

- Topics:** Omega-3 fatty acids, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), long chain polyunsaturated fatty acids (LC-PUFAs), age-related macular degeneration (AMD), zinc, anti-oxidants, Vitamins A, C & E, beta-carotene, lutein/zeaxanthin.
- Objective:** To investigate whether omega-3 fatty acids, zinc, Vitamins A, C & E, beta-carotene and lutein/zeaxanthin can reduce the genetic risk of early AMD conferred by the genetic variants CFHY402H and LOC387715 A69S in a nested case-control study.
- Background:** AMD is the leading cause of blindness in developing countries and accounts for over 50% of blindness<sup>1</sup>. Approximately 2.5 million elderly people are affected by late AMD in Europe and 21 million worldwide<sup>1</sup>. In the United States, AMD is expected to rise by 50% over the next decade to reach 30 million by 2020<sup>2</sup>. While the pathogenesis of AMD remains elusive, risk factors include age, smoking, atherosclerosis-like plaques associated with cardiovascular disease and genetic factors<sup>2</sup> including the two gene variants CFHY402H that increases a person's odds of AMD by 11-fold and LOC387715 A69S that raises them by up to 15-fold. These variants account for over 80% of AMD cases. The long term prognosis for neovascular AMD is poor and for geographic atrophy improved vision is not possible. To date, the only protective factors are nutrients. Previous population studies have shown that higher intake of fish and omega-3 LC-PUFAs may reduce the incidence of advanced AMD, and that combinations of zinc, beta-carotene, Vitamin C & E reduce the risk of progression from intermediate to advanced AMD. However, few studies have investigated the impact of these nutrients plus anti-oxidants on AMD in susceptible individuals. Given the public health importance of AMD, and the lack of successful treatment options, it is important to investigate the use of omega-3 LC-PUFAs for preventive measures.
- Method:** This study was nested in the prospective, population-based Rotterdam Study investigating chronic diseases in 6780 subjects 55 years and older. 6780 participants underwent an assessments including ophthalmic examination during 1990 to 1993 (baseline). This was followed by 3 re-examinations approximately each 3 years apart. Eligible participants included those who either had no AMD during the entire study period or who developed early AMD during the follow up, who tested positive for the genetic variants CFHY402H and LOC387715 A69S, lived independently, had normal cognition, reliable dietary assessment and gradable fundus photographs from at least 1 follow-up examination, leaving 2167 individuals aged 55 years + available for analysis. The following assessments were completed:
- 1) Semiquantitative food frequency questionnaire by self administered checklist and by an interview with a qualified dietician
  - 2) Genetic variants by TaqMan assay
  - 3) Assessment of confounders including smoking status, total serum cholesterol, blood pressure, subclinical atherosclerosis composite score
  - 4) Incident of early AMD was determined on fundus photographs at the 3 follow up visits (median follow-up 8.6 years).
  - 5) Characteristics of participants with and without incident early AMD were compared using analysis of covariance for continuous variables and logistic regression analysis for discrete variables, adjusting for age and sex.
  - 6) Participants were classified as non-carriers or heterozygous or homozygous carriers of the CFHY402H risk variant and non-carriers or carriers of the LOC387715 A69S risk variant.
  - 7) Interaction between risk factors were determined & hazard ratios calculated to estimate risk of early AMD in strata of nutrient intake & genotypes.
- Findings:**
- A) 517 participants developed early AMD
  - B) Higher intake of zinc, beta-carotene, and Vitamins C & E significantly reduced risk of AMD.
  - C) There was biological interaction between CFHY402H and zinc, beta-carotene, lutein/zeaxanthin and EPA/DHA and between LOC387715 A69S and zinc and EPA/DHA.
  - D) In people with two copies of CFHY402H (i.e. homozygotes) with dietary intake of zinc in the highest tertile, their hazard ratio of early AMD was reduced from 2.25 to 1.27.
  - E) For intakes of beta-carotene, lutein/zeaxanthin and EPA/DHA, these risk reductions were from 2.54 to 1.47, 2.63 to 1.72 and 1.97 to 1.30, respectively.
  - F) Carriers of LOC387715 A69S with the highest intake of zinc and EPA/DHA reduced their risk from 1.70 to 1.17 and 1.59 to 0.95, respectively (all P trends <0.05).
- Conclusion:** High dietary intake of EPA/DHA, zinc, beta-carotene and lutein/zeaxanthin reduces the risk of early AMD in people with high genetic risk of developing the condition.
- Relevance to** Efalex Vision, Efalex Active 50+
- Reference:** Ho L, van Leeuwen R, Witteman J, van Duijn C, Uitterlinden A et al. Reducing the genetic risk of age-related macular degeneration with dietary anti-oxidants, zinc and omega-3 fatty acids. Arch Ophthalmol 2001;129(6):758-766.

## **PRESS RELEASE**

### **Fish oil fatty acids and anti-oxidant nutrients reduce risk of age-related macular degeneration in people with a genetic susceptibility<sup>1</sup>.**

A new study found that among people with a genetic susceptibility to age-related macular degeneration (AMD), those who ate more zinc, beta-carotene, lutein/zeaxanthin and the omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) cut their risk of developing the condition by up to a third compared with those who ate less of these nutrients.

AMD gradually destroys sharp, central vision that is needed for seeing objects clearly and for common daily tasks such as reading and driving. It affects the macula, the part of the eye that allows seeing fine detail. It is located in the centre of the retina, the light-sensitive tissue at the back of the eye. The retina is comprised largely of DHA, a dietary omega-3 fatty acid found mainly in fish.

AMD is the leading cause of blindness in developing countries and accounts for over 50% of blindness<sup>1</sup>. Approximately 2.5 million elderly people are affected by late AMD in Europe and 21 million worldwide<sup>1</sup>. In the United States, cases of AMD are expected to rise by about 50% over the next decade to reach 30 million by 2020<sup>2</sup>. While the pathogenesis of AMD remains elusive, several risk factors have been established including age, smoking, atherosclerosis-like plaques associated with cardiovascular disease and certain genetic factors<sup>2</sup> including the two gene variants CFHY402H that increases a person's odds of AMD by 11-fold, and LOC387715 A69S that raises them by up to 15-fold. Together, these variants account for over 80% of AMD cases.

To date, there is no effective treatment for AMD and the only protective factors known for AMD are dietary nutrients. Previous population studies have shown that higher intake of fish and omega-3 long chain polyunsaturated fatty acids (LC-PUFAs) may reduce the incidence of advanced AMD, and that combinations of zinc, beta-carotene, Vitamin C & E reduce the risk of progression from intermediate to advanced AMD. However, up to now, few studies have investigated the impact of these nutrients on AMD in susceptible individuals. Given the public health importance of AMD, and the lack of successful treatment options, the results of this latest collaborative study from Erasmus Medical Centre, Rotterdam, the Netherlands Institute for Neuroscience and the Academic Medical Centre, Amsterdam, The Netherlands, are encouraging.

The researchers studied the eating habits of 2167 people over the age of 55 years who were at risk of developing AMD due to genetic traits. All had eye exams every 3 years for the next decade to determine the development of AMD. Among people who carried the CFHY402H variant, greater intakes of dietary zinc, beta-carotene, EPA/DHA and lutein/zeaxanthin were associated with a lower risk of AMD. For example, 39 out of 100 people who ate the lowest EPA/DHA (about 22 mg/day) developed AMD compared to 28/100 who ate the largest amount of EPA/DHA (268 mg/day). In people with the LOC387715 A69S variant, reduced risk of AMD was seen in people who ate larger amounts of zinc and EPA/DHA. In this case, 25% of people who ate 11.85 mg/day zinc development AMD compared to 33% of people who ate only 7.5 mg/day zinc. The researchers noted that these benefits could be achieved by eating the recommended daily allowance of these nutrients.

This study adds to the current knowledge base recently reviewed linking omega-3 intake to lower incidence of AMD, where the potential benefit of omega-3 fatty acid supplementation is supported by their role normal retinal physiology, their anti-inflammatory properties, and the putative role of inflammation in AMD<sup>2</sup> However, since oxidative stress has a recognised role in the development of AMD, and omega-3 fatty acids are susceptible to oxidation, this may partially masked their benefit. Therefore, co-supplementation with anti-oxidants may be necessary to reap the full benefit. Currently a five year randomized, double-blind, placebo controlled clinical study including over 4000 people is underway to provide proof of that benefit ([www.areds2.org](http://www.areds2.org)).

Not included in the review, was the strongest observational evidence to date showing that increased intake of fish and fish derived omega-3 LC-PUFAs, significantly decreases the risk of developing AMD by up to 42 percent.<sup>3</sup> That study included 38,022 women aged 45 years or older and **initially free of AMD** who were followed for over ten years.

Although results of randomised, controlled trials are still not available, these reports strongly indicate that DHA supplementation may prevent the onset and/or slow the progression of AMD and that combined with anti-oxidants may provide greater benefit.

#### **References:**

1. Ho L, van Leeuwen R, Witteman J, van Duijn C, Uitterlinden A et al. Reducing the genetic risk of age-related macular degeneration with dietary anti-oxidants, zinc and omega-3 fatty acids. *Arch Ophthalmol* 2001;129(6):758-766.
2. Kishan AU, Modjtahedi BS, Martins EN, Modjtahedi SP, Morse LS. Lipids and Age-related Macular Degeneration. *Survey of Ophthalmology* 2011;56(3):195-213.
3. Christen WG, Schaumberg DA, Glynn RJ, Buring JE. Dietary  $\omega$ -3 fatty acid and fish intake and incident age-related macular degeneration in women. *Am J Clin Nutr* Published ahead of print March 14, 2011, doi:10.1001/archophthalmol.2011.34.