

**Nutrition, Weight and Modifiable Factors:
Associated with Macular Degeneration and
Visual Loss**

Nutrition and Health Conference

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STUDY DESIGNS

Genetic and Epidemiologic Studies:

- Case-control
- Cohort, prospective, longitudinal
- Twins- monozygotic and dizygotic
- Family-discordant siblings, concordant siblings
- Genetic Association Studies
- Randomized clinical trials

Seddon, J.

**THE U.S. TWIN STUDY OF AGE-RELATED
MACULAR DEGENERATION**

**US Twin Study of AMD - twins from the WW II
Veterans Twin Registry**

12,126 twins surveyed, 5.6% reported AMD, 840
twins examined and photographed throughout the
US, graded using CARMS (5 stages).

- Substantial Genetic Component: 46% to 71% of
the variation in phenotype
- Important Environmental Influence: 19% to 37%

Seddon et al. IOVS 1994
Seddon et al. Arch Ophthalmol 2005; 123:321-327

AMD: Lifestyle Factors

CIGARETTE SMOKING

- Smoking increases the risk of developing
AMD
- Smoking 25 cigarettes per day or more →
2.4 times the risk of AMD compared with
those who never smoked
- Past smokers also had twice the risk of
AMD

Seddon et. al., JAMA 1996; 276:1141-46

CIGARETTE SMOKING

- The heavier the smoking, the
greater the risk of AMD
- About 29% of cases of AMD
in this study were
attributable to smoking

Seddon et. al., JAMA 1996; 276:1141-46

ESTIMATED RELATIVE RISK OF AMD (ODDS RATIO) BY QUINTILE OF NUTRIENT INTAKE					
Beta-carotene			Lutein/ Zeaxanthin		
	OR	95% CI		OR	95% CI
Quintile 1	1.0		1	1.0	
2	0.89	(0.5-1.4)	2	1.16	(0.7-1.8)
3	1.03	(0.6-1.7)	3	0.85	(0.5-1.4)
4	0.97	(0.6-1.6)	4	0.77	(0.5-1.3)
5	0.91	(0.5-1.6)	5	0.44	(0.2-0.8)
p (trend) = 0.80			p (trend) = .008		
Seddon, J. et. al. JAMA 1994;272:1413-1420					

ESTIMATED RELATIVE RISK OF AMD BY FREQUENCY OF FOODS RICH IN CAROTENOIDS		
	5-6+ /wk (relative to <1/month)	
	RR (95% CI)	p(trend)
Broccoli	0.47 (0.2 - 1.2)	0.06
Cabbage, cauliflower brussel sprouts	0.63 (0.2 - 1.8)	0.57
Carrots	0.72 (0.4 - 1.4)	0.06
Spinach	0.12 (0.01 - 0.9)	<0.001
Sweet potato	0.52 (0.1 - 4.2)	0.2
Winter squash	0.37 (0.1 - 2.1)	0.03

NUTRITIONAL ANCILLARY STUDY 1986 – 1991 LUTEIN AND ZEAXANTHIN
<ul style="list-style-type: none"> Higher dietary intake of <u>lutein/zeaxanthin</u> was associated with a reduced risk of AMD Significant trend for <u>decreasing risk</u> with <u>increasing intake</u> Lowest risk – for intake of 6 mg per day Foods rich in lutein/zeaxanthin (spinach) reduced risk of AMD (5-6 times per week relative to less than once per month)
Seddon J, et al. JAMA 1994;272:1413-1420

OBSERVATIONAL STUDIES OF LUTEIN/ ZEAXANTHIN: ADVANCED AMD			
Study	Outcome	Cases/Controls	OR (95% CI)*
1994 EDCCS (Seddon et al.)	Adv. AMD	356/520	0.4 (0.2 – 0.7)
1996 BDES (Mares et al.)	Late ARM	30/1020	1.6 (0.5 – 5.5)
2001 NHANES (Mares et al.)	Late ARM	16/~3000	0.1 (0.0 – 0.9)
2002 Snellen et al.	Late ARM	72/66	0.2 (0.1 – 0.9)
2007 AREDS (Diet)	NV AMD	658/1115	0.6 (0.5 – 0.9)
	GA	118/1115	0.3 (0.2 – 0.8)
Multivariable Models of lutein or lutein/zeaxanthin intake. Odds ratios are for comparisons of highest vs. lowest quintile.			

NUTRITIONAL ANCILLARY STUDY OF 1986-1991 DIETARY FAT
Presented at ARVO- 1994
<ul style="list-style-type: none"> Higher total fat increased risk of AMD Omega-3 fatty acids reduced risk of AMD Evidence to date- many studies-1994-2009 <p>- Different study designs, direction of effect beneficial, magnitude of effect – reduction of risk by 30% to 50%</p>
<p>Seddon JM, ARVO Abstract #3454, 1994. Mares-Perlman et al, Arch Ophthalmol 1995; 113: 743-748 Smith et al, Arch Ophthalmol 2000; 118: 401-404 Seddon et al, Arch Ophthalmol 2001; 119:1191-1199 Cho et al, Am J Clin Nutr 2001; 73: 209-218 Seddon et al, Arch Ophthalmol 2003, 121:1728-1737 AREDS Research Group, 2004-2009</p>

PROGRESSION OF AGE-RELATED MACULAR DEGENERATION: ASSOCIATION WITH DIETARY FAT, TRANSUNSATURATED FAT, NUTS AND FISH INTAKE
<p>↑ <u>Total fat intake:</u> relative risk (RR) 2.90 for highest vs. lowest</p> <p>↑ <u>Saturated, monounsaturated, polyunsaturated and transunsaturated fats:</u> RRs 2.09, 2.21, 2.28, 2.39</p> <p>↓ <u>Fish intake:</u> Higher fish intake was associated with lower risk when linoleic acid intake was low</p> <p>↓ <u>Nuts:</u> Higher intake was associated with lower rate of progression</p>
IOVS ARVO abstract, 1994 Arch Ophthalmol, 2001 and 2003

CIGARETTE SMOKING, FISH, AND OMEGA-3 FATTY ACID INTAKE AND ASSOCIATIONS WITH AMD

- US Twin Study of AMD
- Elderly male twins in WWII Veteran Twin Registry
- Smoking – (current) 1.9 fold risk
– (past) 1.7 fold risk ↑
- Fish (2 or more x/wk) – risk ↑ (P trend = 0.04)
- Omega-3 fatty acids – ↓ risk (OR 0.55, CI 0.32-0.95) ↓
- Attributable risks – 32% for smoking, 22% for dietary omega-3's

Seddon J. Arch Ophthalmol 2006;124:995-1001

DIETARY OMEGA-3 FATTY ACIDS EVIDENCE TO DATE

- Studies 1994 to 2009
- Different study designs
- Direction of effect - protective
- Magnitude of effect - risk of AMD reduced by 30% - 50%

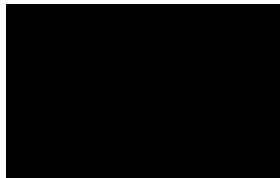
Seddon, J.

AREDS

Reduction in Risk for AMD and VA Outcomes Categories 3 and 4

Anti-ox Zinc Anti-ox & Zinc

Advanced AMD
3 or More Line Loss in Visual Acuity



AREDS Report #8 Arch Ophthalmol 2001;119:1417-1436

Lutein, Zeaxanthin, and Omega-3 Fatty Acids Reduce Risk of AMD

- AREDS 2 is now evaluating supplements containing these nutrients in a clinical trial

VITAMIN D – 25 – HYDROXYVITAMIN D3

- Immune system regulator
- Reduces inflammatory cytokines
- Inhibits VEGF and endothelial cell proliferation
- Inhibits angiogenesis

Schleithoff, Am J Clin Nutr 2006; 83: 731-2
Albert D, Invest Ophthalmol Vis Sci 2007; 48: 2327-34
Parekh N, Arch Ophthalmol 2007; 125:661-9

GREEN TEA

EPIGALLOCATECHIN-3-GALLATE (EGCG) AND POLYPHENOLS

Antioxidant

- Quench reactive oxygen species
- Increase plasma antioxidant status

Anti-inflammatory

- Inhibit TNF-alpha expression
- Block serine proteinase leukocyte elastase, MMP-2, MMP-9

Anti-Angiogenic

- Suppress endothelial cell growth
- Block formation of new blood vessels
- Inhibit VEGF

Zhao B, Cell Biophys 1989; 14: 175-185
Fang Dai, Biochem 2008
Serafina M., Eur J Clin Nutr

Suganuma M., Biofactors 2000; 13: 67-72
Sartor L., Leukoc Bio 2001; 71: 73-79
Cao Y, Cao R., Nature 1999; 398:381-381
Lamy S., Cancer Res 2002; 62: 381-385

**VITAMIN E
TOCOPHEROLS AND TOCOTRIENOLS**

Antioxidant

- Tocotrienols –different chemical structure
- Unsaturated side chain
- Better ability to react with lipid radicals
- More powerful antioxidant

Anti-Angiogenic

- Suppress angiogenesis
- Cell culture studies, in vivo

Tatsuta T, Vitamins 1971; 44: 185-190
Kato A. Abura Kagaku 1985; 34: 375-376
Nagagaw K., J Nutr 2007; 137: 1938-1943

DIETARY AND SUPPLEMENT RECOMMENDATIONS

- Green leafy vegetables
- Fruits
- Fish
- Lutein/zeaxanthin supplements
- Fish oil supplements
- Vitamin C, E, zinc
- Vitamin D, green tea, and tocotrienols

CARDIOVASCULAR RISK PROFILE

Do age-related macular degeneration (AMD) and cardiovascular disease (CVD) share common antecedents?

Snow, K., Seddon, J. Ophthalmic Epidemiology 1999; 6:125-143.

Risk factors for cardiovascular diseases (CVD) are associated with age-related (AMD):

- Smoking
- Dietary antioxidants, fats, omega-3 fatty acids
- Physical activity
- Obesity, Abdominal adiposity
- Hypertension
- Cholesterol

Seddon, J.

**PROGRESSION OF AGE-RELATED
MACULAR DEGENERATION: ASSOCIATION WITH
BODY MASS INDEX, WAIST CIRCUMFERENCE,
AND WAIST-HIP RATIO**

↑ **Body mass index:** relative risk (RR) 2.35 for BMI > 30, vs. < 25

↑ **Waist circumference:** RR 2.04 for highest vs. lowest

↑ **Waist-hip ratio:** RR 1.84 highest vs. lowest

↓ **Physical activity:** RR 0.75 (25% reduction) (p=.05)

Seddon et al, Arch Ophthalmol 2003; 121: 785-792

AMD GENES (CFH, ARMS2, C3), SMOKING, AND BODY MASS INDEX, ARE INDEPENDENTLY ASSOCIATED WITH ADVANCED AGE-RELATED MACULAR DEGENERATION

- For the homozygous risk genotype:

risk was increased with higher BMI

risk was increased with smoking

Seddon J. et al. Human Heredity 2006; 61: 157-165
Seddon J. et al. IOVS 2009; 50:2044-2053
Francis P. et al Human Heredity 2007; 63: 212-218

ANTI-INFLAMMATORY MECHANISM

- C-Reactive Protein, a marker of systemic inflammation, is higher in individuals with AMD compared with controls.

Lower CRP (less inflammation)

- Higher serum lutein/zeaxanthin
- Higher serum vitamin C
- Higher fish intake

Higher CRP (more inflammation)

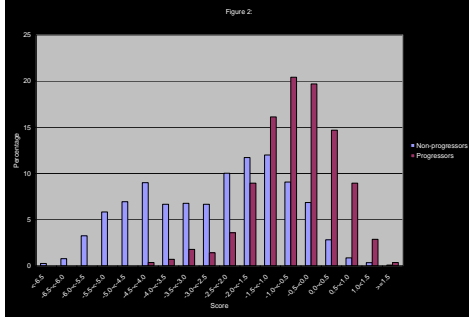
- Smoking
- Higher Body Mass Index

Seddon, J.

Nutrition 2006; 22: 441-443

PREDICTION MODEL FOR INCIDENCE AND PREVALENCE OF AMD

- Risk Scores for progressors and non-progressors
- Variables : age, gender, AMD grade, education, smoking, BMI, supplements, six genetic variants .



Seddon J., et al IOVS 2009; 50: 2044-2053