EPA+DHA		0.45 (Geogr. atrophy)
	DHA	0.70	0.54
	Tuna fish		0.48
	Fish oil	0.65	0.36 (low LA) 0.60 (low LA)

The macula: a specific area of the retina rich in carotenoids

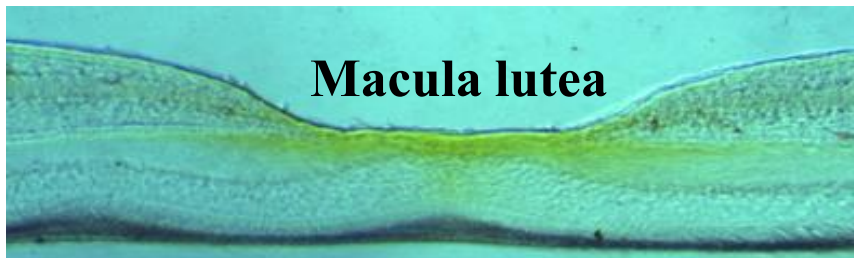


Characteristics

Cone-rich

(\approx 6 millions)

(vs **Rods**, \approx 120 millions,
not specific to the macula)

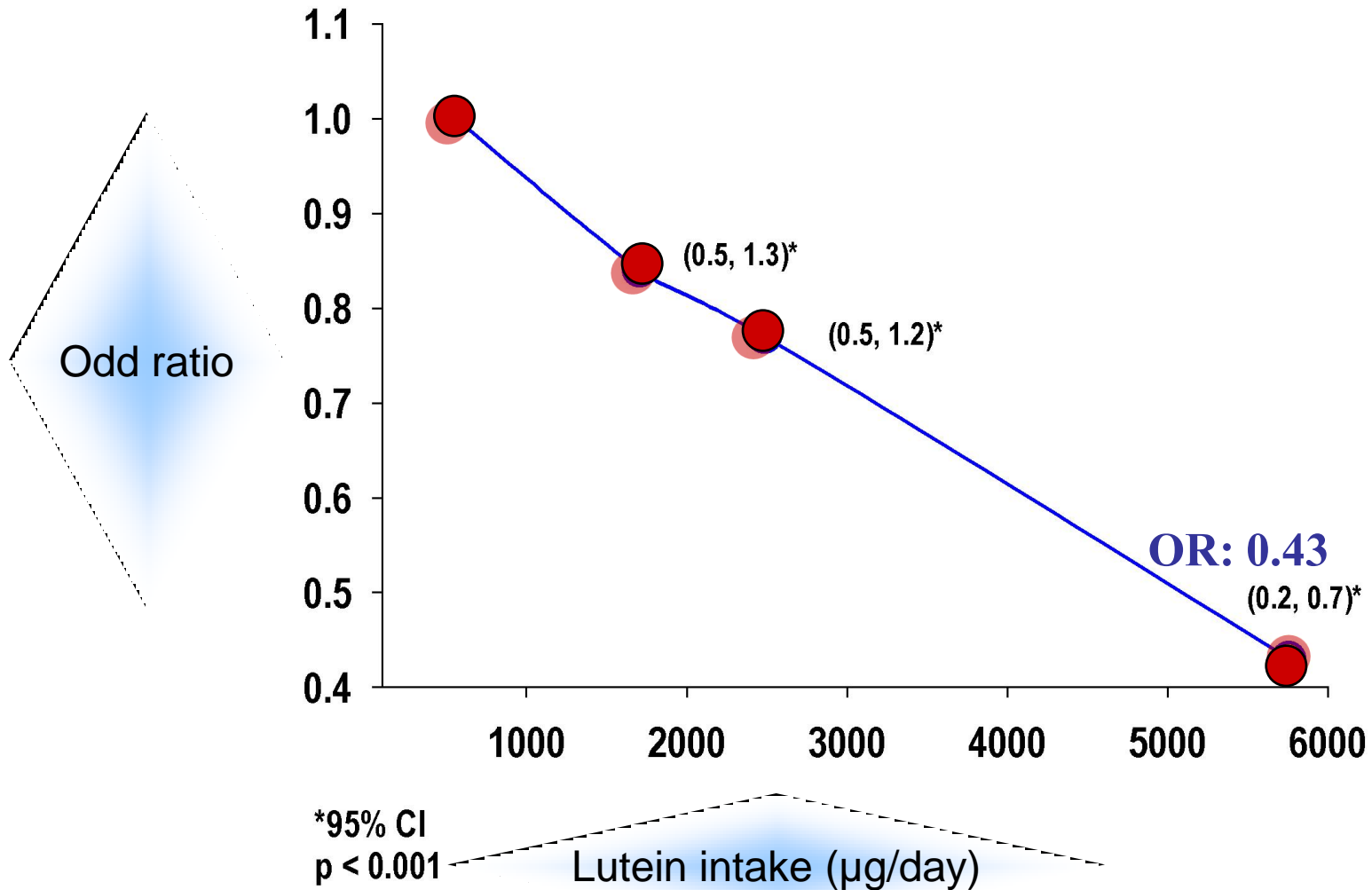


Rich in lutein

Variables associated with the macular pigment

	Nature of the association
Age	∅
Sex	∅, H>F
Right/left eye	∅
Iris color	∅, light<dark
Smoking habits	Smoker<Non-smoker
Obesity	High BMI – low macular pigment
Dietary intake	>0
Plasma levels	>0

Lutein intake reduces the risk for AMD



Clinical trial

AREDS-2 (Age-Related Eye Disease Study-2)

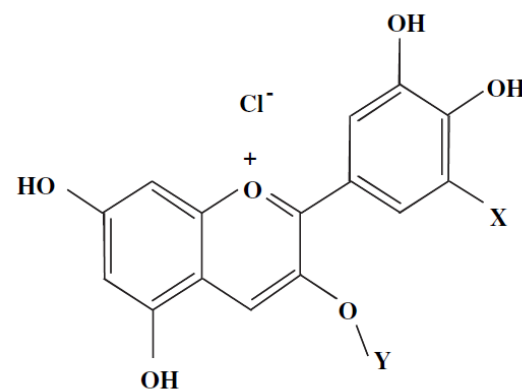
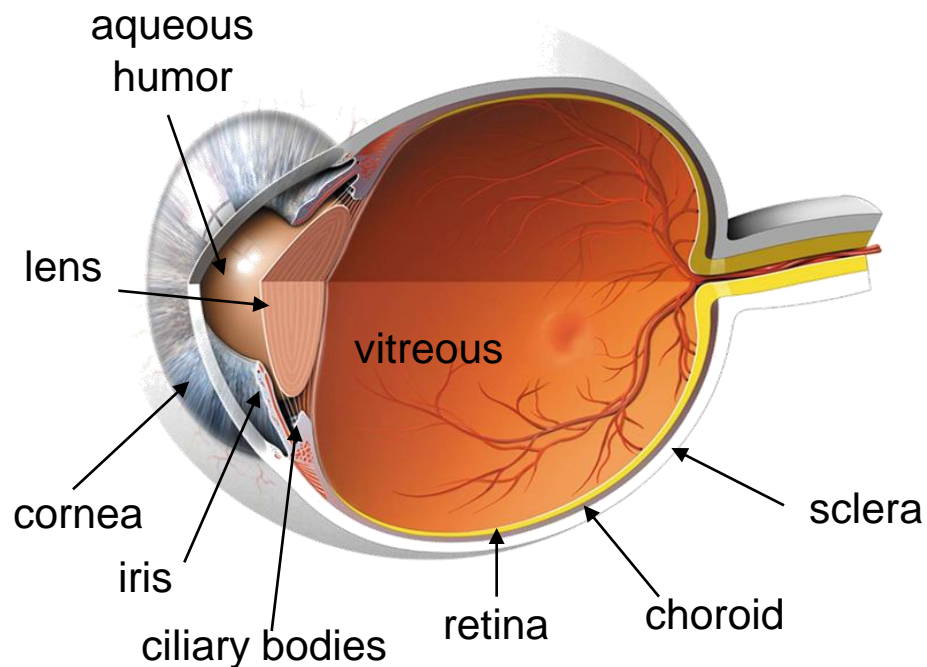
- 11 centers in USA
- randomized clinical trial
- 4000 participants during 5 years
- dietary supplementation with:
 - EPA (650mg/d) + DHA (350mg/d)
 - and/or lutein (10mg/d) + zeaxanthin (2 mg/d)
- Criteria: progression of AMD into late stages

Conclusion

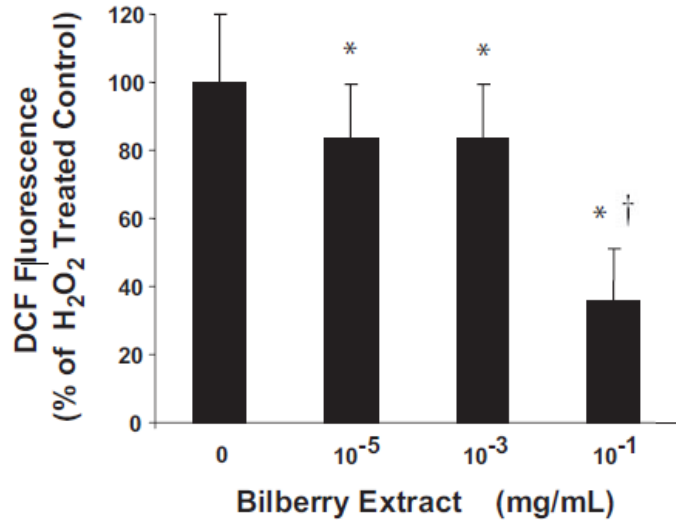
- Oxidative stress is an intimate mechanism of aging of the retina and tightly associated with the development of AMD
- Compounds with anti-oxidant properties may be beneficial in the prevention of oxidative stress-mediated cell dysfunctions

Bioavailability of anthocyanins in ocular tissues

Ocular tissues or body fluid	Intravenously administration in rabbit	
	AC of tissue ($\mu\text{g/g}$ tissue)	Distribution ratio (%)
Aqueous humor	1.19 ± 0.21	10.54
Cornea	0.55 ± 0.05	4.89
Sclera with Choroid	3.02 ± 0.09 (Sclera)	26.73
	3.00 ± 0.06 (Choroid)	26.57
Ciliary body with Iris	2.04 ± 0.28 (Ciliary body)	18.07
	1.11 ± 0.08 (Iris)	9.81
Retina	0.27 ± 0.02	2.41
Vitreous	0.11 ± 0.02	0.98
Lens	0.00 ± 0.00	0.00
Plasma ($\mu\text{g/ml}$)	12.42 ± 1.25	

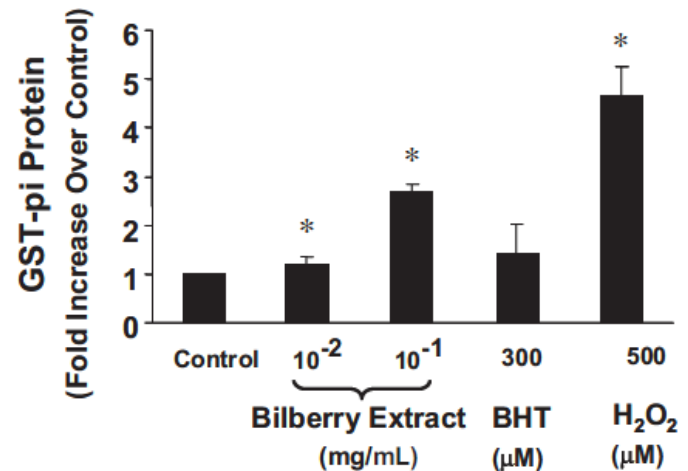
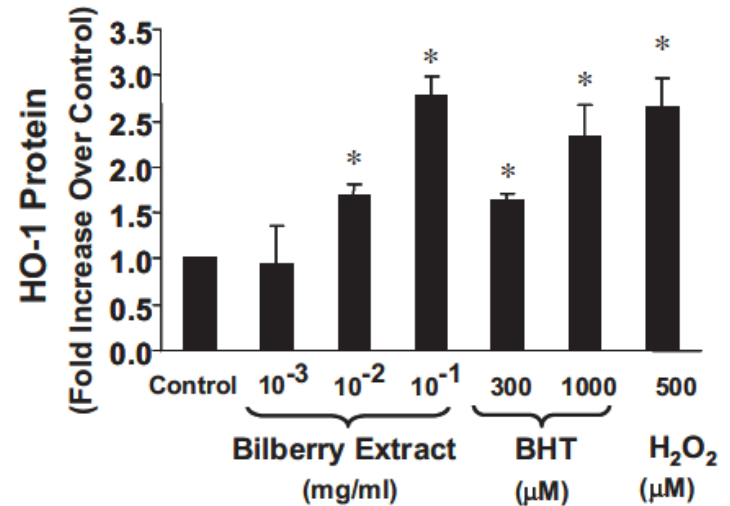


Anthocyanins and AMD processes (*in vitro* expt in cells of the retinal pigment epithelium)

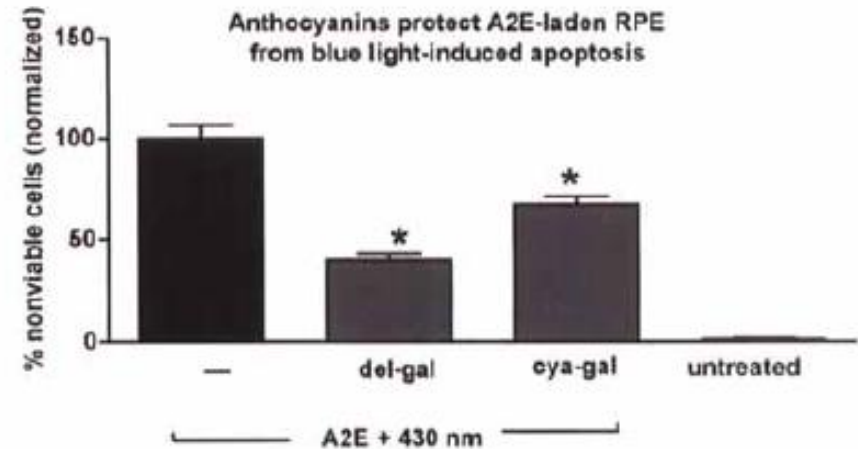
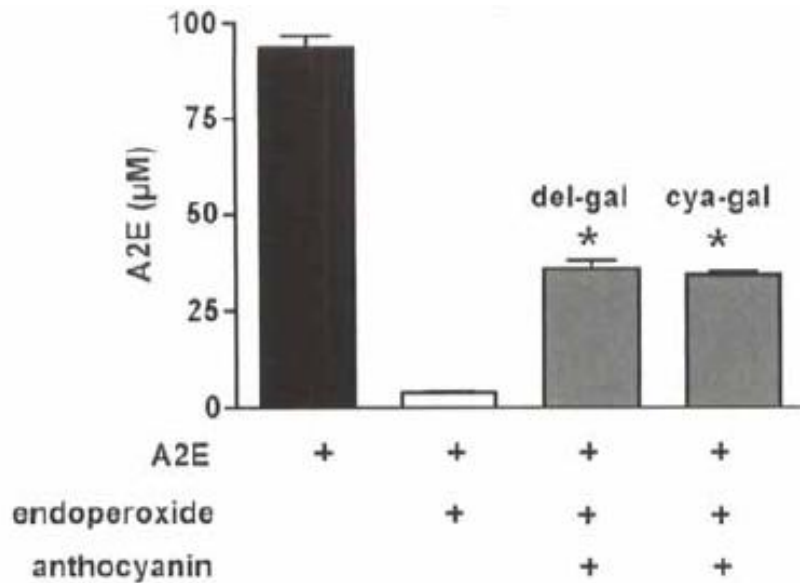


Reduced formation of free oxygenated radicals

Promotion of anti-oxydant mechanisms

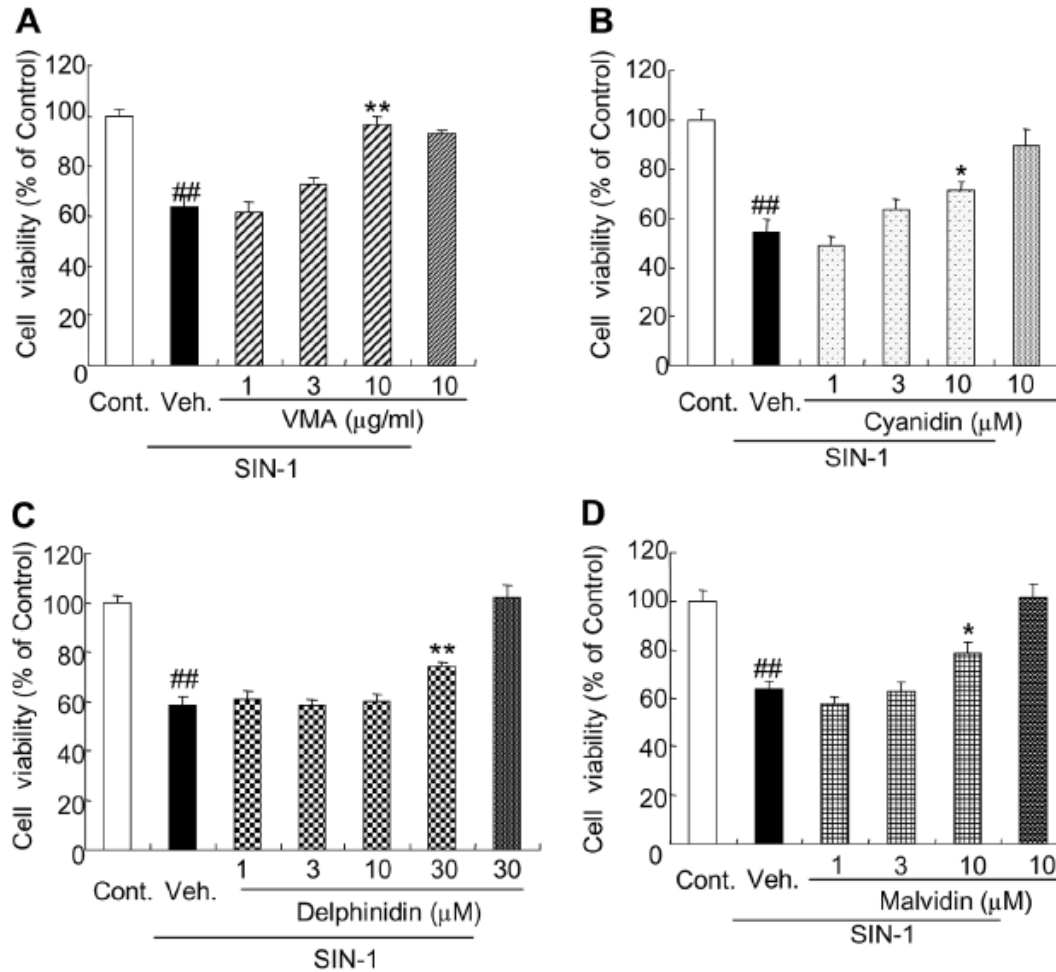


Anthocyanins and AMD processes (*in vitro* expt in cells of the retinal pigment epithelium)



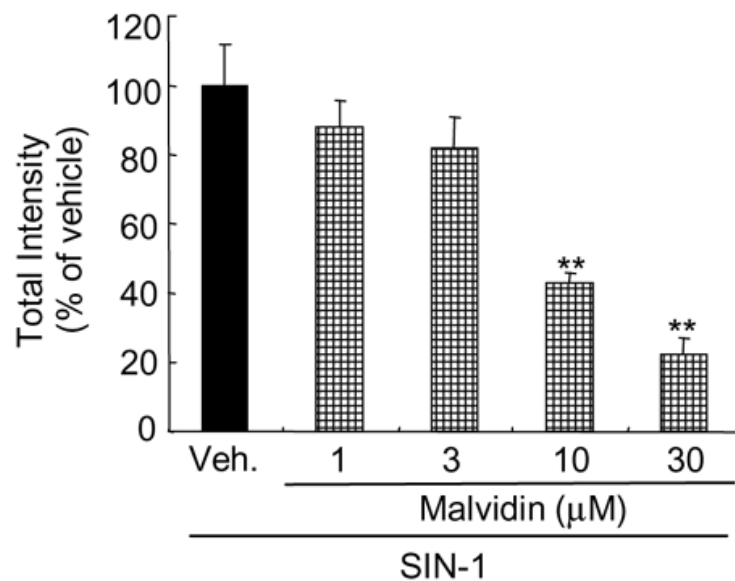
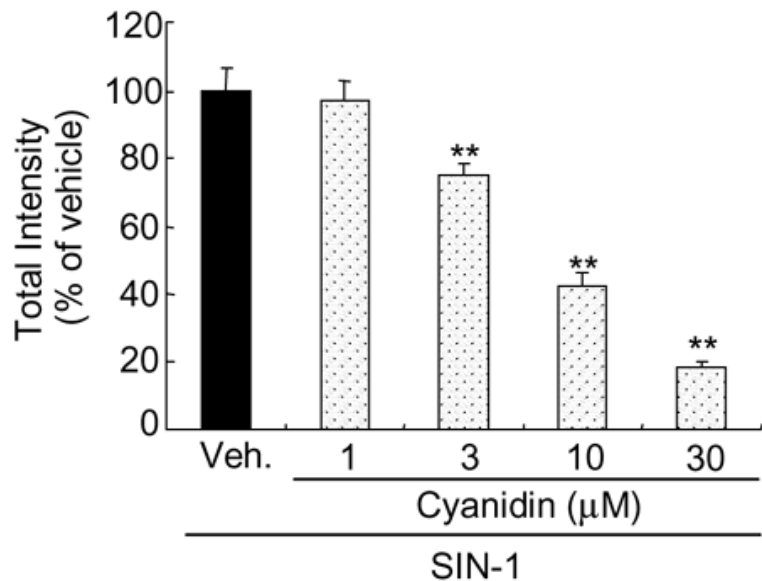
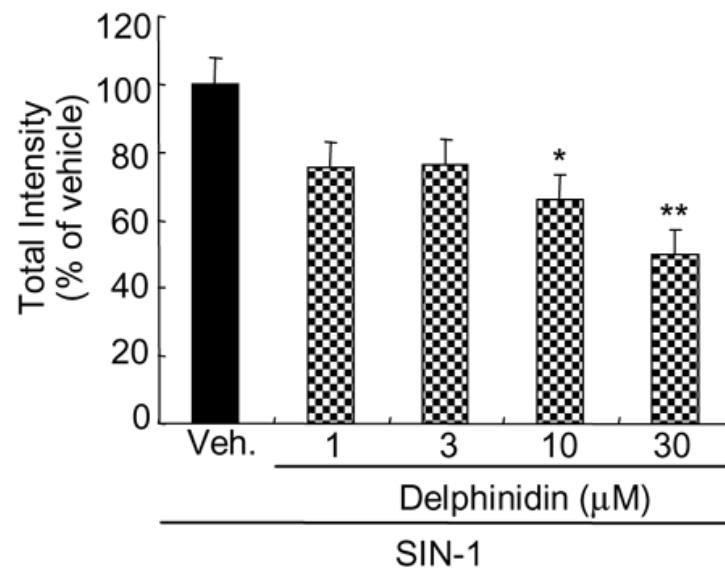
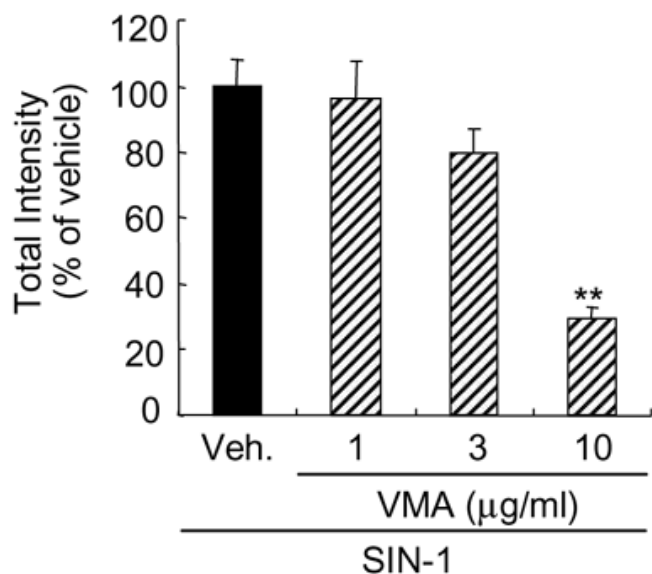
Anthocyanins protect RPE cells from blue-light toxicity by quenching singulet oxygen

Anthocyanins and glaucoma (*in vitro* expt in retinal ganglion cell)

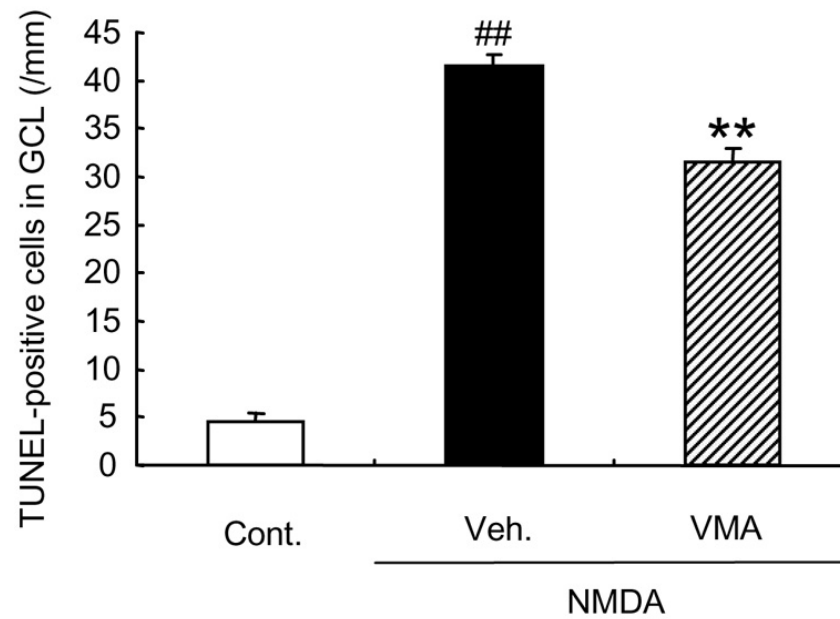


Anthocyanins prevent RGC from death induced by a peroxynitrite donor

By reducing the production of reactive oxygen species



And reducing apoptosis



Conclusion

- Berries are rich in anthocyanins and phenolic compounds which exhibit anti-oxidative properties
- These properties may be beneficial in the course of the leading retinal degenerative diseases (AMD and glaucoma)
- Open questions: availability, dose...