



The LEWIN GROUP

An Evidence-Based Study of the Role of Dietary Supplements in Helping Seniors Maintain their Independence

Prepared for:

Dietary Supplement Education Alliance

Prepared by:

The Lewin Group Inc.

January 20, 2006

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I. EXECUTIVE SUMMARY

By the year 2030, there will be over 70 million people aged 65+, with half over age 75. Health care for Americans over age 65 could increase to nearly \$16 trillion per year. A number of age-related diseases contribute significantly to whether an older person can maintain his or her independence, including coronary heart disease (CHD), osteoporosis, and age-related macular degeneration (AMD).

AMD affects activities central to independent living, which include reading, driving, and writing, which are considerably impaired through the loss of central vision, for example. AMD is the leading cause of irreversible blindness in persons over age 65. Research studies have shown that preventive measures, such as smoking avoidance and good nutrition, that are practiced throughout one's life can help reduce the risk of these conditions, thereby avoiding or delaying a loss of independence or the onset of functional disability. Visual impairment is one of the top four reasons for loss of independence. Furthermore, eighteen percent of all hip fractures among seniors have been attributed to age-related vision loss.¹

The transition to greater dependency, whether by getting more help at home or through moving to a nursing facility, places considerable financial burden on the older person, his or her family, and the health care system.² Studies have shown that there are additional medical and other costs associated with the year when an older person makes the transition to dependency at home or moves to a nursing facility. The prevention (or even delay) in the loss of independence has implications both economically and also for the individual's quality of life.

The purpose of this evidence-based study is twofold: (1) to critically review the research literature for two dietary supplements for which an association has been shown between intake of the supplement and reduced risk of a disease that can and does lead to a loss of independence, and (2) to develop estimates of potential health care savings that could result from daily use of the supplement. Supplement/disease combinations examined in this study are (1) **omega-3 fatty acids and CHD** and (2) **lutein/zeaxanthin and AMD**. Additionally, the literature was reviewed for Vitamin D as it relates to prevention of osteoporosis, but because there currently are no studies yet of Vitamin D alone (without calcium), we were not able to develop a cost model for Vitamin D without calcium.³

The Lewin Group, Inc. was commissioned by the Dietary Supplement Education Alliance (DSEA) to review the existing research literature concerning the above supplements for validity (scientific validity), impact (size of the effect), and applicability (usefulness in actual practice). Lewin was asked to develop estimates of the potential health care expenditure savings that could result from

¹ Alliance for Aging Research; also Martel L, Belanger A, Berthelot JM. (2002) Loss and recovery of independence among seniors. *Statistics Canada: Health Reports*; 13(4): 35-48.

² Guralnik JM, Alexcih L, Branch LB, Wiener JM. (2002). Medical and long-term care costs when older persons become more dependent. *Amer J Pub Health* 92(8): 1244-12245.

³ Calcium is examined in DaVanzo, Dobson, et al. (2004) *A Study of the Health and Cost Effects of Five Dietary Supplements*, Falls Church, VA: The Lewin Group.

daily use of these supplements. Estimates of potential savings were developed for each supplement for specific relevant outcomes. For omega-3 fatty acids, estimates of potential savings associated with a reduced risk of CHD and the potentially avoided hospitalizations and physician services were developed. For lutein/zeaxanthin, estimates of potential savings associated with a reduced risk of AMD were developed through the delay or avoidance of transitioning to dependence as a result of central vision blindness. This report contains a summary of the key findings of the study, a discussion of the conceptual framework and the methodology, and a discussion of the implications of the results.

Key Study Findings

- **Omega-3 fatty acids:** Using a Congressional Budget Office (CBO-type) cost accounting methodology, the estimate of the five-year (2006-2010) net savings in hospital expenditures and physician charges resulting from a reduction in the occurrence of coronary heart disease (CHD) among the over age-65 population through daily intake of approximately 1800 mg⁴ of omega-3 fatty acids is **\$3.1 billion**. Approximately 384,303 thousand hospitalizations due to CHD could be avoided across the five years. See *Table 1* below.
- **Lutein with Zeaxanthin:** Because the loss of vision is widely considered a determinant of dependency among older adults, our cost study comprises the potential avoided transitions to dependency associated with a reduction in the relative risk of AMD among the over age-65 population through daily intake of 6-10 mgⁱ of lutein with zeaxanthin. We estimate a potential cost savings of **\$2.5 billion** if approximately **98,219** individuals avoided the transition to greater dependency through not needing care in the community, and **32,740** are able to avoid admission to a nursing facility that would be necessitated by the loss of their sight from AMD over the five years. See *Table 2* below.
- **Vitamin D:** Studies have shown that a substantial number of women aged 65 and over are deficient in Vitamin D.⁵ Much of the literature on the health effects associated with Vitamin D center on its use in combination with calcium to yield positive bone health outcomes, reduced fractures and reduced risk of falls. We found that when Vitamin D is studied directly, there is a focus on changes in biomarkers versus outcomes that impact costs. While the hypothesized pathway between changes in bone density and vitamin levels in the blood, and the probability of future fractures and falls is well reasoned, the literature is largely absent on making a direct connection between vitamin D on these outcomes.⁶ Out of fourteen randomized or quasi-randomized trials, only one was a trial of Vitamin D alone. Protection against hip fracture was not confirmed in this study.⁷

⁴ The Food and Drug Administration (FDA) recommends that consumers not exceed more than a total of 3000 mg per day of EPA and DHA omega-3, with no more than 2000 mg per day from a dietary supplement.

⁵ Gaugris S, Heaney RP, Booney S, Kurth H, Bentkover JD. (2005). Vitamin D inadequacy among post-menopausal women: a systematic review. *QJM* 98(9): 667-676.

⁶ Bishoff-Ferrari HA, Willett WC, Wong JB, et al. (2005). Fracture prevention with vitamin D supplementation: A meta-analysis of randomized controlled trials. *JAMA* 293(18):2257-2264.

⁷ Gillespie WJ, Henry DA, O'Connell DL, Robertson J. (2000) Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database System Review*; 2:CD000227.

**Table 1:
Costs & Potential Savings Resulting From Reduced CHD Hospitalizations**

	2006	2007	2008	2009	2010	Total
Gross Cost of Providing Daily Omega-3 for Adults over 65 (in millions)						
Total cost of daily omega-3 for new users (adults over 65 not currently taking omega-3)	\$229	\$321	\$449	\$620	\$842	\$2,462
Potential Savings from Reduced Cases of CHD (in millions)						
Cost offset due to avoided CHD hospitalizations and physician services	\$421	\$599	\$862	\$1,242	\$1,794	\$4,919
Net Cost (Savings) of Providing Daily Omega-3 for Adults over 65, Before Premiums (in millions)						
Net cost (savings) of daily omega-3 for adults over 65	(\$192)	(\$278)	(\$412)	(\$622)	(\$952)	(\$2,456)
Premium Offset (in millions)						
Premium offset (25% of additional program spending)	\$57	\$80	\$112	\$155	\$211	\$616
Total Cost (Savings) to Payers, After Premiums (in millions)						
Total potential cost offset from avoided CHD hospitalizations (savings)	(\$250)	(\$357)	(\$525)	(\$780)	(\$1,166)	(\$3,078)

**Table 2:
Costs and Potential Savings Resulting Avoided Transition to Dependency Associated with Reduced Risk of AMD Among Adults Over Age 65**

	2006	2007	2008	2009	2010	Total
Gross Cost of Providing Daily Lutein/Zeaxanthin for Adults over 65 (in millions)						
Total cost of daily lutein/zeaxanthin for new users (adults over 65 not currently taking lutein/ zeaxanthin)	\$72	\$89	\$112	\$140	\$175	\$588
Potential Savings from Reduced Cases of AMD (in millions)						
Cost offset due to avoided transition to dependency associated with reduced risk AMD	\$379	\$461	\$562	\$686	\$838	\$2,926
Net Cost (Savings) of Providing Daily Lutein/Zeaxanthin for Adults over 65 (in millions)						
Net cost (savings) of daily lutein/zeaxanthin for adults over 65	(\$307)	(\$372)	(\$450)	(\$546)	(\$663)	(\$2,338)
Premium Offset (in millions)						
Premium offset (25% of additional program spending)	\$18	\$22	\$28	\$35	\$44	\$147
Total Cost Offset (Savings) to Payers, After Premiums (in millions)						
Total potential cost offset from avoided transition to dependency associated with reduced risk of AMD (savings)	(\$325)	(\$394)	(\$478)	(\$581)	(\$707)	(\$2,485)

II. STUDY METHODS

Analysts at The Lewin Group conducted extensive English-language searches on the internet and in print journals for relevant information on each supplement. Examples of resources used include MedLine, PubMed, Institute of Medicine, the Cochrane Library, and the NHS Economic Evaluation Database. Structured protocols were used to locate materials and evaluate their quality, paying considerable attention to issues of both internal and external validity. In our assessment of the quality of the research and the strength of the existing evidence, the underlying criterion for use in developing a cost model was “the extent to which all aspects of the study’s design and conduct can be shown to protect against systematic bias, nonsystematic bias, and inferential error.”⁸

We examined three types of studies: (1) studies that concerned the physiological effect of the supplement as indicated by biological markers; (2) studies that concerned the clinical effect of either the supplement itself or the change in the biological markers; and (3) the potential reduction in health services utilization that might result from those clinical effects (e.g., avoided hospitalizations and physician services, and avoided instances of a loss of sight due to age-related macular degeneration and subsequent transition to dependency).

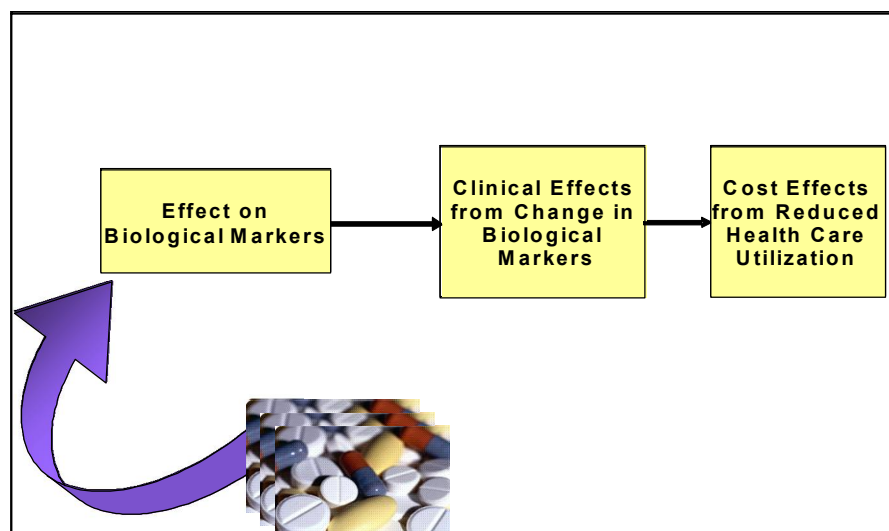
Methodologic rigor is greatest for the meta analysis and randomized controlled trial (RCT). While various observational study designs can detect associations between variables (e.g., a change in one variable is linked to a change in the value of the other), RCTs are the “gold standard” for demonstrating causation, though they may not be able to answer certain research questions. One benefit of using an evidence-based medicine classification of studies is that it allows the reader to gauge the quality of the available literature. In such a review, more weight and credibility is given to designs that control for systematic and unsystematic bias, such as RCTs, prospective cohort and case control studies. For this study, we used only the highest standard of evidence to support the development of the cost models for omega-3 fatty acids and lutein/zeaxanthin. We also evaluated the quantity of studies of various types, as well as the consistency of their findings.

Figure 1 below shows the conceptual framework for the study. For each supplement, we attempted to determine if there was sufficient evidence to support each of three casual links existed:

- 1) Does the supplement produce a physiological effect as shown by a change in biological markers? and if so;
- 2) Does this physiological effect create a positive change in health status? and if so;
- 3) Is the change in health status associated with a decrease in health care expenditures?

⁸ Carey T. (2002). *Quality of Research and the Strength of Scientific Evidence*. Presentation sponsored by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program.

Figure 1: Conceptual Framework



Cost Estimates

Using Congressional Budget Office (CBO) cost accounting approach, gross and net costs to a Medicare-like payer were determined for a five-year period (2006 – 2010). We estimated the current five-year cost of hospitalization for CHD among the country’s seniors to be approximately \$81 billion. We estimated the five year cost of related physician services for CHD to be approximately \$11 billion. Potential savings could be achieved through avoided hospitalizations and physician visits for some number of individuals who had taken omega-3 fatty acids thus achieving a reduction in the risk of CHD.

Likewise, each year approximately 2 percent of seniors are no longer able to function independently and find themselves in the transition to greater dependency. There is a cost associated with that transition that could be avoided if they were able to remain independent. We estimated that over the five year period, 98,219 seniors could avoid the one-year transition cost associated with becoming dependent in the community, and 32,740 seniors could avoid the one-year transition cost associated with transitioning to a nursing facility if a proportion of seniors took lutein on a daily basis and achieved a reduction in the risk of having AMD.

III. FINDINGS FROM THE LITERATURE REVIEW

Consistent with the conceptual framework, we sought to answer each of the above questions for both supplements. For omega-3 fatty acids, we found hundreds of studies dating back nearly thirty years. We found several comprehensive reviews, including two conducted by the Agency for

Healthcare Research and Quality (AHRQ) of the health effects of omega-3 fatty acids on cardiovascular risk factors and the health effects of omega-3 fatty acids on cardiovascular disease.^{9, 10}

In addition, the Food and Drug Administration (FDA) recently announced the availability of a qualified health claim for reduced risk of coronary heart disease (CHD) on conventional foods that contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids. (Earlier, in 2000, FDA announced a similar qualified health claim for dietary supplements containing EPA and DHA omega-3 fatty acids and the reduced risk of CHD.) FDA identified the following endpoints to use in identifying CHD risk reduction for purposes of a health claim evaluation for EPA and DHA omega-3 fatty acids: coronary events (MI, ischemia), cardiovascular death, atherosclerosis, and high blood pressure.

The literature for lutein is less well developed and dates back about fifteen years. There were approximately 75 publications with not nearly as many clinical trials as for omega-3 fatty acids. The Agence Francaise de Securite Sanitaire des Aliments evaluated the scientific merit of the health claims that have been made concerning lutein's protective effect on the lens and retina and found that the allegation that lutein contributes to the protection of the retina and lens from oxidation is substantiated by the scientific evidence.¹¹

The FDA evaluated the scientific evidence for the health claim that lutein and zeaxanthin could reduce the risk of AMD in the general population. The agency concluded that the evidence for the health effect in the general population was insufficient to support the claim, as the studies supporting the relationship were conducted with individuals diagnosed with AMD. FDA said that this evidence could not be generalized to the general population.¹²

We summarize the findings from our literature review below, followed by a presentation of our full cost models with explanatory notes. Additionally, the Appendix to this report contains evidence tables presenting the highlights of the studies that were reviewed for this project.

1. Omega-3 fatty acids

According to the American Heart Association, coronary heart disease (CHD) is the leading cause of death in both men and women in the United States, causing almost 500,000 deaths annually.¹³ Each year, 1.1 million Americans have a myocardial infarction (MI) or fatal CHD; 650,000 are first events, and 50% of men and 63% of women who die suddenly of CHD have no prior symptoms. In addition to the enormous human cost, the total economic cost of CHD each year is estimated at \$368 billion, including direct costs for hospitals and nursing homes, physicians and other health care professionals, drugs, and home health and other medical durables, as well as indirect costs for lost productivity caused by morbidity and mortality. The condition disproportionately affects older individuals, with the average age of an individual having a first heart attack being 65.8 for men and 70.4 for women.

⁹ Agency for Healthcare Research and Quality (2004) *Health Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease*. (Publication No. 04-E010-1)

¹⁰ Agency for Healthcare Research and Quality (2004) *Health Effects of Omega-3 Fatty Acids on Cardiovascular Disease* (Publication No. 04-E009-2).

¹¹ Agence Francaise de Securite Sanitaire des Aliments. Maisons-Alfort, le 23 janvier 2004.

¹² U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition. Docket No. 2004Q-0180. December 19, 2005.

¹³ American Heart Association. 1999 2000 *Heart and stroke statistical update*. Dallas, TX: American Heart Association.

There are three major types of omega-3 fatty acids: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The major source of omega-3 fatty acids is dietary intake of fish (e.g., salmon or sardines), fish oil, vegetable oils (e.g., canola and soybean), certain nuts (e.g., walnuts) and dietary supplements. The early epidemiology studies conducted in the late 1970s and early 1980s noted very low cardiovascular mortality in populations with high fish consumption. Since these early studies, hundreds of observational and clinical trials have been conducted to analyze the effect of both marine and plant sources of omega-3 fatty acids on CHD and a wide range of risk factors and intermediate markers of CHD, and to define and explain the potential benefits of increased intake of the omega-3 fatty acids.

In our earlier report, we found that although studies of omega-3 fatty acids were heterogeneous in that they examined different forms of omega-3 fatty acids, there were three important and very compelling pieces. The largest controlled trial of omega-3 fatty acids supplement with over 11,000 patients was conducted by Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Patients with heart disease received omega-3 fatty acids supplements (850 mg per day of EPA and DHA) for 3.5 years. The study found that patients who took the omega-3 fatty acid supplement had a risk of sudden death from heart failure that was 45 percent lower than those who did not. Furthermore, patients who took the supplement had a 20 percent lower risk of death from all-cause mortality.¹⁴

Results from a trial conducted by Singh¹⁵ showed patients admitted to the hospital with an acute myocardial infarction who were randomized to receive three different conditions: 1) capsules containing fish oil (1.8 g per day of EPA and DHA); 2) mustard seed oil (2.9 g per day of ALA); or 3) a placebo. Total cardiac events (including non-fatal myocardial infarction) were significantly lower in the groups that received the fish oil or mustard seed oil compared to groups receiving the placebo after one year.

Finally, a review of current studies conducted by Holub¹⁶ highlighted the various biological markers of CVD that have been shown to be affected by the increased consumption of omega-3 fatty acids. Specifically, fatty acid analysis of serum and plasma phospholipids indicated that DHA levels are inversely related to coronary heart disease in men.¹⁷

Building on our earlier report, this review also found evidence that omega-3 fatty acids are associated with reduced risk of CHD among those diagnosed with recent myocardial infarctions. Several different mechanisms of action or biomarkers are reported in the intervention studies, including decreased triglyceride levels, decreased inflammation, decreased blood clot formation, and improved vascular endothelial function.

¹⁴ Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet*. 1999;354(9177):447-455.

¹⁵ Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival-4. *Cardiovasc Drugs Ther*. 1997;11(3):485-491.

¹⁶ Holub, Bruce J. (2002). Clinical Nutrition 4. Omega-3 Fatty Acids in Cardiovascular Care. *JAMC*, 5 Mars 2002; 166(5) 608-615.

¹⁷ From the Holub review reference of Simon, JA, Hodgkins, ML, et al. (1995). Serum Fatty Acids and the Risk of Coronary Heart Disease. *Am J Epidemiol*, 1995; 142: 469-476.

Most evidence for the health effects of omega-3 fatty acids in the general population (primary prevention studies) is from observational studies conducted worldwide. Although the observational evidence shows mixed effects, because the biomarkers in both diagnosed and the general population respond in a similar way to omega-3 fatty acids, FDA considered that the research evidence was “suggestive” of a relationship between omega-3 fatty acids and reduced risk of CHD in the general population. FDA considered two randomized, placebo-controlled, double-blind intervention studies identified since their initial 2000 review¹⁸ as capable of supporting the substance/disease relationship^{19, 20} although no clinical benefit was observed in these studies. Given the inability of predicting CHD risk reduction in a general healthy population based on secondary prevention studies in diseased populations, and the limitations of the observational studies in separating the effects of EPA and DHA omega-3 fatty acids from other dietary factors, the agency evaluated several other pieces of available evidence.

In terms of observational studies, Hu et al.²¹ reported results from the Nurses' Health Study, a prospective cohort study on female registered nurses (n=84,688) with a 16 year follow-up. Fish and omega-3 fatty acid intake were calculated as an average intake from all available dietary questionnaires up to the start of each 2-year follow-up interval in which events were reported. There was an inverse correlation observed between fish/omega-3 fatty acid consumption and incidence of CHD, including CHD deaths and nonfatal MI. A subgroup analysis of diabetic nurses from this cohort (n=5,103) observed a reduced risk of CHD from fish consumption but the association did not extend to estimated EPA and DHA omega-3 fatty acid consumption.²²

Albert et al.²³ was a case-control study nested in the U.S. Physicians Health Study, which was considered in our earlier review. The nested case-control study had a 17-year follow-up and reported a significant inverse relationship between whole blood omega-3 fatty acid concentrations and CHD death.

FDA still concludes that the weight of the scientific evidence for a health claim for EPA and DHA omega-3 fatty acids outweighs the scientific evidence against such a claim. The observational studies estimating EPA and DHA omega-3 fatty acid intake from conventional foods support the expansion of the existing qualified health claim for EPA and DHA omega-3 fatty acids from dietary supplements and CHD to conventional foods. The Institute of Medicine (IOM) of the National

¹⁸ Earlier, in 2000, FDA announced a qualified health claim for dietary supplements containing EPA and DHA omega-3 fatty acids and the reduced risk of CHD. FDA recommends that consumers not exceed more than a total of three grams per day of EPA and DHA omega-3 fatty acids, with no more than 2 grams per day from a dietary supplement.

¹⁹ Finnegan, Y.E., A.M. Minihane, E.C. Leigh-Firbank, S. Kew, G.W. Meijer, R. Muggli, P.C. Calder, and C.M. Williams. Plant- and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects. *American Journal of Clinical Nutrition*. 2003;77(4):783-795.

²⁰ Woodman, R.J., T.A. Mori, V. Burke, I.B. Puddey, G.F. Watts, and L.J. Beilin. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *American Journal of Clinical Nutrition*. 2002;76(5):1007-1015.

²¹ Hu FB, Bronner L, Willett WC, et al. (2002) Fish and Omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA*. 287: 1815-1821.

²² Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. (2003) Fish and long-chain ω -3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation*.107(14):1852-1857.

²³ Albert CM, Campos H, Stampfer MJ, et al. (2002) Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *The New England Journal of Medicine*. 346(15):1113-1118.

Academy of Sciences has stated in its most recent Macronutrient Report that "*Growing evidence suggests that dietary n-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) reduce the risk of coronary heart disease (CHD) and stroke.*"^{24, 25}

2. Lutein with Zexanthin

Approximately 17.0 million older persons have symptoms of age-related macular degeneration (AMD), with 1.75 million having advanced or "wet" AMD.²⁶ AMD occurs when the fragile center of the retina—i.e., the macula—deteriorates from a lifetime of slow but steady damage. AMD is a complex disorder, involving genetic, cardiovascular, and environmental components. From a cardiovascular standpoint, AMD is caused by hardening of the arteries that nourish the retina. This deprives the sensitive retinal tissue of oxygen and nutrients that it needs to function and thrive. As a result, the central vision deteriorates. AMD has also been associated with smoking, which depletes serum antioxidants, physical inactivity, overexposure to sunlight, and cardiovascular disease.

According to AMD Alliance International, dry AMD, the more common and milder form of AMD, accounts for 85% to 90% of all cases. AMD develops gradually over time and usually causes only mild loss of vision. About 10% of patients who suffer from macular degeneration have wet AMD. This type occurs when new vessels form to improve the blood supply to oxygen-deprived retinal tissue. However, the new vessels are very delicate and break easily, causing bleeding and damage to surrounding tissue. Wet AMD has historically received the most attention, but dry AMD has a risk of progressing to intermediate and wet AMD.

One key identifier for AMD is the collection of small, round, white-yellow, fatty deposits called drusen in the central part of the retina. Drusen accumulate in the retina pigment epithelium (RPE) tissue beneath the macula and the macula thins and dries out. The amount of vision loss is related to the location and amount of macular thinning caused by the drusen. Sometimes abnormal new blood vessels form. It is therefore important for individuals with dry AMD to have their eyes examined regularly, in order to minimize loss of vision and maximize their quality of life.

There is no proven medical therapy for dry macular degeneration. In selected cases of wet macular degeneration, laser photocoagulation is effective for sealing leaking or bleeding vessels. Unfortunately, laser photocoagulation usually does not restore lost vision, but it may prevent further loss.

AMD has been referred to as a "nutrition-responsive disease."²⁷ Epidemiological studies have found associations between dietary intake of lutein and zeaxanthin and protection from AMD.^{28,29,30} There

²⁴ Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids, Part 2, Chapter 11, Page 11-40 (Institutes of the Medicine of the National Academies, 2002)

²⁵ <http://www.cfsan.fda.gov/~dms/ds-ltr38.html#ftn53>

²⁶ Congdon N, O'Colmain B, Klaver CC et al. (2004) Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol*. 122(4):477-485.

²⁷ Richer S. (1999). A protocol for the evaluation and treatment of atrophic age-related macular degeneration. *J Amer Optom Assn* 70(1): 13-23.

²⁸ Snodderly DM. (1995). Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins. *Am J Clin Nutr* 62S:1488S-1461S.

²⁹ Seddon JM, Ajani UA, Sperduto RD, ET AL. (1994) Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA* 272: 1413-1420.

has also been increasing evidence that lutein and zeaxanthin, both present in the macular pigment (MP) of the human eye are linked to a reduction in risk for AMD.^{31,32,33} Lutein is a yellow pigment which absorbs blue light, protecting the underlying photoreceptor cell layer from light damage. Lutein also acts as an antioxidant protecting the retina from oxidative degradation.³⁴

Correlations have been found between dietary lutein and zeaxanthin, serum levels, and the macula.^{35,36,37,38} Intervention studies have found (1) a dose response relationship between oral lutein supplementation and serum lutein levels,³⁹ (2) that lutein supplementation vs. placebo showed improvements in retinal function,⁴⁰ and (3) that lutein supplementation vs. placebo showed both increased macular pigment density and improved visual function.⁴¹

According to the conceptual framework used in the study, there are three questions that the literature must answer in order for the evidence to be sufficiently rigorous to support the development of a cost estimate. Studies in the literature are organized and examined in terms of these three questions:

- 1) Does the supplement produce a physiological effect as shown by a change in biological markers? and if so;
- 2) Does this physiological effect create a positive change in health status? and if so;
- 3) Is the change in health status associated with a decrease in health care expenditures?

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- ³⁰ Goldberg J, Flowerdew G, Smith E, et al. (1988). Factors associated with age-related macular degeneration: an analysis of data from the First National Health and Nutritional Survey. *Am J Epidemiol* 128:700-710.
- ³¹ Gale CR, Hall NE, Phillips DI, Martyn CN. (2003) Lutein and zeaxanthin status and risk of age-related macular degeneration. *Invest Ophthalmol Vis Sci* 44 (6):2461-2465.
- ³² Beatty S, Murray IJ, Henson DB, et al. (2001) Macular pigment and risk for age-related macular degeneration in subjects from a northern European population. *Invest Ophthalmol Vis Sci* 42(2): 439-446.
- ³³ Young IS, Fletcher AE, Chakravarthy U, et al. (2004) Lutein, zeaxanthin, vitamin C and age-related maculopathy in the EUREYE study. *Invest Ophthalmol Vis Sci* 45(5): 3038.
- ³⁴ Krinsky NI, Landrum JT, Bone RA (2003). Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. *Annu Rev Nutr* 23:171-201.
- ³⁵ Beatty S, Nolan J, Kavanaugh H, O'Donovan O. (2004) Macular pigment optical density and its relationship with serum and dietary levels of lutein and zeaxanthin. *Arch Biochem and Biophysics* 430(1): 70-76.
- ³⁶ Aleman TS, Cideciyan AV, Chico JD, et al. (2004) Macular pigment and lutein supplementation in macular diseases. *Invest Ophthalmol Vis Sci* 4(45): 2972.
- ³⁷ Berendschott TT, Goldbohm RA, Klopping WA, et al. (2000). Influence of lutein supplementation on macular pigment, assessed with two objective techniques. *Invest Ophthalmol Vis Sci* 41:3322-3326.
- ³⁸ Johnson EJ, Hammond BR, Yeum KJ, et al. (2000) Relation among serum and tissue concentrations of lutein and zeaxanthin and macular pigment density. *Am J Clin Nutr* 71:1555-1562.
- ³⁹ Chew EY, Ferris FL, de Monasterio FM, et al. (2003) Dose ranging study of lutein supplementation in persons over age 60. *Invest Ophthalmol Vis Sci* 44(5): 968.
- ⁴⁰ Falsini B, Piccardi M, Iarossi G, et al. (2003). Influence of short term antioxidant supplementation on macular function in age-related maculopathy: A pilot study including electrophysiologic assessment. *Ophthalmol* 110: 51-60.
- ⁴¹ Richer S, Stiles W, Statkute L, et al. (2004) Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry* 75: 216-230.

Does the supplement produce a physiological effect as shown by a change in biological markers?

Macular pigment in the retina contains only lutein and zeaxanthin to the exclusion of other carotenoids, and the concentration of lutein and zeaxanthin is approximately 500 times higher than in other body tissues.⁴² Furthermore, the distribution of lutein and zeaxanthin in the retina suggests a protective role.^{43, 44, 45} Tissue concentrations of lutein and zeaxanthin vary across individuals, this variation reflects both diet and genetic factors.⁴⁶

There are several studies that show that diet will influence lutein and zeaxanthin concentrations.⁴⁷ These studies show increases in macular pigment density associated with taking supplements containing these carotenoids.^{48,49} Beatty et al. reviewed the observational studies of the relationship between dietary intake of lutein and zeaxanthin and serum levels and found that all demonstrated a positive relationship. The largest study, which included 2,786 subjects, found that demographic characteristics, dietary lutein and zeaxanthin intake, serum cholesterol concentration, and lifestyle factors explained 24 percent of the variance in serum lutein concentration, and that every 10 percent increase in estimated dietary intake of lutein and zeaxanthin was associated with a 2.4 percent increase in serum lutein concentration.⁵⁰ Additionally, there are numerous studies of the bioavailability⁵¹ of lutein, with the weight of the evidence being that lutein is absorbed in a similar way to other carotenoids.⁵²

Does this physiological effect create a positive change in health status?

Evidence of the presence of a protective role for lutein with zeaxanthin has been found in numerous studies, both controlled and uncontrolled. Observational studies found that people with AMD tended to have low macular pigment density, and that there is an age-related decline in optical density of macular pigment.⁵³ The Eye Disease Case-Control Study Group (EDCCSG) reported a reduced risk for advanced, neovascular “wet” AMD in subjects having either high levels of lutein

⁴² Bone RA, Landrum JT, Hime G et al. (1991) Stereochemistry of the macular carotenoids. *Investig Ophthalmol Vis Sci* 34:2033-2040.

⁴³ Schmitz HH, Poor CL, Gugger ET, Erdman JW. (1993) Analysis of carotenoids in human and animal tissues. *Methods Enzymol* 214:102-116.

⁴⁴ Bone RA, Landrum JT (1992) Distribution of macular pigment components, zeaxanthin and lutein, in human retina. *Methods Enzymol* 213:360-367.

⁴⁵ Sommerburg O, Siems GW, Hurst SJ, et al (1999) Lutein and zeaxanthin are associated with photoreceptors in the human retina. *Curr Eye Res* 19:491-495.

⁴⁶ Hammond BR, Curran-Celentano J, Judd S (1996) Sex differences in macular pigment optical density: relation to plasma carotenoid concentrations and dietary patterns. *Vis Res* 36:2001-2012.

⁴⁷ Landrum JT, Bone RA, Joa H, et al (1997). A one-year study of the macular pigment:the effect of 140 days of a lutein supplement. *Exp Eye Res* 64:57-62.

⁴⁸ Johnson E, Hammond RB, Yeum KJ et al (2000) Relation among serum tissue concentrations of lutein and zeaxanthin and macular pigment density. *Am J Clin Nutr* 71:1555-1562.

⁴⁹ Landrum JT, Chen Y, et al. (2000) Serum and macular pigment response to 2.4 mg dosage of lutein. *ARVO* 41(4):S60.

⁵⁰ Beatty S, Nolan J, Kavanaugh H, O'Donovan O. (2004) Macular pigment optical density and its relationship with serum and dietary levels of lutein and zeaxanthin. *Arch Biochemistry and Biophysics*, 430(1): 2004.

⁵¹ Bioavailability means the fraction of an ingested nutrient that is available to the body for utilization in normal physiological functions or for storage. Many factors affect bioavailability including nutrient status of the host, genetic factors, amount of nutrient consumed, etc.

⁵² Yeum KJ, Russell RM (2002) Carotenoid bioavailability and bioconversion. *Ann Rev Nutr* 22:483-504.

⁵³ Beatty S, Boulton M, Henson D. (1999). Macular pigment and age-related macular degeneration. *Br J Ophthalmol* 83:867-877.

and zeaxanthin in their serum or in their diet. The investigators divided patients into three groups, based on the blood levels of various micronutrients. Patients in the group with the highest levels of carotenoids had the lowest incidence of AMD.⁵⁴ Bone and colleagues found that macular pigment may be an “important determinant” of retinal health particularly in later life when they examined donor eyes with and without AMD. They were able to estimate the association between low levels of lutein and zeaxanthin and risk of AMD.^{55 56} Several randomized controlled trials found that dietary supplementation with lutein resulted in both macular pigment density increases and improvement in visual functioning.⁵⁷

Several recent pilot trials investigated whether lutein may also be beneficial for patients who already suffer from AMD. In a pilot study conducted by Olmedilla, visual acuity improved, and the patients became less sensitive to glare.⁵⁸ There was no control group used in this study, however. Falsini and colleagues demonstrated improved retinal function with lutein supplementation, both in patients with early AMD, as well as in normal ageing.⁵⁹ These results await confirmation from larger scale placebo-controlled trials.

Not all studies have found a significant relationship between lutein and zeaxanthin and reduced risk of AMD, however. A small case control study using the population from the Beaver Dam Eye Study found no association.⁶⁰ The Blue Mountains Eye Study in Australia used a 145-item Food Frequency Questionnaire (FFQ) to assess intake of 11 micronutrients (*i.e.*, alpha-carotene, beta-carotene, lutein and zeaxanthin, etc.) among 2335 persons aged 49 years or older who attended a 5-year follow-up visit. After adjusting for known AMD risk factors, no significant associations or trends in the positive direction were found between dietary intake of antioxidants or dietary intake combined with modest amounts of antioxidant or zinc supplements at baseline and the incidence of early AMD.⁶¹

In summary, various risk factors have been identified in the development of AMD, which are consistent with the premise that oxidative stress plays an important role. The possibility that antioxidant balance can be manipulated through diet or supplementation has created much interest in the literature. Associations between diet and nutrition and the clinical features of AMD have been well described. There is consistency in the report of notable reductions in serum micronutrients in wet AMD, however, the evidence for causation is still circumstantial. In our review of the clinical

⁵⁴ Seddon JM, Ajani UA, Sperduto RD, et al. (1994) Dietary carotenoids, vitamins A,C,and E, and advanced age-related macular degeneration. *JAMA* 272: 1413-1420.

⁵⁵ Bone RA, Landrum JT, Mayne ST, et al. (2001). Macular pigment in donor eyes with and without AMD: A case-control study. *Inv Ophthalmol Vis Sci* 42(1): 235-240.

⁵⁶ Bone RA, Landrum JT, Dixon Z, et al. (2000) Lutein and zeaxanthin in the eyes, serum, and diet of human subjects. *Exp Eye Res* 71:239-245.

⁵⁷ Richer S, Stiles W, Statkute L, et al. (2004) Double masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry* 75(4):216-230.

⁵⁸ Olmedilla BF, Granado I, Blanco M, et al. (2001) Lutein in patients with cataracts and age-related macular degeneration: a long-term supplementation study. *Journal of Science Food Agriculture*, 81:904-909.

⁵⁹ Falsini B, Piccardi M, Iarossi G, Fadda A, Merendino E, Valentini P. Influence of short-term antioxidant supplementation on macular function in age-related maculopathy: a pilot study including electrophysiologic assessment. *Ophthalmology*. 2003;110(1):51-60.

⁶⁰ Mares-Perlman JA, Brady WE, Klein R, et al. (1995) Serum antioxidants and age-related macular degeneration in a population-based case-control study. *Arch Ophthalmol* 113:1518-1523.

⁶¹ McBee WL, Lindblad AS, Ferris FL (2003) Who should receive oral supplement treatment for age-related macular degeneration? *Curr Op Ophthal* 14(3): 159-162.

literature, we evaluated the evidence for the premise that lutein and zeaxanthin exert a protective effect against the development of AMD. Initial support appears to be moderate, but the evidence that lifetime oxidative stress plays an important role in the development of AMD is very compelling. The positive outcomes in the Age-Related Eye Diseases Study, a major controlled clinical trial, and the LAST study, have given hope that modulation of the antioxidant balance through supplementation with lutein and zeaxanthin can help prevent progression of dry AMD to wet AMD.

Although FDA found no credible science to support the health claim for lutein and zeaxanthin in reducing risk of AMD, there are several important omissions to their review: none of Richer's work is considered (the LAST trial), nor is the work of Chew or the 2004 paper by Beatty and colleagues that quantifies the relationship between serum and dietary intake of lutein and zeaxanthin. The agency said that because scientific information is subject to change, it intends to evaluate information that becomes available to determine whether it necessitates a change in their determination.

There are ongoing work to determine the effect of lutein on measures of visual function in people with and without age-related macular disease.⁶² Additionally, the National Eye Institute is currently recruiting participants for a study of the role of lutein in reducing the risk of AMD. This study will complement the AREDS-II randomized trial currently being planned for 2006 which will involve a large number of sites and run for seven years. Pending the results of the controlled studies currently or soon-to-be underway, we developed a preliminary estimate of potential five-year (2006-2010) net savings associated with lutein and zeaxanthin supplementation.

Is the change in health status associated with a decrease in health care expenditures?

Because there is no widely accepted or effective treatment for AMD, we could not use reductions in health care expenditures as a metric. We therefore used the savings that might accrue if a proportion of older individuals with dry AMD were to avoid losing their sight through disease progression to wet AMD and transition to greater dependency.

IV. ESTIMATES OF COST SAVINGS

In this section of the report, we present our cost models.

⁶² Bartlett H, Eperjesi F. (2003). A randomized controlled trial investigating the effect of nutritional supplementation on visual function in normal, and age-related macular disease affected eyes: design and methodology. *Nutr J* 2:12-19.

Cost Estimation for Daily Omega-3 for Medicare Beneficiaries (Cost offsets derived from Avoided Coronary Heart Disease: 2006 to 2010)

	2005	2006	2007	2008	2009	2010	Total
Gross Cost Estimate of Daily Omega-3 Fatty Acids for Medicare Beneficiaries							
1 Projected Number of Medicare Beneficiaries	41,882,000	42,506,000	43,256,000	44,102,000	44,995,000	45,952,000	
2 Projected Number of Aged Medicare Beneficiaries	35,850,992	36,385,136	37,027,136	37,751,312	38,515,720	39,334,912	
3 Percent of Aged Medicare Beneficiaries Estimated to Take Omega-3 Currently and Pay Out-of-Pocket	3%	5%	6%	9%	13%	18%	
4 Number of Aged Medicare Beneficiaries Estimated to Take Omega-3 Currently and Pay Out-of-Pocket	1,167,185	1,819,257	2,221,628	3,397,618	5,007,044	7,080,284	
5 Percent of Aged Medicare beneficiaries Not Taking Omega-3 (Potential New Users)	97%	95%	94%	91%	87%	82%	
6 Potentially Eligible Group: Number of Aged Medicare Beneficiaries not Taking Omega-3	34,683,807	34,565,879	34,805,508	34,353,694	33,508,676	32,254,628	
7 Take-up Rate - includes new users and switchers (1%)	12%	16.5%	22.7%	31.2%	42.9%	59.0%	
8 Number of New Users	4,162,057	5,703,370	7,896,500	10,716,742	14,373,062	19,023,340	
9 Average Annual Cost of Daily Omega-3 (Excluding Beneficiary Co-payment of 20%)	\$38.91	\$39.88	\$40.88	\$41.90	\$42.95	\$44.02	
10 Gross Cost for Daily Omega-3 for Aged Medicare Beneficiaries Who are New Users	\$161,934,716	\$227,450,753	\$322,785,717	\$449,020,677	\$617,272,225	\$837,409,842	\$ 2,453,939,215
Current Cost of CHD in Aged Medicare Beneficiaries							
11 Total Discharged Aged Beneficiaries with CHD	1,384,051	1,411,732	1,439,967	1,468,766	1,498,142	1,528,104	7,346,712
12 Take-up Rate	12%	16.5%	22.7%	31.2%	42.9%	59.0%	
13 Number Beneficiaries with CHD Who Now Take Omega-3	166,086	232,936	326,873	458,255	642,703	901,255	2,562,021
14 Average spending physician services for CHD	\$1,407	\$1,449	\$1,481	\$1,515	\$1,548	\$1,583	
15 Total physician service cost of CHD	\$1,947,360,171	\$2,045,600,132	\$2,132,591,077	\$2,225,180,953	\$2,319,123,246	\$2,418,989,367	\$11,141,484,775
16 Total Hospital Service Cost of CHD	\$14,362,186,000	\$14,947,666,128	\$15,473,403,386	\$16,190,317,829	\$16,990,872,290	\$17,863,118,195	\$81,465,377,828
17 Average Hospital Service Cost of CHD	\$10,377	\$10,588	\$10,746	\$11,023	\$11,341	\$11,690	
Potential Cost Offset Associated with Avoided CHD in Aged Medicare Beneficiaries who can Benefit from Daily Omega-3							
18 Reduction in CHD Associated with Omega-3	15%	15%	15%	15%	15%	15%	
19 Potential Number of Avoided CHD Discharges from Omega-3	24,913	34,940	49,031	68,738	96,405	135,188	384,303
20 Cost offset for avoided hospitalizations	\$258,519,348	\$369,954,737	\$526,869,385	\$757,706,874	\$1,093,362,632	\$1,580,313,564	\$4,328,207,192
21 Cost offset for avoided physician charges	\$35,052,483	\$50,628,603	\$72,614,726	\$104,138,469	\$149,235,581	\$214,003,046	\$590,620,425
Net Cost Estimate of Medicare Coverage of Daily Omega-3							
22 Gross cost of daily omega-3 for aged Medicare beneficiaries	\$161,934,716	\$227,450,753	\$322,785,717	\$449,020,677	\$617,272,225	\$837,409,842	\$2,453,939,215
23 Total cost offsets (potential savings) from avoided CHD due to omega-3	\$293,571,831	\$420,583,340	\$599,484,111	\$861,845,343	\$1,242,598,213	\$1,794,316,610	\$4,918,827,617
24 Net cost of Medicare coverage of daily omega-3 for aged Medicare beneficiaries - expressed as savings	\$131,637,115	\$193,132,587	\$276,698,394	\$412,824,666	\$625,325,988	\$956,906,768	\$2,464,888,403
25 Premium Offset. Twenty-five percent of the gross cost of the intervention.	\$40,483,679	\$56,862,688	\$80,696,429	\$112,255,169	\$154,318,056	\$209,352,461	\$613,484,804
26 Total potential cost offset from avoided health care utilization associated with avoided omega-3	\$172,120,794	\$249,995,275	\$357,394,823	\$525,079,835	\$779,644,044	\$1,166,259,229	\$3,078,373,206

\$3,078,373,206

Notes to Cost Estimation supported by Summary of Evidence.

Line numbers correspond to the numbered rows

Gross Cost Estimate of Daily Omega-3 for Aged Medicare Beneficiaries

1	The projected number of total Medicare beneficiaries for 2005 to 2010. Source: 2005 Medicare Combined Board of Trustees Annual Report.
2	The projected number of aged Medicare beneficiaries. Non-elderly, disabled Medicare beneficiaries comprise about 14.4 percent of the total Medicare population.
3	NHANES 1999-2000 data estimated that 1.2 percent of the sample take omega-3. Using 1.2 percent as a base, this percentage was grown by 7 percent each year until 2005.
4	Number of aged Medicare beneficiaries estimated to currently take omega-3 and pay out-of-pocket: (Row 2 * Row 3 = Row 4).
5	Percent of aged Medicare beneficiaries currently not taking omega-3 (potential new users): (100 percent minus Row 3 = Row 5)
6	Potentially Eligible Group - Number of aged Medicare beneficiaries not taking omega-3 (potential new users). (Row 2 * Row 5 = Row 6).
7	Take-up rate: 1. Proportion of new users among potential eligibles. We have assumed a take-up rate of 12 percent in the first year and increasing by 20 percent in subsequent years. Also 1% of current users would become switchers.
	Switchers are those currently taking the supplement and paying out of pocket who would take up the benefit - not all current users would switch.
8	Number of new users: (Row 6 * Row 7 = Row 8).
9	Average annual cost of omega-3 (excluding patient copayment of 20% is assumed because Medicare and other fee-for-service payers generally use 80/20 benefit). This cost reflects a synthesis of costs of multiple brands rather than any specific one. Inflated by approximately 2.5% each year.
10	Gross cost for omega-3 for aged Medicare beneficiaries who are new users: (Row 8 * Row 9 = Row 10).

Current Cost of CHD in Aged Medicare Beneficiaries

11	The total number of aged Medicare beneficiaries with CHD. Figure estimated from 2002 hospital discharges of Medicare beneficiaries in short-stay hospitals. Figure inflated by 3 percent annually (Source: Crimmins and Saito. Change in the Prevalence of Diseases Among Older Americans: 1984-1994).
12	Take-up rate: Same as Row 7.
13	Number Beneficiaries with CHD Who Take Omega-3: (Row 11 * Row 12 = Row 13)
14	Average annual spending for physician services for CHD - Decomposing the Change in Medicare Expenditures for Physician Services in <i>Determinants of Increases in Medicare Expenditures for Physician Services</i> . AHRQ Technical Review. Pub No 04-0008, Oct 2003. Inflated from 1998 using Medicare Economic Index (actual and forecasted from CMS Actuary)
15	Calculated: Row 11 * Row 14 = Row 15
16	Total Hospital Service Cost of CHD: Figure estimated from 2002 total Medicare program payments for short-stay hospitals. Figure inflated by actual and projected hospital growth rates.
17	Average Cost of CHD: Row 16 / Row 11 = Row 17

Potential Cost Offsets Associated with Avoided Hospitalization of Aged Medicare Beneficiaries with CHD who can Benefit from Daily Omega-3

18	Source: Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction. Results of the GISSI Prevenzione trial: Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico. <i>Lancet</i> 1999 Aug 7; 354(9177): 447-55.
19	Number of Avoided CHD from Omega-3: (Row 19 = Row 11 * Row 18)
20	Cost offsets (potential savings) from avoided hospitalizations for CHD: (Row 20 = Row 19 * Row 17)
21	Cost offsets for avoided physician charges: (Row 21 = Row 14 * Row 19)

Net Cost Estimate of Medicare Coverage of Daily Omega-3

22	Gross cost of daily Omega-3 for aged Medicare beneficiaries: Row 10.
23	Total cost offsets (potential savings) from avoided CHD due to omega-3 intake: (Row 23 = Row 21 + Row 20)
24	Net cost of Medicare coverage of daily omega-3 for aged Medicare beneficiaries - (Row 24= Row 23 - Row 22)
25	Premium Offset. Twenty-five percent of the gross cost of the intervention. Row 25 = Row 10 * 0.25
26	Total potential cost offset from avoided hospitalization for CHD (Row 26 = Row 24 + Row 25)

Cost Estimation for Daily Lutein with Zeaxanthin for Aged Medicare Beneficiaries (Cost offsets derived from Reduced Risk of AMD Progression among those with AMD who lose Independence: 2006 - 2010)

	Baseline - 2004	2005	2006	2007	2008	2009	2010	Total	
Gross Cost Estimate of Daily Lutein for Aged Medicare Beneficiaries									
1	Projected number of aged Part A Medicare beneficiaries	35,065,000	35,850,992	36,385,136	37,027,136	37,751,312	38,515,720	39,334,912	
2	Percent of aged Medicare beneficiaries estimated to take lutein currently and pay out of pocket	13.5%	13.5%	13.7%	14.7%	15.7%	16.7%	17.7%	
3	Number of aged Medicare beneficiaries estimated to take lutein currently	4,733,775	4,311,879	4,984,764	5,442,989	5,926,956	6,432,125	6,962,279	
4	Percent of aged Medicare beneficiaries not taking lutein (potential new users)	86.5%	86.5%	86.3%	85.3%	84.3%	83.3%	82.3%	
5	Potentially Eligible Group - Number of aged Medicare beneficiaries not taking lutein (potential new users)	30,331,225	31,011,108	31,400,372	31,584,147	31,824,356	32,083,595	32,372,633	
6	Take up rate - Proportion of new users among potentially eligible group	5%	6.05%	7.32%	8.86%	10.72%	12.97%	15.69%	
7	Number of new users	1,516,561	1,876,172	2,298,664	2,797,662	3,410,917	4,160,829	5,079,959	
8	Average Annual Cost of Daily Lutein with Zeaxanthin (excluding beneficiary co-payment of 20%)	\$29.75	\$30.49	\$31.26	\$32.04	\$32.84	\$33.66	\$34.50	
9	Gross cost for daily lutein for aged Medicare beneficiaries who are new users or switchers	\$45,117,697	\$57,211,521	\$71,847,266	\$89,630,090	\$112,009,160	\$140,050,987	\$175,263,067	\$588,800,570
Reduction in Risk of AMD in Aged Medicare Beneficiaries who can Benefit from Daily Lutein									
10	Number of aged beneficiaries with symptoms of AMD	17,000,000	17,500,000	18,000,000	18,500,000	19,000,000	19,500,000	20,000,000	
11	Number of aged beneficiaries with symptoms who do not take lutein currently	12,266,225	13,188,121	13,015,236	13,057,011	13,073,044	13,067,875	13,037,721	
12	Number of beneficiaries with advanced AMD	1,750,000	1,767,500	1,785,175	1,803,027	1,821,057	1,839,268	1,857,660	
13	Number of beneficiaries with symptoms of AMD who do not currently have AMD or take lutein	10,516,225	11,420,621	11,230,061	11,253,984	11,251,987	11,228,607	11,180,060	
14	Proportion of new users with increased macular pigment density	39%	39%	39%	39%	39%	39%	39%	
15	Number of new users with increased macular pigment density	591,459	731,707	896,479	1,091,088	1,330,258	1,622,723	1,981,184	
16	Proportion of new users with increased macular pigment density resulting in reduced risk of AMD	43%	43%	43%	43%	43%	43%	43%	
17	Number of new users with increased macular pigment density and reduced risk of AMD	254,327	314,634	385,486	469,168	572,011	697,771	851,909	
Potential Cost Offset Associated with Avoided Transition to Dependency									
18	Number beneficiaries without disability	30,838,000	30,838,000	30,838,000	30,838,000	30,838,000	30,838,000	30,838,000	
19	Proportion of beneficiaries who require dependent care in nursing facility during year	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	
20	Number of beneficiaries who require dependent care in nursing facility during year	2,798	3,461	4,240	5,161	6,292	7,675	9,371	
21	Proportion of beneficiaries who require dependent care in community during year	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	
22	Number of beneficiaries who require dependent care in community during year	8,393	10,383	12,721	15,483	18,876	23,026	28,113	
23	Total number beneficiaries transitioning to dependent care	11,190	13,844	16,961	20,643	25,168	30,702	37,484	
24	Total cost of beneficiaries transitioning to dependent state	\$250,108,286	\$309,414,587	\$379,091,169	\$461,384,916	\$562,521,640	\$686,195,716	\$837,776,876	2,926,970,317
Net Cost Estimate of Medicare Coverage of Daily Lutein with Zeaxanthin									
25	Gross cost of daily lutein for aged Medicare beneficiaries	\$45,117,697	\$57,211,521	\$71,847,266	\$89,630,090	\$112,009,160	\$140,050,987	\$175,263,067	\$588,800,570
26	Total cost offsets (potential savings) from avoided transitions to dependent state	\$250,108,286	\$309,414,587	\$379,091,169	\$461,384,916	\$562,521,640	\$686,195,716	\$837,776,876	\$2,926,970,317
27	Net cost of Medicare coverage of daily lutein for aged Medicare beneficiaries - expressed as savings	\$ (204,990,588)	\$ (252,203,066)	\$ (307,243,903)	\$ (371,754,826)	\$ (450,512,480)	\$ (546,144,729)	\$ (662,513,809)	\$ (2,338,169,747)
28	Premium Offset. Twenty-five percent of the gross cost of the intervention.	\$11,279,424	\$14,302,880	\$17,961,816	\$22,407,523	\$28,002,290	\$35,012,747	\$43,815,767	\$147,200,143
29	Total potential cost offset from avoided transitions to dependent state	\$ (216,270,013)	\$ (266,505,946)	\$ (325,205,720)	\$ (394,162,348)	\$ (478,514,770)	\$ (581,157,476)	\$ (706,329,576)	\$ (2,485,369,889)

Notes to Cost Model supported by Summary of Evidence.

Line numbers correspond to the numbered rows

Gross Cost Estimate of Daily Lutein for Aged Medicare Beneficiaries

- 1 The projected number of aged Part A Medicare beneficiaries for 2006 – 2010 is from the 2005 Medicare Combined Board of Trustees Annual Report.
- 2 Lewin Group analysis of 1999-2000 National Health and Nutrition Survey (NHANES)
- 3 Number of aged Medicare beneficiaries estimated to currently take lutein: (Row 1 * Row 2 = Row 3). Daily lutein use is considerably lower, so our estimate is an upper bound.
- 4 Percent of aged Medicare beneficiaries currently not taking lutein (potential new users) : (100% minus Row 2 = Row 4)
- 5 Potentially Eligible Group - Number of aged Medicare beneficiaries not taking lutein (potential new users): (Row 5 = Row 1 * Row 4).
- 6 Take-up rate: Proportion of new users among potential eligibles. We assume a 20% increase in new users each year, with an additional 1% of switchers who currently take lutein but would switch to insurance coverage of the supplement.
- 7 Number of new users: (Row 5 * Row 6 = Row 7).
- 8 Average annual cost of lutein (excluding patient copayment of 20% is assumed because Medicare and other fee-for-service payers generally use 80/20 benefit). This cost reflects a synthesis of costs of multiple brands rather than any specific one. Inflated by approximately 2.5% each year.

Note this assumption does not account for Medicare Part D, wherein approximately 12% of seniors would not take coverage or use employer or union coverage, 22 million would enroll on a PDP, and 6 million would enroll in a MA-PD (Lewin Group actuarial analysis)
- 9 Gross cost of lutein for aged Medicare beneficiaries who are new users: (Row 7 * Row 8 = Row 9).

Reduction in Risk of AMD in Aged Medicare Beneficiaries who can Benefit from Daily Lutein

- 10 17 million from Prevent Blindness America: Vision Problems Action Plan: A National Public Health Strategy; then increased by approximately 2% per year
- 11 Calculated: Row 10 minus Row 3 = Row 11
- 12 Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the U.S. Arch Ophthalmol 2004;122:564-572.
- 13 Calculated: Row 11 minus Row 12 = Row 13
- 14 Richer S, Stiles W, Stakute L, et al. Double-masked placebo controlled randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study. Optometry 2004; 75:216-230.
- 15 Calculated: Row 7 * Row 14 = Row 15
- 16 Melton LJ 3rd, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL. (1998) World Health Organization criteria
- 17 Calculated: Row 15 * Row 16 = Row 17

Potential Cost Offset Associated with Avoided Transition to Dependency

- 18 Number of beneficiaries without disability - reference row
- 19 Guralnik LM, Alexch LM, Wiener JM (2002). Medical and long-term care costs when older people become more dependent. *Am J Pub Health* 92(8): 1244- 1245.
- 20 Calculated: Row 19 * Row 17 = Row 20
- 21 Guralnik LM, Alexch LM, Wiener JM (2002). Medical and long-term care costs when older people become more dependent. *Am J Pub Health* 92(8): 1244- 1245.
- 22 Calculated: Row 21 * Row 17 = Row 22
- 23 Sum of Row 20 and Row 22 = Row 23
- 24 by 2.5% per year to \$16,552 in community and \$39,745 where transition is to a nursing facility

Net Cost Estimate of Medicare Coverage of Daily Lutein with Zeaxanthin

- 25 Gross cost of daily lutein for aged Medicare beneficiaries: Row 9.
- 26 Total cost offsets (potential savings) from avoided transitions to dependent state = Row 24
- 27 Row 25 minus Row 26 = net cost of Medicare daily coverage of lutein for aged beneficiaries
- 28 Premium Offset. Twenty-five percent of the gross cost of the intervention. Row 28 = Row 9 * 0.25.
- 29 Total potential cost offset from avoided transitions to dependent state: Row 27 minus Row 28 = Row 29

V. CONCLUSION

Over the next decade, the importance of keeping older persons healthy and independent will become a vitally important public policy concern. In this study, we assessed the potential impact of two supplements on health care and other expenditures related to losing one's independence and transitioning to greater dependency. We conducted an extensive review of the literature and developed cost models to determine the impact if some number of seniors consumed daily omega-3 fatty acids and if some number of seniors with symptoms of AMD consumed daily lutein and zeaxanthin. For each supplement, three questions embodied in our conceptual framework guided the research:

- 1) Does the supplement produce a physiological effect as shown by a change in biological markers? and if so;
- 2) Does this physiological effect create a positive change health status? and if so;
- 3) Is this change in health status associated with a decrease in health care expenditures?

The literature related to the health effects of dietary supplements is maturing in terms of its sophistication, its range, and statistical power. For omega-3 fatty acids, the body of research is extensive, spanning over 30 years. The more recent studies address concerns raised in previous studies. In this instance, the consensus is that findings from the studies reviewed reflect sufficient consistency, validity, and effect size to answer the above three questions affirmatively.

In the case of lutein/zeaxanthin, the literature is promising but not yet completely definitive. Studies have been conducted over a shorter period of time, and fewer exist. Also, recent advances in diagnostic capability have enabled studies to be more precise in their clinical parameters. Visual impairment is one of the top four causes of loss of independence and age-related macular degeneration effects 35 percent of the elderly population. Activities central to independent living (reading, writing, driving) are all considerably impaired with the loss of central vision, so there is impetus to accelerate this basic research.

The key evidence for daily lutein supplementation indicates a dose-response relationship between supplemental lutein and serum lutein levels measured in the eye. Lutein versus placebo clinical trials show improvements in retinal function along with increased macular pigmentation density and improved visual function. Additionally, there are ongoing clinical trials that will be able to answer questions that preclude definitive health claims.

The transition to greater dependency of our seniors, whether in terms of home and community care or transition to a nursing facility, places considerable financial burden on seniors, their families and the health care system. Daily supplementation of omega-3 fatty acids and lutein/zeaxanthin can decrease the risk of disease advancement in seniors and allow them to live longer healthier more independent lives.

The overall conclusion of this study is that in certain instances, supplements are an inexpensive and safe way to improve health status and reduce health care and other expenditures. In these cases, the role of public policy to support their use is unambiguous. As the research literature evolves and

matures, more will be known about the supplements considered in this analysis, as well as the patient populations and applications for which they are best suited.

Appendix A: Lutein Evidence

APPENDIX A EVIDENCE TABLES FOR LUTEIN

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Beatty S, Nolan J, Kavanagh H, O'Donovan O., <i>Macular pigment optical density and its relationship with serum and dietary levels of lutein and zeaxanthin</i> Arch Biochem Biophys. 2004 Oct 1; 430(1):70-6.</p>	Review		Macular pigment optical density and its relationship with serum and dietary levels of lutein and zeaxanthin	<p>RESULTS: Of the seven observational studies analyzing the relationship between dietary intake of lutein (L) and zeaxanthin (Z) and serum levels of these carotenoids, all have demonstrated significant and positive relationships ($p < 0.05$; $r = 0.21-0.74$). Of the seven observational studies investigating the relationship between serum L and Z and macular pigment (MP) optical density, six have found positive and significant correlations ($p < 0.05$; $r = 0.21-0.82$). Of the five observational studies investigating whether there was a demonstrable relationship between dietary intake of L and Z and MP optical density, three found such a relationship to be significant and positive. The studies failing to demonstrate a significant relationship comprised only small numbers of subjects (i.e., $n < 20$ for the serum studies and $n < 50$ for the dietary intake studies).</p> <p>CONCLUSION: There is a growing body of scientific evidence which suggests that MP may protect against age-related maculopathy (ARM), thus rendering our need to comprehend the relationships between L and Z concentrations in the diet, serum, and retina, as well as other tissues, all the more urgent. Of the many lines of enquiry that should be pursued, in the context of the putative protective value of MP for ARM, is the role of tissue and serum carotenoids in the elderly population in whom dietary, digestive, and absorptive characteristics are likely to be compromised. A rise in oxidant load and reduced oxidant defenses associated with increasing age may well affect transport and stabilization of the macular carotenoids in tissues.</p>
<p>Krinsky NI, Landrum JT, Bone RA <i>Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye</i> Annu Rev Nutr. 2003; 23:171-201. Epub 2003 Feb 27</p>	Review		Protective role of lutein (L) and zeaxanthin (Z) in the eye	<p>RESULTS: There is ample epidemiological evidence that the amount of macular pigment is inversely associated with the incidence of age-related macular degeneration, an irreversible process that is the major cause of blindness in the elderly. The macular pigment can be increased in primates by either increasing the intake of foods that are rich in L and Z, such as dark-green leafy vegetables, or by supplementation with L or Z.</p> <p>CONCLUSION: Although increasing the intake of lutein or zeaxanthin might prove to be protective against the development of age-related macular degeneration, a causative relationship has yet to be experimentally demonstrated. Until more information is available, particularly from controlled intervention trials, it is still too early to recommend supplemental L or Z as a means of reducing the risk of eye</p>

Appendix A: Lutein Evidence

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Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Breithaupt DE, Bamedi A, Wirt U, <i>Carotenol fatty acid esters: easy substrates for digestive enzymes?</i> Comp Biochem Physiol B Biochem Mol Biol. 2002 Aug;132(4):721-8	Enzymatic assay		Carotenol fatty acid esters as easy substrates for digestive enzymes	RESULTS: Pancreatic lipase does not appear to accept carotenoid esters whereas retinyl palmitate was hydrolyzed. Cholesterol esterase, which is known to cleave secondary alcohol (e.g., retinyl esters) with high yields, appears a more plausible candidate for the generation of free carotenoids in the gut. CONCLUSION: To determine the accurate rate of cholesterol esterase and other digestive enzymes towards carotenoid ester, further investigations using purified enzymes are necessary.
Castenmiller JJM, Soren TL, Dragsted LO, van het Hof KH, Linssen JPH, West CE, <i>β-carotene does not change markers of enzymatic and nonenzymatic antioxidant activity in human blood</i> , American Society of Nutritional Sciences, 1999	Clinical trial	72 healthy, nonsmoking, normolipidemic volunteers (42 women and 30 men) ages 18- 58	Carotenoid supplement (FloraGLO 60 g/kg lutein and 3 g/kg zeaxanthin) (n = 12) or with a spinach product (n = 12 per group)	Over a 3 week period subjects were on either a basic diet (n = 10) or a basic diet with a carotenoid supplement (FloraGLO 60 g/kg lutein and 3 g/kg zeaxanthin) (n = 12) or with a spinach product (n = 12 per group), i.e., whole-leaf, minced, liquefied or liquefied spinach plus added dietary fiber. Effect of carotenoid supplementation and spinach intake on a range of enzymatic and nonenzymatic antioxidant parameters in human blood. RESULTS: Consumption of spinach resulted in greater responses of erythrocyte GR activity and lower erythrocyte CAT and serum α-tocopherol responses compared with the control group. Consumption of the carotenoid supplement increased erythrocyte GR activity and lowered the serum α-tocopherol response. CONCLUSION: Our data suggest that carotenoid intake of lutein and zeaxanthin, but not β-carotene, is positively associated with erythrocyte GR activity and negatively with serum α-tocopherol concentration, respectively. The effect of spinach consumption on CAT activity is most likely not related to its carotenoid content. With improved analytical assays and more information on antioxidant enzyme activity, a better understanding of the kinetics and mechanisms of complex antioxidant defense systems may be obtained in the future.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Castenmiller JJ, West CE, Linssen JP, van het Hof KH, Voragen AG <i>The food matrix of spinach is a limiting factor in determining the bioavailability of beta-carotene and to a lesser extent of lutein in humans</i> J Nutr. 1999 Feb;129(2):349-55</p>	<p>Dietary controlled intervention study</p>	<p>72 healthy, nonsmoking, normolipidemic volunteers (42 women and 30 men) ages 18- 58</p>	<p>Effect of variously processed spinach products and dietary fiber on serum carotenoid concentrations</p>	<p>Over a 3 week period subjects were on either a control diet (n = 10) or a control diet supplemented with carotenoids (FloraGLO 60 g/kg lutein and 3 g/kg zeaxanthin) or one of four spinach products (n = 12 per group) (whole leaf spinach with an almost intact food matrix, minced spinach with the matrix partially disrupted, enzymatically liquefied spinach in which the matrix was further disrupted and the liquefied spinach to which dietary fiber (10 g/kg wet weight) was added) RESULTS: The lutein response did not differ among spinach groups and addition of dietary fiber to the liquefied spinach had no effect on serum carotenoid responses. CONCLUSION: Bioavailability of lutein from spinach was higher than that of β-carotene. Additionally, the enzymatic disruption of the matrix (cell wall structure) enhanced the bioavailability of β-carotene from whole leaf and minced spinach, but had no effect on lutein bioavailability.</p>
<p>Chan C, Leung I, Lam KW, Tso MO <i>The occurrence of retinol and carotenoids in human subretinal fluid</i> Curr Eye Res. 1998 Sep;17(9):890-5</p>	<p>Case study</p>	<p>Six patients with rhegmatogenous retinal detachment</p>	<p>Presence of retinol and carotenoids in the subretinal space following rhegmatogenous retinal detachment</p>	<p>RESULTS: The retinol concentrations (mean\pmSD) in the serum and subretinal fluid were 305\pm144 and 166\pm96 ng/ml respectively. The 450 nm chromatogram had 7 peaks with the characteristic absorption spectrum of carotenoids. Peak 1 and 7 coincided with the retention time of beta-carotene (1.8 min) and lutein (10.8 min) respectively. The concentrations of beta-carotene and lutein in serum were 161\pm63 and 142\pm98 ng/ml respectively. There was very little beta-carotene in subretinal fluid (4.7\pm2.4 ng/ml). Lutein was the major carotenoid peak in subretinal fluid (41.4\pm14.1 ng/ml). The minor carotenoid peaks of serum were not observed in subretinal fluid. CONCLUSION: There is a substantial amount of retinol and lutein in subretinal fluid. The high proportion of lutein and very low amount of beta-carotene in the subretinal fluid support the occurrence of a highly selection transport mechanism of lutein from the blood to the retina.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Chitchumroonchokchai C, Schwartz SJ, Failla ML <i>Assessment of lutein bioavailability from meals and a supplement using simulated digestion and caco-2 human intestinal cells</i> J Nutr. 2004 Sep;134(9):2280-6</p>	Digestive assay		Assessment of lutein bioavailability from meals and a supplement using simulated digestion and caco-2 human intestinal cells	<p>RESULTS: Lutein and other carotenoids present in spinach puree and lutein from a commercial supplement were relatively stable during in vitro digestion. Micellarization of lutein and zeaxanthin during the small intestinal phase of digestion exceeded that of β-carotene and was greater for xanthophylls in oil-based supplements than in spinach. Apical uptake of lutein from micelles by Caco-2 human intestinal cells was linear for at least 8 h, and accumulation from synthetic micelles exceeded that from micelles generated during simulated digestion. Stimulation of chylomicron synthesis resulted in the secretion of $7.6 \pm 0.1\%$ of cellular lutein into the triglyceride-rich fraction in the basolateral chamber. CONCLUSION: Simulated digestion and the Caco-2 cell model appear to be effective tools for identifying factors affecting absorption of dietary carotenoids.</p>
<p>Johnson EJ, Neuringer M, Russell RM, Schalch W, Snodderly DM <i>Nutritional manipulation of primate retinas, III: effects of lutein or zeaxanthin supplementation on adipose tissue and retina of xanthophyll-free monkeys</i> Invest Ophthalmol Vis Sci. 2005 Feb;46(2):692-702</p>	Dietary controlled intervention study	18 rhesus monkeys who were fed xanthophyll-free diets from birth to 7 - 16 years of age	Effects of lutein (L) and zeaxanthin (Z) supplementation on carotenoid levels	<p>6 supplemented with pure L at 3.9 $\mu\text{mol/kg}$ per day for 24 to 101 weeks and 6 with pure Z at 3.9 $\mu\text{mol/kg}$ per day for 24 to 101 weeks RESULTS: Monkeys fed xanthophyll-free diets had no L or Z in serum or tissues. After L or Z supplementation, serum and adipose tissue concentrations significantly increased in the supplemented groups. Both L and 3R,3'S-Z (RSZ or meso-Z, not present in the diet) were incorporated into retinas of monkeys supplemented with L, with RSZ present only in the macula (central 4 mm). All-trans Z, but no RSZ, accumulated in retinas of monkeys supplemented with Z. CONCLUSION: L is the precursor of RSZ, a major component of macular pigment. Xanthophyll-free monkeys can accumulate retinal xanthophylls and provide a valuable model for examining their uptake and conversion.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Kostic D, White WS, Olson JA <i>Intestinal absorption, serum clearance, and interactions between lutein and β-carotene when administered to human adults in separate or combined oral doses</i> Am J Clin Nutr. 1995 Sep;62(3):604-10</p>	<p>Dietary controlled intervention study</p>	<p>Eight subjects, four males and four females, aged 24-38 years, with body weights between 53 and 91 kg.</p>	<p>Single equimolar doses (0.5 $\mu\text{mol/kg}$ body wt) of lutein and/or beta-carotene Intestinal absorption, serum clearance, and interactions between lutein and β-carotene</p>	<p>RESULTS: Whereas the mean serum concentration of lutein showed a single maximum at 16 h, that of beta-carotene peaked at 6 h and then again at 32 h. Subsequently, lutein and beta-carotene were cleared at approximately the same rate from the serum. The mean (+/- SEM) areas under the curve (AUCs) for lutein and beta-carotene during the first 440 h differed significantly: 59.6 +/- 9.0 and 26.3 +/- 6.4 $\mu\text{mol}\cdot\text{h/L}$, respectively ($P < 0.005$). AUC values did not correlate with initial serum concentrations of the given carotenoid or with the order of dosing. When combined in the same dose, beta-carotene significantly reduced the serum AUC values for lutein to 54-61% of control values ($P < 0.025$), whereas lutein reduced the AUC value for beta-carotene in five subjects but enhanced it in three subjects. CONCLUSION: Effects of lutein on the AUC for beta-carotene were inversely related to the AUC for beta-carotene alone. Carotenoids clearly interact with each other during intestinal absorption, metabolism, and serum clearance, although individual responses can differ markedly.</p>
<p>van het Hof KH, Brouwer IA, West CE, Haddeman E, Steegers-Theunissen RP, van Dusseldorp M, Weststrate JA, Eskes TK, Hautvast JG <i>Bioavailability of lutein from vegetables is 5 times higher than that of beta-carotene.</i> Am J Clin Nutr. 1999 Aug;70(2):261-8</p>		<p>54 healthy adult subjects</p>	<p>Assess the bioavailability of beta-carotene and lutein from vegetables and the effect of increased vegetable consumption on the ex vivo oxidizability of LDL</p>	<p>Over a 4 week period 22 subjects were on a high-vegetable diet (490 g/d), 22 consumed a low-vegetable diet (130 g/d), and 10 consumed a low-vegetable diet supplemented with pure beta-carotene (6 mg/d) and lutein (9 mg/d) RESULTS: Plasma concentrations of vitamin C and carotenoids (i.e., alpha-carotene, beta-carotene, lutein, zeaxanthin, and beta-cryptoxanthin) were significantly higher after the high-vegetable diet than after the low-vegetable diet. In addition to an increase in plasma beta-carotene and lutein, the pure carotenoid-supplemented diet induced a significant decrease in plasma lycopene concentration of -0.11 micromol/L (95% CI: -0.21, -0.0061). The responses of plasma beta-carotene and lutein to the high-vegetable diet were 14% and 67%, respectively, of those to the pure carotenoid-supplemented diet. Conversion of beta-carotene to retinol may have attenuated its plasma response compared with that of lutein. There was no significant effect on the resistance of LDL to oxidation ex vivo. CONCLUSION: Increased vegetable consumption enhances plasma vitamin C and carotenoid concentrations, but not resistance of LDL to oxidation. The relative bioavailability of lutein from vegetables is higher than that of beta-carotene.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Yemelyanov AY, Katz NB, Bernstein PS <i>Ligand-binding characterization of xanthophyll carotenoids to solubilized membrane proteins derived from human retina</i> Exp Eye Res. 2001 Apr;72(4):381-92</p>	<p>Case-controlled study</p>	<p>Human donor globes received within 24 hours of death</p>	<p>Ligand-binding characterization of xanthophyll carotenoids to solubilized membrane proteins derived from human retina</p>	<p>RESULTS: A carotenoid-rich membrane fraction derived from human macula or peripheral retina was prepared by homogenization, differential centrifugation, detergent solubilization, and other purification methods. The most highly purified preparations contained two major protein bands at 25 and 55 kDa that consistently co-eluted with endogenous lutein (L) and zeaxanthin (Z). The visible absorbance spectrum of the binding protein preparation closely matches the spectral absorbance of the human macular pigment, and it is bathochromically shifted about 10 nm from the spectrum of L and Z dissolved in organic solvents. Binding of exogenously added L and Z is saturable and specific with an apparent Kd of approximately 1 microM. Canthaxanthin and beta-carotene exhibit no significant binding activity to solubilized retinal membrane proteins when assayed under identical conditions. Other potential mammalian xanthophyll-binding proteins such as albumin, tubulin, lactoglobulin and serum lipoproteins possess only weak non-specific binding affinity for carotenoids when assayed under the same stringent binding conditions. CONCLUSION: This investigation provides the first direct evidence for the existence of specific xanthophyll-binding protein(s) in the vertebrate retina and macula. The possible roles of xanthophyll-binding proteins in normal macular function and in the pathogenesis of age-related macular degeneration remain to be elucidated.</p>
<p>Bone RA, Landrum JT, Dixon Z, Chen Y, Llerena CM <i>Lutein and zeaxanthin in the eyes, serum and diet of human subjects</i> Exp Eye Res. 2000 Sep;71(3):239-45</p>	<p>Case-controlled study</p>	<p>Nineteen healthy subjects (16 female, three male) in the age range 18-59 who were nonsmokers, did not take dietary supplements that included carotenoids, and had no visual abnormalities, apart from mild myopia or astigmatism; Forty-six human eyes from adult donors aged 58-98</p>	<p>Lutein (L) and (Z) zeaxanthin in the eyes, serum and diet of human subjects</p>	<p>RESULTS: The results generally support the premise that the quantity of L and Z in an individual's average diet will be reflected in the serum concentration of these carotenoids, and that this in turn will determine the density of the macular pigment. CONCLUSION: Roughly 55% of the variability in the subjects' serum concentration of L and Z can be explained by their dietary intake of L and Z. About 30% of the variability in the subjects' macular pigment density can be attributed to their serum concentration of L and Z. The present study forges a link between those studies in which associations have been reported between the incidence of AMD and dietary L and Z, incidence of AMD and serum L and Z, and incidence of AMD and retinal L and Z. Thus, this study lends support to the hypothesis that low levels of macular pigment may be one of several causal risk factors in the development of the disease.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Beatty S, Boulton M, Henson D, Koh HH, Murray IJ <i>Macular pigment and age-related macular degeneration</i> Br J Ophthalmol. 1999 Jul;83(7):867-77	Review		Macular pigment and age-related macular degeneration (AMD)	<p>RESULTS: Macular pigment is entirely of alimentary origin, and although its absorptive and transport characteristics have yet to be fully elucidated it has been shown that macular pigment density can be augmented through dietary modification. In addition to restricting photochemical retinal injury by screening blue light, macular pigment is also suspected of limiting oxidative damage by quenching reactive oxygen species. AMD remains the leading cause of blindness in the developed world, and its prevalence is likely to rise because of increasing longevity. This disease, in addition to causing severe visual disability, will have profound socioeconomic implications in the future as it affects the fastest growing section of the Western world population. We have presented the mounting circumstantial, epidemiological, experimental, and clinical evidence that supports the hypothesis that macular pigment protects against age-related maculopathy (ARM) and AMD.</p> <p>CONCLUSION: Well designed, prospective and randomized clinical trials are needed to evaluate the effects of dietary carotenoid supplementation on the risk for AMD. Until such time as the beneficial effects of dietary lutein and zeaxanthin supplements have been substantiated, and their long term safety established, routinely prescribing micronutrient preparations containing these compounds to prevent progression of ARM cannot be justified. However, patients with ARM, or at risk of developing the disease, should be encouraged to eat a balanced diet rich in fruit and vegetables.</p>
Bernstein PS, Zhao DY, Wintch SW, Ermakov IV, McClane RW, Gellermann W <i>Resonance Raman measurement of macular carotenoids in normal subjects and in age-related macular degeneration patients</i> Ophthalmology. 2002 Oct;109(10):1780-7	Observational study	Ninety-three AMD eyes from 63 patients and 220 normal eyes from 138 subjects	Resonance Raman measurement of macular carotenoids in normal subjects and in age-related macular degeneration (AMD) patients	<p>RESULTS: Carotenoid Raman signal intensity declined with age in normal eyes ($P < 0.001$). Average levels of lutein and zeaxanthin were 32% lower in AMD eyes versus normal elderly control eyes as long as the subjects were not consuming high-dose lutein supplements ($P = 0.001$). Patients who had begun to consume supplements containing high doses of lutein ($> \text{or} = 4 \text{ mg/day}$) regularly after their initial diagnosis of AMD had average macular pigment levels that were in the normal range ($P = 0.829$) and that were significantly higher than in AMD patients not consuming these supplements ($P = 0.038$).</p> <p>CONCLUSION: These findings are consistent with the hypothesis that low levels of lutein and zeaxanthin in the human macula may represent a pathogenic risk factor for the development of AMD. Resonance Raman measurement of macular carotenoid pigments could play an important role in facilitating large-scale prospective clinical studies of lutein and zeaxanthin protection against AMD, and this technology may someday prove useful in the early detection of individuals at risk for visual loss from AMD.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Bone RA, Landrum JT, Mayne ST, Gomez CM, Tibor SE, Twaroska EE <i>Macular pigment in donor eyes with and without AMD: a case-control study</i> Invest Ophthalmol Vis Sci. 2001 Jan;42(1):235-40</p>	Case-controlled study	Retinas from 56 donors with AMD and 56 controls	Association between the density of macular pigment in the human retina and the risk of age-related macular degeneration (AMD).	<p>RESULTS: Lutein (L) and zeaxanthin (Z) levels in all three concentric regions were less, on average, for the AMD donors than for the controls. The differences decreased in magnitude from the inner to medial to outer regions. The lower levels found in the inner and medial regions for AMD donors may be attributable, in part, to the disease. Comparisons between AMD donors and controls using the outer (peripheral) region were considered more reliable. For this region, logistic regression analysis indicated that those in the highest quartile of L and Z level had an 82% lower risk for AMD compared with those in the lowest quartile (age- and sex-adjusted odds ratio = 0.18, 95% confidence interval = 0.05-0.64)</p> <p>CONCLUSION: The results are consistent with a theoretical model that proposes an inverse association between risk of AMD and the amounts of L and Z in the retina. The results are inconsistent with a model that attributes a loss of L and Z in the retina to the destructive effects of AMD.</p>
<p>Rapp LM, Maple SS, Choi JH <i>Lutein and zeaxanthin concentrations in rod outer segment membranes from perifoveal and peripheral human retina</i> Invest Ophthalmol Vis Sci. 2000 Apr;41(5):1200-9</p>	Case study	Retinas from 9 donors ages 46 - 73	Presence of lutein (L) and zeaxanthin (Z), the major carotenoids comprising the macular pigment, in rod outer segment (ROS) membranes where concentration of long-chain polyunsaturated fatty acids, and susceptibility to oxidation, is highest	<p>RESULTS: ROS membranes prepared from perifoveal and peripheral regions of human retina were found to be of high purity as indicated by the presence of a dense opsin band on protein gels. Fatty acid analysis of human ROS membranes showed a characteristic enrichment of docosahexaenoic acid relative to residual membranes. Membranes prepared from bovine retinas had protein profiles and fatty acid composition similar to those from human retinas. Carotenoid analysis showed that lutein and zeaxanthin were present in ROS and residual human retinal membranes. The combined concentration of lutein plus zeaxanthin was 70% higher in human ROS than in residual membranes. Lutein plus zeaxanthin in human ROS membranes was 2.7 times more concentrated in the perifoveal than the peripheral retinal region. Lutein and zeaxanthin were consistently detected in human retinal pigment epithelium at relatively low concentrations.</p> <p>CONCLUSION: The presence of lutein and zeaxanthin in human ROS membranes raises the possibility that they function as antioxidants in this cell compartment. The finding of a higher concentration of these carotenoids in ROS of the perifoveal retina lends support to their proposed protective role in age-related macular degeneration.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Hammond BR Jr, Wooten BR, Snodderly DM <i>Preservation of visual sensitivity of older subjects: association with macular pigment density</i> Invest Ophthalmol Vis Sci. 1998 Feb;39(2):397-406</p>	Case study	27 healthy older subjects (ages 60-84) were compared with data from 10 younger subjects (ages 24-36)	Individual differences in macular pigment (MP) density and relation to loss of visual sensitivity with age	<p>RESULTS: Consistent with past reports, photopic sensitivity declined significantly with age for both 440-nm ($P < 0.025$) and 550-nm ($P < 0.0003$) light. For older subjects, photopic sensitivity was positively related to MP density, although more strongly for 440-nm ($P < 0.001$) than for 550-nm ($P < 0.01$) light. Parafoveal scotopic sensitivity of the older subjects was also positively related to MP density ($P < 0.02$). Visual sensitivity of the young subjects was not significantly related to MP density.</p> <p>CONCLUSION: For subjects older than 60 years, visual sensitivity of those with high MP density was not significantly different from that of young subjects. Conversely, older subjects with low MP density had lower sensitivity than young subjects. Although this study cannot prove causality, the results show that high MP density was associated with the retention of youthful visual sensitivity, which suggested that MP may retard age-related declines in visual function.</p>
<p>Hammond BR Jr, Fuld K, Curran-Celentano J <i>Macular pigment density in monozygotic twins</i> Invest Ophthalmol Vis Sci. 1995 Nov;36(12):2531-41</p>	Case study	6 female pairs and 4 male pairs of Caucasian identical twins ages 19 - 22	Correlation between variation in macular pigment density variation and genetics	<p>RESULTS: Statistically significant differences in macular pigment optical density were found for 5 of the 10 twin pairs. For these five pairs, differences in macular pigment density were moderately related to differences in the intake of dietary fat, iron, linoleic and oleic acid, fiber, and total calories ($P < 0.10$, individually; $P < 0.05$, for an equally weighted composite of these variables). There was no significant relationship, however, found between macular pigment density and carotenoids in the blood and diet.</p> <p>CONCLUSION. Given the putative protective role of macular pigment, variations in macular pigment density may have clinical significance. The conclusion that macular pigment is not completely determined genetically allows the possibility that macular pigment density may be modified for the protective purposes. The current data suggest that dietary fat, iron, and fiber may influence macular pigment levels (perhaps through their influence on carotenoid metabolism). These data suggest that the eventual deposition of macular pigment in the retina is complex and probably is influenced by a number of variables.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Bone RA, Landrum JT, Hime GW, Cains A, Zamor J <i>Stereochemistry of the human macular carotenoids</i> Invest Ophthalmol Vis Sci. 1993 May;34(6):2033-40</p>		<p>Donor eyes</p>	<p>Identification of the major components of the human macular pigment</p>	<p>RESULTS: The mass spectrometry data supported earlier work in which high-performance liquid chromatography, UV-visible spectrometry and chemical modification showed that the macular pigment comprises two carotenoids with identical properties to those of zeaxanthin and lutein. Chiral column chromatography showed that the "zeaxanthin" fraction is a mixture of two stereoisomers, zeaxanthin itself [(3R,3'R)-beta,beta-Carotene-3,3'-diol] and meso-zeaxanthin [(3R,3'S)-beta,beta-Carotene-3,3'-diol]. The other fraction is the single stereoisomer, lutein [(3R,3'R,6'R)-beta,epsilon-Carotene-3,3'-diol]. In human blood plasma, only zeaxanthin and lutein were found. CONCLUSION: The results strongly suggest that meso-zeaxanthin results from chemical processes within the retina. Noting that lutein exceeds zeaxanthin in plasma but that the combined zeaxanthin stereoisomers exceed lutein in the retina, the possibility was considered that meso-zeaxanthin is a conversion product derived from retinal lutein. Under nonphysiologic conditions, the authors demonstrate that a base-catalyzed conversion of lutein to zeaxanthin yields only the meso-(3R,3'S) stereoisomer.</p>
<p>Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE <i>A prospective study of cigarette smoking and risk of age-related macular degeneration in men</i> JAMA. 1996 Oct 9;276(14):1147-51</p>	<p>Cohort study</p>	<p>21,157 US male physicians, who did not have a diagnosis of AMD at baseline, were followed for at least 7 years. Based on information reported at baseline, 11% were current smokers, 39% were past smokers, and 50% never smokers</p>	<p>Association between cigarette smoking and the incidence of age-related macular degeneration (AMD) in men</p>	<p>RESULTS: A total of 268 incident cases of AMD with vision loss were confirmed. In multivariate analysis, current smokers of 20 or more cigarettes per day, compared with never smokers, had an increased risk of AMD (relative risk [RR], 2.46; 95% confidence interval [CI], 1.60-3.79). Past smokers had a modest elevation in risk of AMD (RR, 1.30; 95% CI, 0.99-1.70). For current smokers of fewer than 20 cigarettes per day, there was a nonsignificant 26% increased risk of AMD (RR, 1.26; 95% CI, 0.61-2.59) CONCLUSION: These prospective data provide support for the hypothesis that cigarette smoking increases the risk of developing AMD.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Hammond BR Jr, Wooten BR, Snodderly DM <i>Cigarette smoking and retinal carotenoids: implications for age-related macular degeneration</i> Vision Res. 1996 Sep;36(18):3003-9</p>	Case-controlled study	34 smokers and 34 nonsmokers	Cigarette smoking and retinal carotenoids: implications for age-related macular degeneration	<p>RESULTS: Subjects were matched with respect to age, sex, dietary patterns and overall pigmentation (i.e., eye, skin and hair color). The smoking group had a mean macular pigment (MP) of 0.16 (SD = 0.12) compared to a mean MP of 0.34 (SD = 0.15) for nonsmokers ($P < 0.0001$). MP density and smoking frequency were inversely related ($r = -0.498$ $P < 0.001$) in a dose-response relationship. A variety of evidence suggests that MP protects the macula from actinic damage both passively (by screening potentially harmful short-wave light) and actively as an antioxidant (e.g., by quenching reactive oxygen species).</p> <p>CONCLUSION: If smoking causes a reduction in MP density, then smokers may be at risk for age-related macular degeneration (AMD). Epidemiologic data identifying smoking as a risk factor for the neovascular form of age-related macular degeneration are consistent with this hypothesis.</p>
<p>Khachik F, Beecher GR, Smith JC Jr <i>Lutein, lycopene, and their oxidative metabolites in chemoprevention of cancer</i> J Cell Biochem Suppl. 1995;22:236-46</p>		3 healthy Caucasian males ages 42 - 59	Role of lutein, lycopene, and their oxidative metabolites in chemoprevention of cancer	<p>Phase 1: daily supplement of 10 mg/day purified lutein for 18 days; Phase 2: daily supplement of 10 mg/day purified zeaxanthin</p> <p>RESULTS: Lutein and lycopene, abundant in most fruits and vegetables as well as human serum, have been shown to possess strong antioxidant capability. Among the metabolites of lutein, four results from oxidation and two from non-enzymatic dehydration. The metabolite of lycopene has been identified as 5,6-dihydroxy-5,6-dihydrolycopene, which apparently results from oxidation of lycopene to an intermediate, lycopene epoxide. This intermediate may undergo metabolic reduction to form the lycopene metabolite. Although in vivo oxidation of lutein to its metabolites has been demonstrated based on data obtained from two human studies, in vivo oxidation of lycopene to its metabolite has not yet been established. Data generated from these studies demonstrated, for the first time, that in vivo oxidation of lutein (L) and zeaxanthin (Z) is a key reaction in the metabolism of non-vitamin A active dihydroxycarotenoids.</p> <p>CONCLUSION: Based on these findings, lutein and lycopene, the most abundant carotenoids in the diet as well as in human plasma, are believed to possess strong antioxidant potentials. Dietary carotenoids, including lutein and lycopene as well as their metabolites, need further investigation as potential chemopreventive agents.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Richer S <i>Part I: A protocol for the evaluation and treatment of atrophic age-related macular degeneration</i> J Am Optom Assoc. 1999 Jan;70(1):13-23</p>	Review	Male veterans with atrophic ARMD matched to patients of similar age, sex, and socioeconomic status with minimal atrophic ARMD	Basic science and epidemiologic rationale for evaluating atrophic age-related macular degeneration (ARMD) using a standardized low-cost, "low-technology," clinical approach	<p>RESULTS: The ophthalmic component involves baseline and serial measurements of contrast sensitivity (CSF), low-luminance, low-contrast visual acuity (SKILL), and glare recovery (GR) in each eye. The systemic component includes self-administered evaluation of nutritional status (food and supplement intake), exercise and activities of daily living associated with ARMD (night driving/glare adaptation disturbance and dark green-leafy vegetable/plant food consumption).</p> <p>CONCLUSION: The literature supports careful baseline and serial evaluation of high-risk patients using germane parameters of ocular function and systemic health specific to ARMD. This "ARMD workup" is analogous to a glaucoma workup, but involves less equipment and chair time. Any optometrist can obtain these measurements using inexpensive testing protocols. (Part II of this paper presents serial environmental intervention case report data.)</p>
<p>Richer S <i>Part II: ARMD - Pilot (case series) environmental intervention data</i> J Am Optom Assoc. 1999 Jan;70(1):24-36</p>	Clinical Trial	Fourteen male patients (70 +/- 9 years), receiving 0.73 +/- 0.45 portions of dark-green, leafy vegetables/day base intake, were placed on an additional portion of 5 ounces sautéed spinach 4 to 7 times per week or lutein-based antioxidant (three patients)	Demonstration of a standardized clinical low-cost, "low-technology," ocular and systemic "ARMD work-up" protocol	<p>.73 ± 0.45 portions of dark-green, leafy vegetable/day base was supplemented by 5 ounces sautéed spinach 4 to 7 times/week or lutein-based antioxidants (3 patients)</p> <p>RESULTS: Patients demonstrated short-term positive effects in visual function in one or both eyes with this mild therapeutic approach: Amsler grid (87%); Snellen Acuity (71%); Contrast sensitivity (92%); SKILL (65%); Glare recovery (69%); and Activities of Daily Vision Subscale (60%). There was no obvious correlation between ophthalmoscopic appearance of the retina and visual outcome and patient symptoms did not necessarily correlate with observed changes in visual function.</p> <p>CONCLUSION: The approach to atrophic ARMD presented here warrants informal practitioner replication and formal randomized prospective clinical case-control evaluation.</p>

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Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Pratt S <i>Dietary prevention of age-related macular degeneration</i> J Am Optom Assoc. 1999 Jan;70(1):39-47</p>	<p>Clinical trial</p>			<p>RESULTS: Biochemical studies of such vegetables have found that they contain several nutrients that may account for this effect, including high concentrations of the related carotenoids lutein and zeaxanthin. Structural and clinical studies have shown that these carotenoids are concentrated in the retinal macular pigment and that such accumulation is dependent on dietary intake. Further studies have indicated that the density of the macular pigment is related to preservation of visual sensitivity and (possibly) protection from ARMD. CONCLUSION: Large-scale clinical trials will be necessary to demonstrate that specific agents can reduce the incidence of ARMD. Nevertheless, specific dietary components--particularly, the carotenoids found in dark green, leafy vegetables--have shown great promise. While lifestyle modifications such as smoking cessation, reduction of alcohol consumption, and the wearing of sunglasses may reduce the risk of ARMD, it is likely that consumption of specific dietary components can reduce the risk further.</p>
<p>Richer S <i>Atrophic ARMD - a Nutrition Responsive Chronic Disease</i> J Am Optom Assoc. 1996 Jan;67(1):6-10</p>	<p>Review</p>	<p>71 male veterans with advanced ARMD and a control group</p>	<p>Association of age-related macular degeneration (ARMD) and cardiac disease</p>	<p>Veteran: antioxidant capsule po BID; Control group: placebo po BID RESULTS: The results of the pilot supports and strengthens the association of ARMD and cardiac disease by reporting that ARMD is associated with decreased B vitamin and magnesium intake. Male veterans with advanced atrophic ARMD who took an antioxidant capsule po BID maintained the vision in their better functioning eyes for more than 1.5 years while the control group taking a placebo demonstrated a clinically significant LogMAR equivalent loss of 1 line of distance Snellen acuity during the same time period (p=0.03; repeated factors ANOVA). CONCLUSION: The ARMD Study Group of clinician-researchers make specific recommendations for further study of atrophic ARMD.</p>

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Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Richer S, Stiles W, Statkute L, Pulido J, Frankowski J, Rudy D, Pei K, Tshipursky M, Nyland J <i>Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the veterans LAST study (Lutein Antioxidant Supplementation Trial)</i> Optometry. 2004 Apr;75(4):216-30</p>	<p>Randomized, double-masked, placebo-controlled trial</p>	<p>Ninety veterans with atrophic ARMD</p>	<p>Lutein (L) and antioxidant supplementation in the intervention of atrophic age-related macular degeneration (ARMD)</p>	<p>Group 1 (n = 29): lutein 10 mg (L); Group 2 (n =30): lutein 10 mg/antioxidants/vitamins and minerals broad spectrum supplementation formula (L/A); Group 3 (n = 31): a maltodextrin placebo (P) over 12 months RESULTS: In Groups 1 L and 2 L/A, mean eye macular pigment optical density increased approximately 0.09 log units from baseline, Snellen equivalent visual acuity improved 5.4 letters for Group 1 L and 3.5 letters for Group 2 L/A, and contrast sensitivity improved. There was a net subjective improvement in Amsler grid in Group 1 L. VFO-14 questionnaires concerning subjective glare recovery were nearly significant at 4 months for Group 2 L/A. Patients who received the placebo (Group 3) had no significant changes in any of the measured findings. CONCLUSION: In this study, visual function is improved with lutein alone or lutein together with other nutrients. Further studies are needed with more patients of both genders and for longer periods of time to assess long-term effects of lutein or lutein together with a broad spectrum of antioxidants, vitamins, and minerals in the treatment of atrophic age-related macular degeneration.</p>
<p>Eye Disease Case-Control Study Group: Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, Farber MD, Gragoudas ES, Haller J, Miller DT, et al <i>Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration.</i> JAMA. 1994 Nov 9;272(18):1413-20</p>	<p>Case-controlled study</p>	<p>356 case subjects who were diagnosed with the advanced stage of AMD within 1 year prior to their enrollment, ages 55 - 80 years, and residing near a participating clinical center. The 520 control subjects were from the same geographic areas as case subjects, had other ocular diseases, and were frequency-matched to cases according to age and sex</p>	<p>Relationships between dietary intake of carotenoids plus vitamins A, C, and E and the risk of neovascular age-related macular degeneration (AMD)</p>	<p>RESULTS--A higher dietary intake of carotenoids was associated with a lower risk for AMD. Adjusting for other risk factors for AMD, we found that those in the highest quintile of carotenoid intake had a 43% lower risk for AMD compared with those in the lowest quintile (odds ratio, 0.57; 95% confidence interval, 0.35 to 0.92; P for trend = .02). Among the specific carotenoids, lutein and zeaxanthin, which are primarily obtained from dark green, leafy vegetables, were most strongly associated with a reduced risk for AMD (P for trend = .001). Several food items rich in carotenoids were inversely associated with AMD. In particular, a higher frequency of intake of spinach or collard greens was associated with a substantially lower risk for AMD (P for trend < .001). The intake of preformed vitamin A (retinol) was not appreciably related to AMD. Neither vitamin E nor total vitamin C consumption was associated with a statistically significant reduced risk for AMD, although a possibly lower risk for AMD was suggested among those with higher intake of vitamin C, particularly from foods. CONCLUSION--Increasing the consumption of foods rich in certain carotenoids, in particular dark green, leafy vegetables, may decrease the risk of developing advanced or exudative AMD, the most visually disabling form of macular degeneration among older people. These findings support the need for further studies of this relationship.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Seddon JM, Willett WC, Speizer FE, Hankinson SE <i>A prospective study of cigarette smoking and age-related macular degeneration in women</i> JAMA. 1996 Oct 9;276(14):1141-6</p>	<p>Prospective cohort study</p>	<p>31,843 registered nurses enrolled in the Nurses' Health Study who were ages 50 - 59 years in 1980 and did not report a diagnosis of cancer or AMD at the beginning of the study. Additional women entered the analytic cohort as they reached 50 years of age.</p>	<p>Relationship between cigarette smoking and incidence of age-related macular degeneration (AMD) among women</p>	<p>RESULTS: During 556,338 person-years of follow-up, 215 women were newly diagnosed as having AMD. After adjusting for other risk factors for AMD, women who currently smoked 25 or more cigarettes per day had a relative risk (RR) of AMD of 2.4 (95% confidence interval [CI], 1.4-4.0) compared with women who never smoked. Past smokers of this amount also had a 2-fold increased risk (RR=2.0; 95% CI, 1.2-3.4) relative to never smokers. Compared with current smokers, little reduction in risk was suggested even after quitting smoking for 15 or more years. Risk of AMD also increased with an increasing number of pack-years smoked (P for trend <.001); among women who smoked for 65 or more pack-years, the risk was 2.4 times the risk of never smokers (95% CI, 1.5-3.8). Analyses of dry and exudative types of AMD and other alternative definitions of AMD revealed similar results. CONCLUSION: Cigarette smoking is an independent and avoidable risk factor for AMD among women. Because AMD is the most common cause of severe visual impairment among the elderly and treatment is not available or is ineffective for most patients, reducing the risk of this disease is another important reason to avoid smoking.</p>
<p>Snodderly DM <i>Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins</i> Am J Clin Nutr. 1995 Dec;62(6 Suppl):1448S-1461S</p>	<p>Review</p>		<p>Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins</p>	<p>RESULTS: Epidemiologic data indicate that individuals with low plasma concentrations of carotenoids and antioxidant vitamins and those who smoke cigarettes are at increased risk for age-related macular degeneration (AMD). Laboratory data show that carotenoids and antioxidant vitamins help to protect the retina from oxidative damage initiated in part by absorption of light. Primate retinas accumulate two carotenoids, lutein and zeaxanthin, as the macular pigment, which is most dense at the center of the fovea and declines rapidly in more peripheral regions. The retina also distributes alpha-tocopherol (vitamin E) in a nonuniform spatial pattern. The region of monkey retinas where carotenoids and vitamin E are both low corresponds with a locus where early signs of AMD often appear in humans. CONCLUSION: The combination of evidence suggests that carotenoids and antioxidant vitamins may help to retard some of the destructive processes in the retina and the retinal pigment epithelium that lead to age-related degeneration of the macula.</p>

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Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Eye Disease Case-Control Study Group <i>Antioxidant status and neovascular age-related macular degeneration</i> Arch Ophthalmol. 1993 Jan;111(1):104-9</p>	<p>Case-controlled study</p>	<p>421 cases of neovascular age-related macular degeneration (AMD) ages 55 - 80 who were diagnosed in the year prior to enrollment and satisfied certain diagnostic criteria and 615 controls ages 55 - 80 who were free of any of the five case diagnoses</p>	<p>Association between higher serum levels of micronutrients with antioxidant capabilities and a decreased risk of neovascular age-related macular degeneration</p>	<p>RESULTS: Data from the Eye Disease Case-Control Study are consistent with hypotheses suggesting a reduced risk of neovascular AMD when higher levels of circulating micronutrients with antioxidant capabilities, in particular, carotenoids are present. CONCLUSION: It would be premature to use this finding to make recommendations about use of vitamin supplements. The possibility that persons with higher levels of nutrients differ from others in important but unrecognized ways that explain the decreased risk of AMD cannot be excluded. Unadjusted confounding may be of less concern in a randomized clinical trial.</p>
<p>Bernstein PS, Khachik F, Carvalho LS, Muir GJ, Zhao DY, Katz NB <i>Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye</i> Exp Eye Res. 2001 Mar;72(3):215-23</p>		<p>Human donor globes</p>	<p>Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye</p>	<p>RESULTS: Nearly all ocular structures examined with the exception of vitreous, cornea, and sclera had quantifiable levels of dietary (3R,3'R,6'R)-lutein, zeaxanthin, their geometrical (E / Z) isomers, as well as their metabolites, (3R,3'S,6'R)-lutein (3'-epilutein) and 3-hydroxy-beta,epsilon-caroten-3'-one. In addition, human ciliary body revealed the presence of monohydroxycarotenoids and hydrocarbon carotenoids, while only the latter group was detected in human RPE/choroid. Uveal structures (iris, ciliary body, and RPE/choroid) account for approximately 50% of the eye's total carotenoids and approximately 30% of the lutein and zeaxanthin. In the iris, these pigments are likely to play a role in filtering out phototoxic short-wavelength visible light, while they are more likely to act as antioxidants in the ciliary body. Both mechanisms, light screening and antioxidant, may be operative in the RPE/choroid in addition to a possible function of this tissue in the transport of dihydroxycarotenoids from the circulating blood to the retina. CONCLUSION: This report lends further support for the critical role of lutein, zeaxanthin, and other ocular carotenoids in protecting the eye from light-induced oxidative damage and aging.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Brown L, Rimm EB, Seddon JM, Giovannucci EL, Chasan-Taber L, Spiegelman D, Willett WC, Hankinson SE <i>A prospective study of carotenoid intake and risk of cataract extraction in US men</i> Am J Clin Nutr. 1999 Oct;70(4):517-24</p>	<p>Prospective cohort study</p>	<p>US male health professionals (n = 36644) who were 45 - 75 in 1986. Others were subsequently included as they became age 45.</p>	<p>Examine prospectively the association between carotenoid and vitamin A intakes and cataract extraction in men</p>	<p>RESULTS: We observed a modestly lower risk of cataract extraction in men with higher intakes of lutein and zeaxanthin but not of other carotenoids (alpha-carotene, beta-carotene, lycopene, and beta-cryptoxanthin) or vitamin A after other potential risk factors, including age and smoking, were controlled for. Men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract relative to men in the lowest fifth (relative risk: 0.81; 95% CI: 0.65, 1.01; P for trend = 0.03). Among specific foods high in carotenoids, broccoli and spinach were most consistently associated with a lower risk of cataract. CONCLUSION: Lutein and zeaxanthin may decrease the risk of cataracts severe enough to require extraction, although this relation appears modest in magnitude. The present findings add support for recommendations to consume vegetables and fruit high in carotenoids daily.</p>
<p>Chasan-Taber L, Willett WC, Seddon JM, Stampfer MJ, Rosner B, Colditz GA, Speizer FE, Hankinson SE <i>A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women</i> Am J Clin Nutr. 1999 Oct;70(4):509-16</p>	<p>Prospective cohort study</p>	<p>50,461 registered female nurses, ages 45 - 71 and free of diagnosed cancer, were followed beginning in 1980. Others were included as they became 45 years (Total n = 77,466)</p>	<p>Association between carotenoid and vitamin A intakes and cataract extraction in women</p>	<p>RESULTS: During 761,762 person-years of follow-up, 1,471 cataracts were extracted. After age, smoking, and other potential cataract risk factors were controlled for, those with the highest intake of lutein and zeaxanthin had a 22% decreased risk of cataract extraction compared with those in the lowest quintile (relative risk: 0.78; 95% CI: 0.63, 0.95; P for trend = 0.04). Other carotenoids (alpha-carotene, beta-carotene, lycopene, and beta-cryptoxanthin), vitamin A, and retinol were not associated with cataract in multivariate analysis. Increasing frequency of intakes of spinach and kale, foods rich in lutein, was associated with a moderate decrease in risk of cataract. CONCLUSION: Lutein and zeaxanthin and foods rich in these carotenoids may decrease the risk of cataracts severe enough to require extraction.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Chitchumroonchokchai C, Bomser JA, Glamm JE, Failla ML <i>Xanthophylls and alpha-tocopherol decrease UVB-induced lipid peroxidation and stress signaling in human lens epithelial cells</i> J Nutr. 2004 Dec;134(12):3225-32</p>			<p>Effects of xanthophylls and alpha-tocopherol (alpha-TC) on lipid peroxidation and the mitogen-activated stress signaling pathways in human lens epithelial (HLE) cells following ultraviolet B light (UVB) irradiation</p>	<p>RESULTS: When presented with LUT, ZEA, astaxanthin (AST), and alpha-TC as methyl-beta-cyclodextrin complexes, HLE cells accumulated the lipophiles in a concentration- and time-dependent manner with uptake of LUT exceeding that of ZEA and AST. Pretreatment of cultures with either 2 micromol/L xanthophyll or 10 micromol/L alpha-TC for 4 h before exposure to 300 J/m(2) UVB radiation decreased lipid peroxidation by 47-57% compared with UVB-treated control HLE cells. Pretreatment with the xanthophylls and alpha-TC also inhibited UVB-induced activation of c-JUN NH(2)-terminal kinase (JNK) and p38 by 50-60 and 25-32%, respectively. There was substantial inhibition of UVB-induced JNK and p38 activation for cells containing <0.20 and approximately 0.30 nmol xanthophylls/mg, respectively, whereas >2.3 nmol alpha-TC/mg protein was required to significantly decrease UVB-induced stress signaling. CONCLUSION: These data suggest that xanthophylls are more potent than alpha-TC for protecting human lens epithelial cells against UVB insult.</p>
<p>Hammond BR Jr, Wooten BR, Snodderly DM <i>Density of the human crystalline lens is related to the macular pigment carotenoids, lutein and zeaxanthin</i> Optom Vis Sci. 1997 Jul;74(7):499-504</p>		<p>Younger subjects (7 females ages 24 - 36 and 5 males ages 24 - 31) were compared with older subjects (23 females ages 55 - 78 years and 16 males ages 48 - 82)</p>	<p>Relationship between retinal carotenoids (i.e., macular pigment) used as a long-term measure of tissue carotenoids, and lens optical density used as an indicator of lens health</p>	<p>RESULTS: Lens density (440 nm) increased as a function of age ($r = 0.65$, $p < 0.001$), as expected. For the oldest group, a significant inverse relationship ($y = 1.53 - 0.83x$, $r = -0.47$, $p < 0.001$) was found between macular pigment density (440 nm) and lens density (440 nm). No relationship was found for the youngest group ($p < 0.42$). CONCLUSION: The main finding of this study was an age-dependent, inverse relationship between macular pigment density and lens density. Macular pigment is composed of lutein and zeaxanthin, the only two carotenoids that have been identified in the human lens. Thus, an inverse relationship between these two variables suggests that lutein and zeaxanthin, or other dietary factors with which they are correlated, may retard age-related increases in lens density.</p>

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Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Hankinson SE, Stampfer MJ, Seddon JM, Colditz GA, Rosner B, Speizer FE, Willett WC <i>Nutrient intake and cataract extraction in women: a prospective study</i> BMJ. 1992 Aug 8;305(6849):335-9</p>	<p>Prospective cohort study</p>	<p>Female registered nurses ages 45 - 67. 50,828 women were included in 1980 and others were added as they became age 45</p>	<p>Association between dietary intake of vitamins C and E, carotene, and riboflavin and cataract extraction in women</p>	<p>RESULTS: 493 cataracts were extracted during 470,302 person years of follow up. Intake of carotene and vitamin A was inversely associated with cataract: in multivariate analyses, women in the highest fifth of total vitamin A intake (excluding supplements) had a 39% lower risk of cataract relative to women in the lowest fifth (relative risk 0.61; 95% confidence interval 0.45 to 0.81). Neither riboflavin nor dietary vitamins E or C were associated with cataract in a multivariate analysis. Among specific food items spinach (rather than carrots, the greatest source of beta carotene) was most consistently associated with a lower relative risk. The risk of cataract was 45% lower among women who used vitamin C supplements for 10 or more years (relative risk 0.55 (0.32 to 0.96)), but no association was noted for multivitamin intake. CONCLUSION: Dietary carotenoids, although not necessarily beta carotene, and long term vitamin C supplementation may decrease the risk of cataracts severe enough to require extraction.</p>
<p>Lyle BJ, Mares-Perlman JA, Klein BE, Klein R, Greger JL <i>Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study</i> Am J Epidemiol. 1999 May 1;149(9):801-9</p>		<p>Normal and cataractous human lenses</p>	<p>Determine the levels of carotenoids, retinoids, and tocopherols in normal and cataractous human lenses</p>	<p>RESULTS: On a per gram wet weight of tissue basis, human lenses contained 11 to 25 ng xanthophylls (lutein and zeaxanthin), 31 to 50 ng retinol, 21 to 25 ng retinyl palmitate, 1573 to 2550 ng alpha-tocopherol, and 257 to 501 ng gamma-tocopherol. Concentrations of lutein, zeaxanthin, and retinol were significantly higher in Indian cataractous lenses than in American normal or cataractous lenses. There were no differences in the lutein-zeaxanthin, retinoid, or alpha-tocopherol contents between American normal lenses and American cataractous lenses. The range of ratios of lutein to zeaxanthin in human lenses was 1.6 to 2.2. The mean age of the Indian lens donors was 20 years younger than the American lens donors. Comparisons using contralateral lenses indicated that there was significant interindividual variance in human lens concentrations of xanthophylls, retinoids, and tocopherols. beta-carotene and lycopene, major carotenoids in human serum and other tissues, were not detected in human lenses. CONCLUSION: Xanthophylls (lutein and zeaxanthin) are the only carotenoids detected in human lens. Retinol, retinyl palmitate, and alpha- and gamma-tocopherols also are present in human lens. Determinants of lens concentration of nutrients are not defined, but dietary factors are likely to be important.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Kruger CL, Murphy M, DeFreitas Z, Pfannkuch F, Heimbach J <i>An innovative approach to the determination of safety for a dietary ingredient derived from a new source: case study using a crystalline lutein product</i> Food Chem Toxicol. 2002 Nov;40(11):1535-49	Review		Safety of crystalline lutein product	RESULTS: There is no evidence in the available information that demonstrates or suggests reasonable grounds to suspect a hazard to public health when crystalline lutein product is used at levels that are now current or that might reasonably be expected from the proposed applications. CONCLUSION: FloraGLO crystalline lutein is a safe and generally recognized as safe (GRAS) source of its proposed use in food.
Age-Related Eye Disease Study Research Group <i>A Randomized, Placebo-controlled Clinical Trial of High-dose Supplementation with Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss (AREDS Report No. 8)</i> Arch Ophthalmol, Vol 119, Oct 2001	Randomized placebo-controlled trial	3640 enrolled study participants, aged 55-80 years, for an average of 6.3 years, 2.4% attrition in follow-up	Evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity	RESULTS: Compared with placebo demonstration, a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc. Both zinc and antioxidants with zinc significantly reduced the odds of developing advanced AMD in the higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants plus zinc. No statistically significant adverse effect was associated with any of the formulations. CONCLUSION: Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large drusen, noncentral geographic atrophy in 1 or both eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc.
Ciulla, T, Curran-Celantano, J, et al <i>Macular Pigment optical density in a Midwestern sample</i> OphSource, Ophthalmology, Vol 108, Issue 4, pages 730-737, April 2001	Prevalence study in self-selected population	280 health adult volunteers, 138 male, 142 female, ages 18-50, recruited from the general population	Macular pigment optical density	Assess the distribution of the macular pigments lutein and zeaxanthin in a health sample more representative of the general population than past studies. Which dietary factors and personal characteristics might explain the large interindividual differences in the density of macular pigment? RESULTS: When all variables were considered together in a general linear model of determinants of macular pigment, statistically significant relationships were found between MP density and serum L and Z, dietary L and Z intake, fiber intake, and iris color. CONCLUSION: These data suggest that MP values in this health adult population are lower than in smaller select samples. Moreover, these data indicate that MP is related to serum L and Z, dietary L and Z, fiber intake and iris color.
Parkinson, J. <i>AMD: A Changing Diagnostic and Management Paradigm: a new detection device and research findings are empowering general ophthalmologists to treat AMD patients</i> OphthalManagement, 2005	Editorial			

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Richer, S, O.D., Ph.D., FAA <i>Gaining Ground In the War on AMD</i> Review of Optometry Online	Editorial			
Bartlett, H and Eperjesi, F <i>A randomized controlled trial investigating the effect of nutritional supplementation on visual function in normal, and age-related macular disease affected eyes: design and methodology</i> Nutrition Journal 2003, 2:12	Randomized controlled trial	63 normal (w/o AMD) and 96 w /AMD	Nutritional supplement containing lutein, vitamins A, C, E, zinc and copper on measure of visual function in people w and w/o AMD	A positive effect on normals may be indicative of a role of nutritional supplementation in preventing or delaying onset of the condition. An observed benefit in the age-related macular disease group may indicate a potential role of supplementation in prevention of progression, or even a degree reversal of the visual effects caused by this condition.
Mares-Perlman, J., Millen, A., Ficek, T., Hankinson, S. <i>The Body of Evidence to Support a Protective Role for Lutein and Zeaxanthin in Delaying Chronic Disease. Overview</i> J Nutr 132:518S-524S, 2002 American Society for Nutritional Sciences, Supplement 0022-3166, 2002	Overview			Recent evidence introduces the possibility that L and Z may protect against the development of the two common eye diseases of aging, cataract and AMD. This potential and the lack of other effective means to slow the progression of AMD have fueled high public interest in the health benefits of L and Z and the proliferation of supplements containing them on pharmacy shelves. [The] overall body of evidence is insufficient to conclude that increasing levels of L and Z specifically, will confer an important health benefit. Future advances in scientific research are required to understand the effect of their consumption, independent of other nutrients in fruits and vegetables, on human health. The newly advanced ability to measure level of L and Z in the retina in vivo creates a unique opportunity to contribute some of this needed evidence.
Garattini L, Castelnovo E, Lanzetta P, Viscarra C, Ricci E, Parazzini F, CARMA Study Group <i>Direct Medical Costs of Age-Related Macular Degeneration in Italian Hospital Ophthalmology Departments. A Multicenter, prospective 1-year study.</i> Eur J Health Econ. 2004 Feb; 5(1):22-7	Multicenter prospective 1-year study	7 centers, 476 patients, aged 50+ years into three groups (a) drusen (b) geographic atrophy (c) retinal changes with CNV	Reimbursed costs plus patient out of pocket	RESULTS: Mean cost per patient per year was 383,2 euro; patients with CNV were far more costly (540,1 euro, vs. 158,1 euro for drusen and 147,9 euro for geographic atrophy). Hospital costs and diagnostics were the main cost determinants. Services directly paid for by the patients (private consult and OTC) amounted to 46,5 euro for patients with CNV, 50,3 euro for drusen, and 68,8 euro for geographic atrophy. CONCLUSION: The major finding of the study was that the presence of CNV involved higher expenditure than drusen or geographic atrophy. This suggests that the costs of AMD rise significantly with the severity of illness.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<i>Preferred Practice Pattern: Age-Related Macular Degeneration</i> Prepared by the American Academy of Ophthalmology Retinal Panel, 2003	Overview			
Young I S, Fletcher A E, Chakravarthy U, DeJong P V T M, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F and Vioque J <i>Lutein, Zeaxanthin, Vitamin C and Age-Related Maculopathy in the EUREYE Study</i> Invest Ophthalmol Vis Sci 2004; 45	Evaluation of a random sample population	4760 randomly sampled people aged 65 and over, eye exam and risk factor assessment in seven study centers across Europe	Investigate the association of lutein, zeaxanthin and vitamin C with age related maculopathy	RESULTS: In either age or sex adjusted or fully adjusted analyses there were no significant trends for lutein, zeaxanthin or vitamin C with early ARM or with AMD. The lowest decile of vitamin C was in the range associated with biochemical depletion and suggested a small adverse association with AMD. Similar effects were observed also from the lowest decile of zeaxanthin and a weaker association for lutein. People with the lowest levels of both vitamin C and zeaxanthin were at highest risk of AMD. CONCLUSION: In a European population, we found no evidence to support an important association across the full distribution of vitamin C, lutein or zeaxanthin levels with stage of ARM. A high risk for AMD was observed for a small portion of people with very low levels of antioxidant.
Cardinault N, Gorrard J M, Tyssandier V, Grolier P, Rock E, Borel P <i>Short-term Supplementation with Lutein Affects Biomarkers of Lutein Status Similarly in Young and Elderly Subjects</i> ExperGerontol, Vol 38:5, May 2003, Pages 573-82			Effect of age on lutein status	Are there major differences in the status of lutein between young and elderly subjects? Initial lutein status and the effect of a 5-week supplementation (9 mg/d) on the most common markers of lutein status were compared in 12 young (26.9 +/- 0.8 yr) and 17 older subjects (67.3 +/- 1.1 yr). RESULTS: Plasma and buccal mucosa cells lutein concentrations significantly increased in both groups after lutein supplementation, but not macular pigment optical density or adipose tissue lutein. There was no significant difference between the two groups. CONCLUSION: These results suggest that there is no major effect of age on lutein status in healthy subjects.
Congdon N, O'Colmain B, Klaver CC, Klein R, Freidman DS, Kempen J, Taylor HR, Mitchell P; Eye Diseases Prevalence Research Group <i>Causes and Prevalence of Visual Impairment Among Adults in the United States</i> ArchOphthalmol. 2004 Apr;122 (4):477-85.	Review			RESULTS: Based on demographics from the 2000 US Census, an estimated 937,000 (0.785) Americans older than 40 years were blind (US definition). An additional 2.4 million Americans (1.98%) had low vision. The leading cause of blindness among white persons was age-related macular degeneration (54.4% of the cases), while among black persons, cataract and glaucoma accounted for more than 60% of blindness. CONCLUSIONS: Blindness or low vision affects approx 1 in 28 Americans older than 40 years. The specific causes of visual impairment, and especially blindness, vary greatly by race/ethnicity. The prevalence of visual disabilities will increase markedly during the next 20 years, owing largely to the aging of the US population.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Berendschot TTJM, Willemsse-Assink JJM, Bastiaanse M, de Jong PTVM, van Norren D; <i>Macular Pigment and Melanin in Age-Related Maculopathy in a General Population</i> Invest Ophthalmol Vis Sci 2002 Jun; 43(6):1928-1932.	Random population based sample	Subset of a population based cohort study among residents 55 years of age and older in a suburb of Rotterdam		CONCLUSIONS: No differences in macular pigment and melanin optical density were found between eyes with and without age-related maculopathy (ARM) or between the various ARM stages.
Beatty S, Murray IJ, Henson DB, Carden D, Koh HH, Boulton ME; <i>Macular Pigment and Risk for Age-Related Macular Degeneration in Subjects from a Northern European Population</i> Invest Ophthalmol Vis Sci 2001 Feb; 42(2):439-446.	Recruited volunteers	46 volunteers between 21-81 years of age with healthy maculae and 9 patients with advanced neovascular AMD in one eye	Each high-risk eye was matched with a control subject based on iris color, age, smoking habits, gender, and lens density.	RESULTS: There was an age-related decline in the optical density of macular pigment among volunteers with no ocular disease. Healthy eyes predisposed to AMD had significantly less MP than healthy eyes at no such risk. CONCLUSIONS: The two most important risk factors for AMD are associated with a relative absence of MP. These findings are consistent with the hypothesis that supplemental lutein and zeaxanthin may delay, avert, or modify the course of this disease.
Wooten BR, Hammond Jr BR, Land RI, Snodderly DM; <i>A Practical Method for Measuring Macular Pigment Optical Density</i> Invest Ophthalmol Vis Sci 1999 Oct; 40(11):2481-2489.	30 subjects	14 men and 16 women between 16-60 years of age	Macular pigment density measured using two techniques.	RESULTS: Macular pigment density of 30 subjects was measured with both stimulus systems. Macular pigment measured with the LED tabletop device in free view was highly correlated with MP measured in Maxwellian view. The average absolute difference between the two techniques was 0.04. The new technique was not significantly affected by variations in lens optical density, pupil size, or small head movements. CONCLUSIONS: Psychosocial measurement of MP provides a unique opportunity to make repeated noninvasive assessment of the concentration of a protective nutrient in the retina. The availability of this new device should make this measurement technology accessible to a wide variety of investigators for application to diverse populations.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Rock CL, Thornquist MD, Neuhouser ML, Kristal AR, Neumark-Sztainer D, Cooper DA, Patterson RE, Cheskin LJ; <i>Symposium: Can Lutein Protect Against Chronic Disease? Diet and Lifestyle Correlates of Lutein in the Blood and Diet</i> JNutr 2002; 132:525S-530S.	Cross-sectional analysis of a larger project	Heterogeneous community-based sample of adults aged 18-92 across 3 US sites. Those with a medical condition that would confound the measurement of associations between dietary and serum fat-soluble nutrients were excluded. To participate, individuals also had to meet specific criteria.	Correlation between dietary + zeaxanthin intake and the determinants of serum lutein and zeaxanthin concentrations	RESULTS: Demographic characteristics, dietary intake, serum cholesterol concentration, body mass index and smoking explained 24% of the variance in serum lutein concentration. Race/ethnicity, education level and smoking explained 24% of the variance in serum lutein concentration. Race/ethnicity, education level and smoking had the strongest associations with serum lutein concentration. Every 10% increase in dietary lutein + zeaxanthin intake was associated with a 2.4% increase in serum lutein concentration. CONCLUSION: The amount of variance in serum concentration that is explained by demographic characteristics, health-related behaviors and lifestyle factors remains substantial.
Krinsky NI; <i>Symposium: Can Lutein Protect Against Chronic Disease? Possible Biologic Mechanisms for a Protective Role of Xanthophylls</i> JNutr 2002; 132:540S-542S.	Literature survey			This contribution surveys the evidence linking the presence of the two xanthophylls, lutein and zeaxanthin, to a protective role in the macular region of the retina. Although the evidence is still associative in nature, it is biologically plausible, and may be resolved with additional intervention trials.
Bone RA, Landrum JT, Guerra LH, Ruiz CA; <i>Biochemical and Molecular Actions of Nutrients Lutein and Zeaxanthin Dietary Supplements Raise Macular Pigment Density and Serum Concentrations of these Carotenoids in Humans</i> JNutr 2003; 133:992-998.	Subjects were recruited from a University community	Subjects over 18 years and of either sex were trained then screened for proficiency in flicker photometry. 90% passed this criterion.	Comparison of the effects of a range of lutein doses as well as a high zeaxanthin dose on the serum and macular pigment in a series of experiments	RESULTS: Serum lutein concentrations in each subject reached a plateau that was correlated with the dose. Zeaxanthin was less well absorbed than an equal lutein dose. The rate of increase in macular pigment optical density was correlated with the plateau concentration of carotenoids in the serum, but not with the presupplemental optical density. CONCLUSIONS: It remains to be demonstrated whether lutein or zeaxanthin dietary supplements reduce the incidence of AMD.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Beatty S, Nolan J, Kavanagh H, O'Donovan O; <i>Macular pigment optical density and its relationship with serum and dietary levels of lutein and zeaxanthin</i> Archives of Biochemistry and Biophysics 2004 Oct; 430(1):70-76.	Literature review			It has been shown that MP is entirely of dietary origin, and that L and Z levels in serum, diet, and retina correlate. However, the nature of the relationships between L and Z in foodstuffs, blood, and macula is confounded by many variables including processes which influence digestion, absorption, and transport of the compounds in question, and accumulation and stabilization of the carotenoids in the tissues. If macular pigment is protective for age-related maculopathy, a clear understanding of the mechanisms whereby L and Z arrive at the target tissue (retina) from their source (foodstuff) is essential. This paper reviews the literature gemane to this growing interest.
Aleman TS, Cideciyan AV, Chico JD, Schwartz SB, Windsor EAM, Smilko EE, Pantelyat AY, Maguire MG, Jacobson SG; <i>Macular Pigment And Lutein Supplementation In Macular Diseases</i> Invest Ophthalmol Vis Sci 2004; 45		25 patients with inherited macular disease and documented foveal fixation had MP optical density measured with heterochromatic flicker photometry	Effects on MP and central vision of 6 months of lutein supplementation at 20 mg/day were determined.	RESULTS: MP density in the patients, as a group, was significantly lower than normals, but there was a large range of MPOD. Patients with lower MP tended to have more severe disease expression. Foveal retinal thickness by OCT was positively correlated with MP density in the patients. After 6 months of supplementation, a subset of patients showed a statistically significant increase in MP; all participants showed an increase in serum lutein. Central vision was unchanged 6 months post-supplementation. CONCLUSIONS: As a group, patients with inherited maculopathies showed lower MP levels than normals. MP in patients may be affected by stage of retinal disease, especially that leading to abnormal foveal architecture. MP could be augmented with 6 months of lutein supplementation in some patients. There was no change in central vision in the short-term. The long-term influence of lutein supplementation on the natural history of macular disease is worthy of further study.
Aleman TS, Duncan JL, Bieber ML, de Castro E, Marks DA, Gardner LM, Steinberg JD, Cideciyan AV, Maguire MG, Jacobson SG; <i>Macular Pigment and Lutein Supplementation in Retinitis Pigmentosa and Usher Syndrome</i> Invest Ophthalmol Vis Sci 2001 Jul; 42(8):1873-1881.		Patients with diagnosis of RP or Usher Syndrome and normal subjects; Patients were categorized into 2 groups: the entire study group of patients with retinal degeneration and a subset of this group who underwent a pilot trial of supplementation with lutein	Determine macular pigment in patients with inherited retinal degeneration and the response of MP and vision to supplementation of Lutein.	RESULTS: MP density in the patients as a group did not differ from normal. Among patients with lower MP, there was a higher percentage of females, smokers, and light-colored irides. Disease expression tended to be more severe in patients with lower MP. Inner retinal thickness by OCT correlated positively with MP density in the patients. After supplementation, all participants showed an increase in serum lutein. Only approximately half the patients showed a statistically significant increase in MP. Retinal nonresponders had slightly greater disease severity but were otherwise not distinguishable from responders. Central vision was unchanged after supplementation. CONCLUSIONS: Factors previously associated with lower or higher MP density in normal subjects showed similar associations in RP and Usher syndrome. In addition MP in patients may be affected by stage of retinal disease, especially that leading to abnormal foveal architecture. MP could be augmented by supplemental lutein in many but not all patients. There was no change in central vision after 6 months of lutein supplementation, but long-term influences on the natural history of these retinal degenerations require further study.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C; <i>Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation</i> Health Technology Assessment 2003; 7(9)	Review of randomized controlled trials and economic evaluations addressing the clinical effectiveness and cost-utility of PDT in AMD was undertaken			CONCLUSIONS: There is a need to conduct a large, multicenter, publicly funded pragmatic double-blind RCT with parallel health economic evaluation to assess not just the impact of PDT on visual acuity and adverse events, but also directly measured global quality of life and survival. There is no indication of the relationship between benefits and costs where wet AMD effects the worse-seeing eye first. Treatment of wet AMD, with verteporfin, other types of PDT, and other new technologies is an area under very active investigation, so this technology should be kept under close review.
American Academy of Ophthalmology. <i>Complementary Therapy Assessment: Antioxidant Supplements and Age-Related Macular Degeneration</i> 2002 Jan	Survey of several studies focusing on the Age-Related Eye Disease Study			CONCLUSIONS: A prospective, randomized, controlled clinical trial supports the use of antioxidant vitamins and minerals in patients with intermediate-risk non-neovascular AMD to reduce the rate of progression to advanced AMD. The role of antioxidant supplements in the prevention of AMD or in slowing progression of AMD for those with the early stages of the disease has not been adequately answered in randomized, controlled trials. Observational studies have returned conflicting results. It is possible that there are long-term risks in high levels of supplementation of specific antioxidants.
Thomson LR, Toyoda Y, Langner A, Delori FC, Garnett KM, Craft N, Nichols CR, Cheng KM, Dorey CK; <i>Elevated Retinal Zeaxanthin and Prevention of Light-Induced Photoreceptor Cell Death in Quail</i> Invest Ophthalmol Vis Sci 2002 Nov; 43(11):3538-3549.	Animal study	First generation chicks from selected adult Japanese quail raised in the Dept of Animal Science in Vancouver.	Test whether retinal zeaxanthin prevents light-induced photoreceptor cell death.	RESULTS: After 7 days' supplementation, concentrations of zeaxanthin in serum, liver, and fat had increased. In contrast, retinal zeaxanthin fluctuated significantly upward on day 3, but there was no net change on day 7. The number of apoptotic rods and cones in light-damaged eyes correlated significantly and inversely with zeaxanthin concentration in the contralateral retina, but not with serum zeaxanthin. Similar correlations were observed with retinal lutein, which correlated strongly with retinal zeaxanthin. CONCLUSIONS: Retinal zeaxanthin dose dependently reduced light-induced photoreceptor apoptosis; elevated serum levels did not. These data provide the first experimental evidence that xanthophylls carotenoids protect photoreceptors in vivo.
Ciulla TA, Hammond BR Jr; <i>Macular pigment density and aging, assessed in the normal elderly and those with cataracts and age-related macular degeneration</i> Am J Ophthalmol 2004 Oct; 138(4):582-7.	Prospective, observational, cross-sectional study	Cross-section of elderly including those with lenticular or age-related macular degeneration, or both.	MP density measured based on flicker photometry	MP does not change significantly with age, even when elderly subjects with cataracts and AMD are considered. Using heterochromic flicker photometry, elderly subjects display a full range of MP density that is similar to young subjects.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Gale CR, Hall NF, Phillips DIW, Martyn CN; <i>Lutein and Zeaxanthin Status and Risk of Age-Related Macular Degeneration</i> Invest Ophthalmol Vis Sci 2003 Jun; 44(6):2461-2465	Cohort	Office for National Statistics traced 4793 individual whose births were recorded between 1922-1930. Those living were asked to take part.	Investigate the relation between plasma concentrations of lutein and zeaxanthin and age-related macular degeneration	RESULTS: Risk of age-related macular degeneration (early or late) was significantly higher in people with lower plasma concentrations of zeaxanthin. Compared with those whose plasma concentrations of zeaxanthin were in the highest third of the distribution, people whose plasma concentration as in the lowest third had an odds ratio for risk of age-related macular degeneration of 2.0 after adjustment for age and other risk factors. Risk of age-related macular degeneration was increased in people with the lowest plasma concentrations of lutein plus zeaxanthin and in those with the lowest concentrations of lutein, but neither of these relations was statistically significant. CONCLUSIONS: These findings provide support for the view that zeaxanthin may protect against age-related macular degeneration.
Wintch SW, Zhao D, Emakov IV, McClane RW, Gellermann W, Bernstein PS; <i>A Double Blind, Placebo Controlled, Lutein Supplementation Study Evaluating Two Macular Carotenoid Measurement Methods: Resonance Raman Spectroscopy and Heterochromatic Flicker Photometry</i> Invest Ophthalmol Vis Sci 2003; 44:1744.		20 subject; 9 took lutein supplements and 11 took placebos	Comparison of two optical techniques to quantify macular pigments: resonance Raman spectroscopy and heterochromatic flicker photometry	RESULTS: RRS and HFP correlated significantly throughout the test period. RRS showed significant rises in macular pigment after lutein supplementation; HFP showed no such rise. The placebo group remained unchanged during the test period. RRS intrasession and intersession measurements were more repeatable than those of HFP. Neither method correlated significantly with serum levels of lutein. CONCLUSIONS: RRS is a specific and sensitive method for measuring macular pigment levels that in our hands is more precise and repeatable than HFP. As an objective method, RRS is reliable even in individuals with significant macular pathology, and we have previously shown with RRS and macular carotenoid levels are significantly lower in AMD eyes relative to age-matched controls. The ability to raise ocular lutein levels in healthy eyes encourages further study into whether similar rises would occur in AMD eyes.
Chew EY, Ferris FL, de Monasterio FM, Thompson DJ, Kim J, Csaky CG, Woods M, Khachik F, Bone R, Landrum J; <i>Dose Ranging Study of Lutein Supplementation in Persons Over Age 60</i> Invest Ophthalmol Vis Sci 2003; 44:968.	Random assignment	15 patients with small drusen, 15 with large drusen, and 15 with advanced AMD were randomly assigned to receive one of three oral daily doses of lutein for 6 months	Evaluate association of varying doses of oral supplementation of lutein with plasma levels of lutein in people over age 60 with and without AMD.	RESULTS: Serum lutein levels increased at 1 month and peaked by 3 months of supplementation. When the lutein was discontinued, all serum lutein levels returned to near pretreatment values. No adverse effects were observed that could be attributed to lutein supplementation. Visual acuity remained essentially unchanged during the 6-month dosing period. At baseline, heterochromatic flicker estimates of macular pigment density were observably lower in the end stage AMD group compared with the others. However, there were no large changes in estimated macular pigment density within or between groups during the supplementation period. CONCLUSIONS: A dose response relationship exists between oral lutein supplementation and serum lutein levels. No adverse experiences were attributed to the lutein supplementation and serum levels. Other epidemiologic evidence suggests that lutein may play an important role in the treatment of age-related macular degeneration. A large cohort study of oral supplementation with adequate sample size is needed to investigate the potential and long-term treatment effects of lutein for AMD.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Carpenter KJ, Harper AE, Olson RE; <i>Symposium: Experiments That Changed Nutritional Thinking</i> <i>Experiments that Changed Nutritional Thinking</i> J Nutr 1997; 127:1017S-1053S.	Review of nutritional experiments			The objective of this symposium was to describe some of the discoveries made during the past 150 years that changed the direction of thinking in nutrition.
Mayne ST; <i>Biomarkers of Nutritional Exposure and Nutritional Status</i> <i>Antioxidant Nutrients and Chronic Disease: Use of Biomarkers of Exposure and Oxidative Stress Status in Epidemiologic Research</i>	Review			This review concentrates on the following antioxidant nutrients: β -carotene and other carotenoids, vitamin E, vitamin C and selenium. The first part of the review emphasizes the utility of biological markers of exposure for these nutrients and the relationship to dietary intake data. The second part considers functional assays of oxidative stress status in humans including the strengths and limitations of various assays available for use in epidemiologic research. The review concludes with a discussion of methodologic issues and challenges for studies involving biomarkers of exposure to antioxidant nutrients and of oxidative stress status.
Marshall JR, <i>Biomarkers of Nutritional Exposure and Nutritional Status</i> <i>Methodologic and Statistical Considerations Regarding Use of Biomarkers of Nutritional Exposure in Epidemiology</i> J Nutr 2003; 133:881S-887S				The goal of this paper is to describe aspects of accuracy – reproducibility, reliability, and validity – as they apply to biomarkers in nutritional epidemiology.
Heber D, Bowerman S; <i>American Institute for Cancer Research 11th Annual Research Conference on Diet, Nutrition and Cancer</i> <i>Applying Science to Changing Dietary Patterns</i> J Nutr 2001; 131:3078S-3081S				The intake of 400-600 g/d of fruits and vegetables is associated with reduced incidence of many common forms of cancer. These foods contain phytochemicals that can modulate gene expression to inhibit carcinogenesis via multiple pathways. Many phytochemicals are colorful, providing an easy way to communicate increased diversity of fruits and vegetables to the public. The color code provides simplification, but it is also important as a way to help consumers to find common fruits and vegetables easily while traveling, eating in restaurants or working. At home, simple ways of preparing foods rapidly and easily are needed to influence dietary patterns.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Koh HH, Murray IJ, Feather JW, Carden D, Nolan DJ; <i>Macular Pigment Optical Density in Early, Age-Related Maculopathy (ARM); Comparisons With Normals and Effects of a Lutein Supplement</i> Invest Ophthalmol Vis Sci 2002; 43:2562</p>		<p>First study: 8 patients (age range 60-81, normal visual acuity) with early ARM compared with normals matched for sex, eye color, and age. Second study: MP optical density is measured in 8 patients (6 from first group) and 6 normals who are taking lutein over an 18 week period</p>	<p>MP optical density and effect of Lutein supplement in both groups</p>	<p>RESULTS: ARM unaffected eyes had significantly lower MP optical density than normals. After 12 weeks of the Lutein supplement the increase in MP optical density was slightly greater in the normals than the patients. This difference did not reach statistical significance. In the 8 cases of unilateral ARM, both right and left eyes showed a similar increase in MP optical density. CONCLUSION: Eyes at risk of developing ARM have lower MP optical density than those at no such risk. The data add credibility to the prospective protective role of MP. Second affected and fellow ARM patients' eyes respond equally to a lutein supplement suggesting that, at least in the early stages of ARM, the disease does not impede the deposition of Lutein in the retina.</p>
<p>Richer SP, Tsipursky M, Pulido J; <i>Macula Pigment Optical Density is Enhanced with Lutein Supplementation Independent of AREDS AMD Disease Stage</i> Invest Ophthalmol Vis Sci 2003; 44-969</p>		<p>Subset of patients in the Veterans LAST Study</p>	<p>Evaluated AREDS retinal disease stage vs. MPOD/visual function</p>	<p>RESULTS: Lutein supplementation enhanced MPOD in AREDS geographic stage IV, stage III and stage II. Lutein quickened glare recovery independent of AREDS retinal stage. Lutein supplementation had no significant effect on CSF for AREDS stage II or III, however significantly improved CSF at 3 of 4 spatial frequencies in geographic stage IV advanced disease. CONCLUSIONS: This small population, brief time frame study demonstrates 1) Lutein supplementation increases MPOD at each AREDS stage compared with placebo; 2) Lutein may be beneficial at all stages of atrophic AMD; 3) GR appears the best indicator of enhanced macula pigment.</p>

Appendix A: Lutein Evidence

TECHNICAL LITERATURE REVIEWED

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Alves-Rodrigues A., Ph.D. Absorption of Lutein vs. Lutein Esters: do we know the differences? Kemin Health Technical Literature 2004	Review	Johnson study: 10 volunteers; Bowen study: 18 volunteers	Absorption of lutein versus lutein esters	Johnson study: daily doses over nine days from four sources, including lutein from spinach (6 mg), lutein supplements (6 mg), lutein esters supplements (10.23 mg); Bowen study: single dose of lutein or lutein esters based on per kilogram body weight RESULTS: There is increasing evidence that lutein plays an important role in eye health. Several clinical studies have shown that consumption of lutein from foods and from supplements containing lutein or lutein esters can increase serum lutein levels and macular pigment density. There are no published studies showing the bio-equivalence of lutein versus lutein esters. Prior to absorption, lutein esters require conversion into lutein by hydrolysis of the fatty acids. A conversion rate of 2:1 between lutein esters and lutein is theoretical and does not reflect what happens in the human body. Absorption of lutein and lutein esters is affected by several variables such as period of supplementation, formulation, dietary fat, and age. CONCLUSION: . The studies (of Johnson and Bowen) discussed in this article do not address all the pharmacokinetic variables referred to above and, hence, are inconclusive regarding the absorption or the bioavailability of lutein versus lutein esters.
Alves-Rodrigues A. Ph.D., Enzymatic digestion of lutein diesters Kemin Health Technical Literature 2004	Review		Enzymatic digestion of lutein diesters	RESULTS: With the exception of human pancreatic lipase enzymes, which did not react with carotenoid esters at all, all other enzymes accepted carotenol esters. Considerably low yields of lutein esters were observed for all enzymes tested. CONCLUSION: The first enzymatic assay for hydrolysis of carotenoid esters has been developed. Human pancreatic lipase is not involved in the conversion of lutein esters to free lutein. Cholesterol esterase is a candidate for conversion of lutein esters to lutein, which occurs with efficiency below 5%.
Sousa-Martins D. Pharm.D., Alves-Rodrigues A. Ph.D., Overview of lutein absorption and distribution in humans Kemin Health Technical Literature 2004	Review		Lutein absorption and distribution	RESULTS: Lutein follows an absorption model similar to that of other dietary lipids. The exclusive serum transport of lutein by lipoproteins as well as its high specificity for the xanthophyll-binding-protein (XBP) are key factors in lutein distribution and may, in part, explain the selective presence of lutein in the macula. Only lutein, not lutein esters, is found in chylomicrons. CONCLUSION: Several studies have been performed, yet little is known about the absorption and distribution of lutein. Existing scientific evidence about absorption and distribution of lutein seems to be more clear and consensual. New in depth studies of the lutein absorption pattern are needed in order to consistently build an ADME model for lutein and support the results mentioned above.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Barnes H. Ph.D., Lewis B. Ph.D., Fullmer L., FloraGLO lutein - A natural source of the macular xanthophylls Kemin Health Technical Literature 2005</p>			<p>FloraGLO lutein - A natural source of the macular xanthophylls</p>	<p>RESULTS: The macula is the center of the retina and provides the maximal level of visual acuity due to its high concentration of cone receptors. Photooxidative damage to this area can progress to the leading cause of blindness (age-related macular degeneration (AMD)) in Americans. Lutein is concentrated in the macula and thought to limit photo-oxidative damage in the eye both passively, by absorbing blue light, and actively, by quenching free radicals. CONCLUSION: Epidemiological and clinical data continue to support the role of lutein (L) and zeaxanthin (Z) in ocular health. FloraGLO lutein is a natural source of both lutein (L) and zeaxanthin (Z) and contains L Z ratios similar to green vegetables. FloraGLO lutein (from marigold flower oleoresins) is safe, effective, and available in all natural, preservative-free, Kosher, non-GMO, and vegetarian grade FloraGLO formulations.</p>
<p>Alves-Rodrigues A. Ph.D., Carotenoids interactions in humans Kemin Health Technical Literature 2004</p>		<p>20 women ages 21 - 39 randomly divided into 2 groups of 10</p>	<p>Carotenoids Interactions</p>	<p>Three week supplementation with 96 g of tomato puree/day (15 mg lycopene + 1.5 mg β-carotene) or 92 g cooked chopped spinach/day (12 mg lutein + 8 mg β-carotene) or 96 g tomato puree/day + 92 g chopped spinach/day or 96 g tomato puree/day + 2 lutein pills (12 mg FloraGLO)/day or 92 g chopped spinach/day + 1 lycopene pill (15 mg Lycored)/day RESULTS: Carotenoids may interact with each other at any point during the absorption, metabolism, and transport processes, however, available research shows numerous inconsistencies with respect to the nature and extent of this interaction. When given simultaneously, lutein, β-carotene, and lycopene compete for incorporation into chylomicrons. Three weeks cosupplementation trial did not diminish plasma concentrations of lutein, β-carotene, or lycopene. CONCLUSION: There is competition between lutein, β-carotene, and lycopene regarding their post prandial appearance in the plasma. Future research on potential carotenoid interactions should not rely solely on portprandial testing because such studies do not reflect medium or long-term observations and can be misleading.</p>

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Shao A. Ph.D., Bioavailability of lutein: spinach vs. FloraGlo lutein Kemin Health Technical Literature 2004			Specific role of lutein in protection from age-related macular degeneration (AMD)	RESULTS: Evidence to support a protective role for lutein in AMD continues to be generated. Putative xanthophyll-binding protein (XBP) has been shown to bind selectively and specifically to the xanthophylls (lutein, zeaxanthin, β -cryptoxanthin) with the highest affinity being for lutein. In contrast, other plasma binding proteins had little or no affinity for any of the carotenoids. CONCLUSION: A specific lutein binding protein is present in the human retina. The results suggest that the XBP may serve as a transport protein, whose function is to transport lutein and zeaxanthin from the serum and/or retina into the macula.
Shao A, Lewis B Lutein supplementation and age-related macular degeneration: the body of evidence Kemin Health Technical Literature			Lutein (L) supplementation and age-related macular degeneration (AMD)	RESULTS: Current research appears to support a beneficial role for lutein in eye health. Increased lutein intake, through lutein-rich food or dietary supplements, may increase the deposition of lutein in the eye and may be linked to a reduction in AMD risk. 10 mg daily lutein supplementation was suggested to have an impact on the progression of AMD symptoms among 90 Veterans diagnosed with AMD. CONCLUSION: The body of evidence must be evaluated collectively in order to determine the merits of supplementing a given nutrient.
Shao A, Barnes HT Human trials with FloraGLO brand lutein Kemin Health Technical Literature			Human trials with FloraGLO brand lutein	RESULTS: Macular pigment density increased following ingestion of FloraGLO lutein. Visual function improved in patients suffering from age-related macular degeneration following ingestion of FloraGLO lutein. Plasma concentration of lutein increased following ingestion of FloraGLO lutein. CONCLUSION: Human studies published in peer-reviewed scientific journals show that consumption of FloraGLO lutein may provide significant benefits to eye health.
Sousa-Martins D The Lutein Antioxidant Supplementation Trial Kemin Health Technical Literature		90 predominantly male veterans with objective signs and symptoms of atrophic age-related macular degeneration (AMD)	Effect of lutein (L) alone and in combination with a set of additional carotenoids, antioxidants, vitamins, and minerals on the macular pigment and on the main ophthalmic parameters that evaluate central vision integrity in atrophic AMD	Group 1 (n = 29): lutein 10 mg (L); Group 2 (n =30): lutein 10 mg/antioxidants/vitamins and minerals broad spectrum supplementation formula (L/A); Group 3 (n = 31): a maltodextrin placebo (P) over 12 months RESULTS: Supplementation with 10 mg/day of FloraGLO lutein significantly increased macular pigment ocular density (MPOD). Visual function was improved with FloraGLO lutein supplementation alone or together with other nutrients. CONCLUSION: Improvements seen may be due to the protective role of lutein as a blue light filter and an antioxidant, quenching the triplet state of photosensitizers and singlet oxygen. Lutein may play an important role in eye health as a useful bioactive agent in reducing the risk of AMD. AMD may be a lutein responsive disorder and there may be a link between macular pigment optical density (MPOD) and visual function. Lutein supplementation may be beneficial to people with atrophic AMD because it may increase MPOD and reduce AMD risk.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Sousa-Martins D, Alves-Rodrigues A Retinal antioxidants improve macula function Kemin Health Technical Literature		Early ARM patients ages 54 - 84, 17 with antioxidants and 13 without antioxidants plus normal subjects ages 55 - 84, 4 with antioxidants and 4 without antioxidants	Influence of short-term antioxidant supplementation on macula function	Daily oral supplement of FloraGLO lutein (15 mg), vitamin E (20 mg), and nicotinamide RESULTS: Focal Electroretinogram (FERG) parameters are measures of retinal function. Daily short-term supplementation with FloraGLO Lutein, vitamin E and nicotinamide improves macular FERG parameters. CONCLUSION: Antioxidants may act both in the prevention and in the treatment of early retinal dysfunction associated with age-related macular degeneration (ARM). Among the extensive group of antioxidants, lutein has gathered the consensus of the scientific community as an efficient and specific protective agent against ARM. Due to elevated costs involved in the correlation of long-term research on chronic disease, these can only go forward after brief initial studies have identified short-term biologic effects that might explain, prevent, or treat the chronic condition.
Shao A AREDS report: A randomized, placebo-controlled, clinical trial of high dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss Kemin Health Technical Literature		3,640 patients ages 55 - 80 at varying stages of AMD	Effect of high dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration (AMD) and vision loss	Oral supplements of either a placebo or zinc (80 mg Zn as zinc oxide; 2 mg CU as cupric oxide) or antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg β -carotene) or antioxidants + zinc RESULTS: After approximately six years of follow up, subjects using a combined zinc plus antioxidant supplement had a 32% decreased risk of developing advanced AMD relative to those using a placebo. Similar results were obtained for risk of visual acuity loss (27% decreased risk for antioxidants plus zinc relative to placebo). No serious side effects were reported as a result of using these supplements. CONCLUSION: AREDS, the largest clinical AMD study to date, shows definitely that nutritional intervention, in the form of an antioxidant and zinc-containing supplement slows the progression of AMD and the decline in visual function associated with the disease. Combined with the results from many observational and intervention studies with lutein, this study supports the exciting possibility that nutritional intervention can be used to reduce the incidence of this costly disease.
No author listed Macular pigment in donor eyes with and without AMD: a case control study Kemin Health Technical Literature		Chasan-Taber study: 77,466 female nurses ages 45 - 71; Brown study: 36,344 male health professionals ages 45 - 75	Lutein intake and risk of cataract extraction in U.S. men and women	RESULTS: Of the female nurses studied, those with the highest intake of lutein (L) and zeaxanthin (Z) has 22% lower risk of cataract extraction compared to those in the lowest quintile of intake. Of the male health professionals studied, those with the highest consumption of L and Z had a 19% lower risk of cataract extraction compared to men with the lowest consumption. CONCLUSION: Based on the results from these studies, the researchers concluded that L and Z may reduce the risk of developing cataracts severe enough to require extraction in U.S. men and women.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
No author listed Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye Kemin Health Technical Literature 2004			Identification and quantitation of carotenoids and their metabolites (L and Z) in the tissues of the human eye, specifically the retinal pigment epithelium/choroid (RPE/choroid), ciliary body, and the iris	RESULTS: Lutein (L) and zeaxanthin (Z) are present in relatively high amounts in ocular tissues other than the retina. Of all the carotenoids detected, L and Z were found in the highest levels, up to nearly 7-fold higher than other carotenoids. CONCLUSION: The discovery of two lutein oxidative metabolites provides further evidence that L and Z serve as antioxidants in the eye and play a protective role against photo oxidative damage in human ocular tissues. The lack of any esterified form of carotenoid reinforces the notion that the free forms are bioactive and that dietary sources of esterified carotenoids must first be deesterified prior to absorption.
Shao A Antioxidants and carotenoids have protective effect against age-related cataracts Kemin Health Technical Literature 2004		200 elderly men and 172 elderly women from Sheffield, England	Antioxidants and carotenoids and protective effect against age-related cataracts	RESULTS: The strongest inverse relationship between serum levels and risk of the three forms of cataract was observed among carotenoids α -, and β -carotene, lycopene, and lutein. No significant relationship was observed between serum vitamin C and E and cataracts. For posterior subcapsular cataract, only increased serum lutein levels were found to be protective. Those subjects having a serum lutein level of 0.20 $\mu\text{mol/l}$ had 50 percent lower risk for posterior subcapsular cataract relative to those subjects with a serum lutein level 0.14 $\mu\text{mol/l}$. CONCLUSION: The data presented suggests that carotenoids may have a protective effect against cataracts. The finding that serum lutein specifically is associated with decreased cataract risk is consistent with previous findings from several studies which have shown an inverse relation between lutein intake and risk for cataract extraction in large cohorts. Together these studies provide strong evidence for the hypothesis that increasing one's consumption of lutein may prevent or delay the onset of cataracts. This notion is supported by the finding that lutein and zeaxanthin are the only carotenoids found in the human lens. The reason for the carotenoid-specific protective effect against cataract subclass is unclear. The investigators hypothesize that the differing forms of cataract may develop via different pathologic mechanisms and thus may be affected differently by various nutrients. Prospective intervention trial with a much larger sample size are essential to confirm the beneficial effects of these nutrients on the various forms of cataract.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Shao A Improving lutein consumption by Americans Kemin Health Technical Literature 2004			Improving lutein consumption by Americans	RESULTS: American intake of lutein is far below the level of 6 mg to 14 mg/day that has been associated with more than 50% reduction in risk for age-related macular degeneration (AMD) and 20% cataracts. FloraGLO brand lutein is generally recognized as safe (GRAS) in the United States and can be used in certain food and beverage applications. CONCLUSION: By consuming foods fortified with lutein, consumers stand a better chance of receiving a level of lutein in their diet equivalent to that indicated by the USDA Dietary Guidelines and may even reach levels associated with eye health benefits.
Shao A Lewis B FloraGLO lutein: a natural source of lutein Kemin Health Technical Literature 2004			FloraGLO lutein: a natural source of lutein	RESULTS: FloraGLO lutein, a natural source of lutein, is obtained by a patented isolation and purification processes. FloraGLO is the same form of lutein that is present in dark green-leafy vegetables and in the eyes. Doses as low as approximately 2 mg/day resulted in significant increases in serum lutein levels and macular pigment. Doses as high as 40 mg/day have been used for 9 weeks with no negative effects. An independent expert panel has determined that FloraGLO lutein is generally recognized as safe (GRAS) for use in foods and beverages. CONCLUSION: FloraGLO is safe and effective as a supplement for humans.
Alves-Rodrigues A The toxicology of FloraGLO crystalline lutein Kemin Health Technical Literature 2004			Toxicology of FloraGLO crystalline lutein	RESULTS: The safety of FloraGLO lutein has been evaluated by various complementary methods including animal toxicology studies, mutagenicity studies, and intervention studies. There have been no reported negative side effects resulting from long-term exposure to lutein and zeaxanthin from foods or supplements. A panel of independent scientists has approved FloraGLO lutein as generally recognized as safe (GRAS) for human consumption. CONCLUSION: The safety of lutein and zeaxanthin is now well established in scientific, peer-reviewed literature. Adding to numerous in vitro and in vivo toxicology studies, several intervention studies have been conducted both with dietary lutein and with supplemented FloraGLO lutein. It can therefore be said with reasonable evidence-based certainty that supplementation with FloraGLO lutein in adults is safe up to at least 20 mg of a total daily intake of lutein.
Thompson B JECFA approves FloraGLO crystalline lutein for an acceptable daily intake (ADI) level and identity and purity specifications Kemin Health Technical Literature 2004			JECFA approval of: 1. FloraGLO crystalline lutein for ADI level and 2. new identity and purity specifications for lutein based on FloraGLO crystalline lutein specifications	RESULTS: The Joint FAO/WHO (U.N.'s Food & Agricultural Organization/World Health Organization) Expert Committee on Food Additives (JECFA) approves an acceptable daily intake (ADI) of 0 - 2 mg/kg bw or 140 mg/day for a 70 kg person. JECFA set new specifications for the identity and purity of lutein and zeaxanthin. The ADI set by JECFA does not apply to other xanthophyll-containing extracts with a lutein or zeaxanthin content lower than that cited in the specifications.

Appendix A: Lutein Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
Thompson B FloraGLO crystalline lutein receives GRAS letter of non-objection from FDA Kemin Health Technical Literature 2004			FloraGLO crystalline lutein GRAS letter of non-objection from FDA (Food and Drug Administration)	RESULTS: FloraGLO crystalline lutein received generally recognized as safe (GRAS) letter of non-objection from FDA. FloraGLO crystalline lutein may be added to a variety of food and drinks.
DeFreitas Z Skin Safety of FloraGLO brand lutein Kemin Health Technical Literature 2004		106 subjects	FloraGLO brand lutein and skin safety	RESULTS: Three standard safety studies were conducted in humans to demonstrate the safety of FLoraGLO lutein when applied to human skin. CONCLUSION: FloraGLO lutein has no irritation, sensitization, phototoxicity, or photoallergenic properties.

Appendix B: Omega-3 Fatty Acid Evidence

APPENDIX B: EVIDENCE TABLES FOR OMEGA-3 FATTY ACIDS

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Kris-Etherton PM, Harris WS, Appel LJ; <i>Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease.</i> Circulation 2002; 106:2247</p>	<p>AHA Scientific Statement</p>			<p>This statement addresses distinctions between plant-derived and marine-derived omega-3 fatty acids. Evidence from epidemiological studies and randomized controlled trials are reviewed, and recommendations reflecting the current state of knowledge will be made with regard to both fish consumption and omega-3 fatty acid supplementation.</p>
<p>Mark SD, Wang W, Fraumeni Jr JF, Li JY, Taylor PR, Wang GQ, Guo W, Dawsey SM, Li B, Blot WJ; <i>Lowered Risks of Hypertension and Cerebrovascular Disease after Vitamin/Mineral Supplementation – The Linxian Nutrition Intervention Trial.</i> Am J Epidemiol 1996; 143:658-64</p>	<p>Randomized control study</p>	<p>3318 men and women from a region in rural China</p>	<p>Multiple vitamin/mineral supplement or a placebo. At the end of supplementation blood pressure was taken and prevalence of hypertension determined.</p>	<p>There was a slight reduction in overall mortality in the supplement group, with the decreased relative risk most pronounced for cerebrovascular disease deaths. This benefit was greater for men than for women. Among the survivors, the presence of elevations in both systolic and diastolic blood pressures was less common in those who received the supplement. This study indicates that supplementation with a multivitamin/mineral combination may have reduced mortality from cerebrovascular disease and the prevalence of hypertension in this rural population with a micronutrient-poor diet.</p>

Appendix B: Omega-3 Fatty Acid Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. <i>Blood Levels of Long-Chain n-3 Fatty Acids and the Risk of Sudden Death.</i> N Engl J Med Apr 11, 2002; 346(15):1113-1118.</p>	<p>Prospective, nested case-control analysis</p>	<p>22,071 male physicians who were 40-84 years old and had no history of myocardial infarction, stroke, transient ischemic attacks, or cancer</p>	<p>Asprin, beta carotene, both active drugs, or both placebos</p>	<p>RESULTS: Base-line blood levels of long-chain n-3 fatty acids were inversely related to the risk of sudden death both before adjustment for potential confounders and after such adjustment. As compared with men whose blood levels of long-chain n-3 fatty acids were in the lowest quartile, the relative risk of sudden death was significantly lower among men with levels in the third quartile and the fourth quartile. CONCLUSIONS: The n-3 fatty acids found in fish are strongly associated with a reduced risk of sudden death among men without evidence of prior cardiovascular disease.</p>
<p>Covington MB. <i>Omega-3 Fatty Acids.</i> Am Fam Phys Jul 1, 2004; 70(1):133-140.</p>	<p>Clinical Review</p>			<p>This paper reviews the pharmacology of, and previous studies and meta-analyses done to determine uses and efficacy of, omega-3 fatty acids.</p> <p>Therapy with low-dose omega-3 fatty acids significantly reduces the incidence of sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known CHD. More studies are needed to confirm the benefits of omega-3 fatty acids in the primary and secondary prevention of CHD. Although higher dosages of omega-3 fatty acids are effective in lowering triglyceride levels in patients with hypertriglyceridemia, the clinical significance of elevations in LDL cholesterol resulting from high-dose fish oil therapy remains unclear.</p>

Appendix B: Omega-3 Fatty Acid Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Appel LJ. <i>Effects of Omega-3 Fatty Acids on Cardiovascular Health.</i> Am Fam Phys July 1, 2004; 70(1):34.</p>	<p>Editorial</p>			
<p>Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, Hunter D, Manson JE. <i>Fish and Omega-3 Fatty Acid Intake and Risk of Coronary Heart Disease in Women.</i> JAMA April 10, 2002; 287(14):1821.</p>	<p>Prospective Study</p>	<p>84,688 female registered nurses</p>	<p>Consumption of fish and long-chain omega-3 fatty acids and risk of CHD in women.</p>	<p>RESULTS: During 16 years of follow-up, there were 1513 incident cases of CHD. Compared with women who rarely ate fish, those with a higher intake of fish had a lower risk of CHD. CONCLUSIONS: Among women, higher consumption of fish and omega-3 fatty acids is associated with a lower risk of CHD, particularly CHD deaths.</p>

Appendix B: Omega-3 Fatty Acid Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE., <i>"Fish and Long Chain Omega-3 Fatty Acid Intake and Risk of Coronary Heart Disease and Total Mortality in Diabetic Women"</i>. Circulation. 2003; 107:1852.</p>	<p>Cohort</p>	<p>5103 female nurses with diagnosed type II diabetes but free of cardiovascular disease or cancer.</p>	<p>Intake of fish and 3 fatty acids for six years; Outcome: risk of CHD, total mortality.</p>	<p>Between 1980 and 1996 (45 845 person-years of follow-up), we documented 362 incident cases of CHD (141 CHD deaths and 221 nonfatal myocardial infarctions) and 468 deaths from all causes. Compared with women who seldom consumed fish (<1 serving/mo), the relative risks (RRs) (95% CI) of CHD adjusted for age, smoking, and other established coronary risk factors were 0.70 (0.48 to 1.03) for fish consumption 1 to 3 times per month, 0.60 (0.42 to 0.85) for once per week, 0.64 (0.42 to 0.99) for 2 to 4 times per week, and 0.36 (0.20 to 0.66) for 5 or more times per week (P for trend=0.002). Higher consumption of fish was also associated with a significantly lower total mortality (multivariate RR=0.48 [0.29 to 0.80] for 5 times per week [P for trend=0.005]). Higher consumption of long-chain -3 fatty acids was associated with a trend toward lower incidence of CHD (RR=0.69 [95% CI 0.47 to 1.03], P for trend=0.10) and total mortality (RR=0.63 [95% CI, 0.45 to 0.88], P for trend=0.02). Conclusions— A higher consumption of fish and long-chain -3 fatty acids was associated with a lower CHD incidence and total mortality among diabetic women.</p>
<p>Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, Hunter D, Manson JE. <i>"Fish and Omega-3 Fatty Acid Intake and Risk of Coronary Heart Disease in Women"</i>. JAMA. 2002 Apr 10; 287(14):1815-21.</p>	<p>Cohort</p>	<p>84 688 female nurses enrolled in the Nurses' Health Study, aged 34 to 59 years and free from cardiovascular disease and cancer at baseline.</p>	<p>Consumption of fish and omega-3 fatty acids; Outcome: incident non-fatal myocardial infarctions, CHD deaths.</p>	<p>RESULTS: During 16 years of follow-up, there were 1513 incident cases of CHD (484 CHD deaths and 1029 nonfatal myocardial infarctions). Compared with women who rarely ate fish (<1 per month), those with a higher intake of fish had a lower risk of CHD. After adjustment for age, smoking, and other cardiovascular risk factors, the multivariable relative risks (RRs) of CHD were 0.79 (95% confidence interval [CI], 0.64-0.97) for fish consumption 1 to 3 times per month, 0.71 (95% CI, 0.58-0.87) for once per week, 0.69 (95% CI, 0.55-0.88) for 2 to 4 times per week, and 0.66 (95% CI, 0.50-0.89) for 5 or more times per week (P for trend =.001). Similarly, women with a higher intake of omega-3 fatty acids had a lower risk of CHD, with multivariable RRs of 1.0, 0.93, 0.78, 0.68, and 0.67 (P<.001 for trend) across quintiles of intake. For fish intake and omega-3 fatty acids, the inverse association appeared to be stronger for CHD deaths (multivariate RR for fish consumption 5 times per week, 0.55 [95% CI, 0.33-0.90] for CHD deaths vs 0.73 [0.51-1.04]) than for nonfatal myocardial infarction. CONCLUSION: Among women, higher consumption of fish and omega-3 fatty acids is associated with a lower risk of CHD, particularly CHD deaths.</p>

Appendix B: Omega-3 Fatty Acid Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, Ruskin JN, Manson JE. <i>"Fish Consumption and Risk of Sudden Cardiac Death"</i>. JAMA. 1998 Jan 7; 279(1):23-8.</p>	<p>Cohort</p>	<p>20 551 US male physicians 40 to 84 years of age and free of myocardial infarction, cerebrovascular disease, and cancer at baseline</p>	<p>Fish consumption; Outcome: incidence of sudden cardiac death.</p>	<p>RESULTS: There were 133 sudden deaths over the course of the study. After controlling for age, randomized aspirin and beta carotene assignment, and coronary risk factors, dietary fish intake was associated with a reduced risk of sudden death, with an apparent threshold effect at a consumption level of 1 fish meal per week (P for trend=.03). For men who consumed fish at least once per week, the multivariate relative risk of sudden death was 0.48 (95% confidence interval, 0.24-0.96; P=.04) compared with men who consumed fish less than monthly. Estimated dietary n-3 fatty acid intake from seafood also was associated with a reduced risk of sudden death but without a significant trend across increasing categories of intake. Neither dietary fish consumption nor n-3 fatty acid intake was associated with a reduced risk of total myocardial infarction, non-sudden cardiac death, or total cardiovascular mortality. However, fish consumption was associated with a significantly reduced risk of total mortality. CONCLUSION: These prospective data suggest that consumption of fish at least once per week may reduce the risk of sudden cardiac death in men.</p>
<p><i>"Dietary Supplementation with N-3 Polyunsaturated Fatty Acids and Vitamin E after Myocardial Infarction: Results of the GISSI-Prevenzione Trial"</i>. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999 Aug 7; 354(9177):447-55.</p>	<p>RCT</p>	<p>11,324 patients surviving recent (< or = 3 months) myocardial infarction.</p>	<p>Supplements of n-3 PUFA (1 g daily, n=2836), vitamin E (300 mg daily, n=2830), both (n=2830), or none (control, n=2828) for 3.5 years; Outcomes: death, non-fatal myocardial infarction, and stroke.</p>	<p>FINDINGS: Treatment with n-3 PUFA, but not vitamin E, significantly lowered the risk of the primary endpoint (relative-risk decrease 10% [95% CI 1-18] by two-way analysis, 15% [2-26] by four-way analysis). Benefit was attributable to a decrease in the risk of death (14% [3-24] two-way, 20% [6-33] four-way) and cardiovascular death (17% [3-29] two-way, 30% [13-44] four-way). The effect of the combined treatment was similar to that for n-3 PUFA for the primary endpoint (14% [1-26]) and for fatal events (20% [5-33]). INTERPRETATION: Dietary supplementation with n-3 PUFA led to a clinically important and statistically significant benefit. Vitamin E had no benefit. Its effects on fatal cardiovascular events require further exploration.</p>

Appendix B: Omega-3 Fatty Acid Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H., <i>"The Effect of Dietary Omega-3 Fatty Acids on Coronary Atherosclerosis. A Randomized, Double-blind, Placebo-controlled Trial"</i>. Ann Intern Med. 1999 Apr 6; 130(7):554-62.</p>	<p>RCT</p>	<p>223 patients from a university preventative cardiology unit with angiographically proven CAD.</p>	<p>Fish oil concentrate (55% eicosapentaenoic and docosahexaenoic acids), placebo with a fatty acid composition resembling that of the average European diet, 6 g/d for 3 months and then 3 g/d for 21 months; Outcomes: coronary atherosclerosis, cardiovascular events.</p>	<p>RESULTS: Pairs of angiograms (one taken at baseline and one taken at 2 years) were evaluated for 80 of 112 placebo recipients and 82 of 111 fish oil recipients. At the end of treatment, 48 coronary segments in the placebo group showed changes (36 showed mild progression, 5 showed moderate progression, and 7 showed mild regression) and 55 coronary segments in the fish oil group showed changes (35 showed mild progression, 4 showed moderate progression, 14 showed mild regression, and 2 showed moderate regression) (P = 0.041). Loss in minimal luminal diameter, as assessed by quantitative coronary angiography, was somewhat less in the fish oil group (P > 0.1). Fish oil recipients had fewer cardiovascular events (P = 0.10); other clinical variables did not differ between the study groups. Low-density lipoprotein cholesterol levels tended to be greater in the fish oil group. CONCLUSION: Dietary intake of omega-3 fatty acids modestly mitigates the course of coronary atherosclerosis in humans.</p>

Appendix B: Omega-3 Fatty Acid Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M., "Randomized, Double-blind, Placebo-controlled Trial of Fish Oil and Mustard Oil in Patients with Suspected Acute Myocardial Infarction: The Indian Experiment of Infarct Survival--4". Cardiovasc Drugs Ther. 1997 Jul; 11(3):485-91.</p>	<p>RCT</p>	<p>122+ 120 in experimental group, 118 patients in placebo group with suspected acute myocardial infarction (AMI): Outcomes:</p>	<p>Fish oil (eicosapentaenoic acid, 1.08 g/day); mustard oil (alpha-linolenic acid, 2.9 g/day), placebo for 1 year: Outcomes: total cardiac events, nonfatal infarctions, total cardiac deaths, total cardiac arrhythmias, left ventricular enlargement, angina pectoris.</p>	<p>After 1 year total cardiac events were significantly less in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% vs. 34.7%, $p < 0.01$). Nonfatal infarctions were also significantly less in the fish oil and mustard oil groups compared with the placebo group (13.0% and 15.0% vs. 25.4%, $p < 0.05$). Total cardiac deaths showed no significant reduction in the mustard oil group; however, the fish oil group had significantly less cardiac deaths compared with the placebo group (11.4% vs. 22.0%, $p < 0.05$). Apart from the decrease in the cardiac event rate, the fish oil and mustard oil groups also showed a significant reduction in total cardiac arrhythmias, left ventricular enlargement, and angina pectoris compared with the placebo group. Reductions in blood lipoproteins in the two intervention groups were modest and do not appear to be the cause of the benefit in the two groups. Diene conjugates showed a significant reduction in the fish oil and mustard oil groups, indicating that a part of the benefit may be caused by the reduction in oxidative stress. The findings of this study suggest that fish oil and mustard oil, possibly due to the presence of n-3 fatty acids, may provide rapid protective effects in patients with AMI. However, a large study is necessary to confirm this suggestion.</p>

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<p>Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M., "Effect of Dietary Supplementation with N-3 Fatty Acids on Coronary Artery Bypass Graft Patency". Am J Cardiol. 1996 Jan 1; 77(1):31-6.</p>	<p>RCT</p>	<p>610 patients undergoing coronary artery bypass grafting.</p>	<p>4 g/day of fish oil concentrate, or control group, all patients received antithrombotic treatment, either aspirin or warfarin for one year; Outcomes: 1 year graft patency.</p>	<p>Vein graft occlusion rates per distal anastomoses were 27% in the fish oil group and 33% in the control group (odds ratio 0.77, 95% confidence interval, 0.60 to 0.99, p = 0.034). In the fish oil group, 43% of the patients had > or = 1 occluded vein graft(s) compared with 51% in the control group (odds ratio 0.72, 95% confidence interval, 0.51 to 1.01, p = 0.05). Moreover, in the entire patient group, there was a significant trend to fewer patients with vein graft occlusions with increasing relative change in serum phospholipid n-3 fatty acids during the study period (p for linear trend = 0.0037). Thus, in patients undergoing coronary artery bypass grafting, dietary supplementation with n-3 fatty acids reduced the incidence of vein graft occlusion, and an inverse relation between relative change in serum phospholipid n-3 fatty acids and vein graft occlusions was observed.</p>
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Appendix B: Omega-3 Fatty Acid Evidence

Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Sacks FM, Stone PH, Gibson CM, Silverman DI, Rosner B, Pasternak RC., "Controlled Trial of Fish Oil for Regression of Human Coronary Atherosclerosis". HARP Research Group. J Am Coll Cardiol. 1995 Jun; 25(7):1492-8.</p>	<p>RCT</p>	<p>Patients with angiographically documented coronary heart disease and normal plasma lipid levels (n=31+28)</p>	<p>Fish oil capsules containing 6 g of n-3 fatty acids, olive oil capsules for an average duration of 28 months; Outcomes: coronary atherosclerosis.</p>	<p>RESULTS. Mean (+/- SD) baseline characteristics were age 62 +/- 7 years, plasma total cholesterol concentration 187 +/- 31 mg/dl (4.83 +/- 0.80 mmol/liter) and triglyceride levels 132 +/- 70 mg/dl (1.51 +/- 0.80 mmol/liter). Fish oil lowered triglyceride levels by 30% (p = 0.007) but had no significant effects on other plasma lipoprotein levels. At the end of the trial, eicosapentaenoic acid in adipose tissue samples was 0.91% in the fish oil group compared with 0.20% in the control group (p < 0.0001). At baseline, the minimal lumen diameter of coronary artery lesions (n = 305) was 1.64 +/- 0.76 mm, and percent narrowing was 48 +/- 14%. Mean minimal diameter of atherosclerotic coronary arteries decreased by 0.104 and 0.138 mm in the fish oil and control groups, respectively (p = 0.6 between groups), and percent stenosis increased by 2.4% and 2.6%, respectively (p = 0.8). Confidence intervals exclude improvement by fish oil treatment of > 0.17 mm, or > 2.6%. CONCLUSIONS. Fish oil treatment for 2 years does not promote major favorable changes in the diameter of atherosclerotic coronary arteries.</p>

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Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, Weiner BH, Slack JD, Kellett MA, Raizner AE, et al., "Do Fish Oils Prevent Restenosis after Coronary Angioplasty?" <i>Circulation</i>. 1994 Nov; 90(5):2248-57.</p>	<p>RCT</p>	<p>551 patients after percutaneous intraluminal coronary angioplasty.</p>	<p>Daily dietary supplement of ten 1.0-g capsules containing 80.6% ethyl esters of omega-3 fatty acids providing 4.1 g eicosapentaenoic acid (EPA) and 2.8 g docosahexaenoic acid (DHA) for 6 months or an equal amount of an ethyl ester of corn oil; Outcomes: restenosis rate.</p>	<p>The restenosis rate among analyzable patients was 46% for corn oil and 52% for fish oil (P = .37). The addition of 200 mg alpha-tocopherol for all subjects during the study had no effect on restenosis rates. CONCLUSIONS--This was the largest of such trials to date, and a supplement of 8 g/d of omega-3 fatty acids failed to prevent the usual high rate of restenosis after PTCA. No adverse effects were attributable to this large daily supplement of omega-3 fatty acids.</p>
<p>Morris MC, Taylor JO, Stampfer MJ, Rosner B, Sacks FM., "The Effect of Fish Oil on Blood Pressure in Mild Hypertensive Subjects: A Randomized Crossover Trial". <i>Am J Clin Nutr</i>. 1993 Jan; 57(1):59-64.</p>	<p>RCT</p>	<p>18 healthy, untreated mildly hypertensive subjects.</p>	<p>6 or 12 g fish oil/d (50% n-3 fatty acids) as compared with an olive oil placebo for six weeks; Outcome: blood pressure in mild hypertensive patients.</p>	<p>No significant changes in home or clinic blood pressure measurements were noted for either dose after 6 or 12 wk of treatment. Clinic blood pressure after 12 g fish oil/d was slightly lower than after placebo treatment by -0.8/-0.4 mm Hg [95% CI: systolic blood pressure (-4.4, +2.8); diastolic blood pressure (-3.2, +2.4)]. Blood pressure changes were not correlated with compliance, baseline dietary fish consumption, or blood pressure. Moderate doses of fish oil did not have a substantial effect on blood pressure. We conclude that fish oil is not a practical treatment for mild hypertension.</p>

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Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM., <i>"Effects of Changes in Fat, Fish, and Fibre Intakes on Death and Myocardial Reinfarction: Diet and Reinfarction Trial (DART)"</i>. Lancet. 1989 Sep 30; 2(8666):757-61.</p>	<p>RCT</p>	<p>2033 men who had recovered from MI.</p>	<p>To receive or not to receive advice on each of three dietary factors: a reduction in fat intake and an increase in the ratio of polyunsaturated to saturated fat, an increase in fatty fish intake, and an increase in cereal fibre intake; Outcomes: death and myocardial reinfarction.</p>	<p>The advice on fat was not associated with any difference in mortality, perhaps because it produced only a small reduction (3-4%) in serum cholesterol. The subjects advised to eat fatty fish had a 29% reduction in 2 year all-cause mortality compared with those not so advised. This effect, which was significant, was not altered by adjusting for ten potential confounding factors. Subjects given fibre advice had a slightly higher mortality than other subjects (not significant). The 2 year incidence of reinfarction plus death from ischaemic heart disease was not significantly affected by any of the dietary regimens. A modest intake of fatty fish (two or three portions per week) may reduce mortality in men who have recovered from MI.</p>

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Knapp HR, FitzGerald GA., <i>"The Antihypertensive Effects of Fish Oil. A Controlled Study of Polyunsaturated Fatty Acid Supplements in Essential Hypertension"</i> . N Engl J Med. 1989 Apr 20; 320(16):1037-43.	RCT	32 men with mild essential hypertension; groups of 8 subjects in each treatment arm.	10 ml or 50 ml of fish oil (3 or 15 g of n-3 fatty acids) daily, 50 ml of safflower oil (39 g of n-6 fatty acids), or 50 ml of a mixture of oils that approximated the types of fat present in the American diet for four weeks; Outcomes: blood pressure.	Blood pressure decreased in the men who received the high dose of fish oil (systolic pressure by a mean of 6.5 mm Hg [P less than 0.03] and diastolic pressure by 4.4 mm Hg [P less than 0.015]), but not in the other groups. Although the formation of vasodilatory prostacyclins (prostaglandins I2 and I3) increased initially, this increase was not maintained as blood pressure fell. The level of thromboxane A2 metabolites fell; metabolites of thromboxane A3 were detected in the groups receiving fish oil. The formation of prostaglandin E2 increased during supplementation with safflower oil and tended to decrease with fish oil; no prostaglandin E3 metabolite was detected. Our data indicate that high doses of fish oil can reduce blood pressure in men with essential hypertension. However, the clinical usefulness and safety of fish oil in the treatment of hypertension will require further study.
Stark, Ken D and Holub, Bruce J. "Differential Eicosapentaenoic Acid Elevations and Altered Cardiovascular Disease Risk Factor Responses After Supplementation with Docosahexaenoic Acid in Postmenopausal Women Receiving and Not Receiving Hormone Replacement Therapy". Am J Clin Nutr, 2004; 79: 765-773.	RCT	Postmenopausal women receiving (n=18) and not receiving (n=14) hormone replacement therapy. Randomized, double-blind, placebo-controlled crossover trial with DHA supplement (2.8g DHA/d)	A washout period of > or equal 6 weeks divided the two 28-day intervention periods. Fasting blood samples were collected for analysis.	Objective: To study the effect of supplementation with DHA (free of EPA) on the resulting elevation in EPA and on selected cardiovascular disease risk factors in postmenopausal women. Results: In all women, DHA supplementation was associated with significant changes (P<0.05), including 20% lower serum triacylglycerol concentrations, 8% higher HDL-cholesterol concentrations, a 28% lower overall ratio of serum triacylglycerol HDL cholesterol, and a 7% decrease in resting heart rate. DHA supplementation resulted in a 45% lower net increase (P=0.02) in EPA and a 42% lower (P=0.0028) estimated percentage retroconversion of DHA to EPA in women receiving than in those not receiving HRT. Conclusion: With DHA supplementation, the accumulation of EPA in serum phospholipids is significantly attenuated in postmenopausal women receiving HRT compared with that of women not receiving HRT. DHA supplementation can also favorably influence selected cardiovascular disease risk factors in postmenopausal women.

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Citation	Study Type	Sample Population	Variables	Results (Conclusions)
<p>Dewailly E, Blanchet C, Gingras S, Lemieux S, Holub B, “<i>Cardiovascular Disease Risk Factors and n-3 Fatty Acid Status in the Adult Population of James Bay Cree</i>”. Am J Clin Nutr 2002, 76:85-92.</p>	<p>RCT</p>	<p>917 subjects aged 18-74 y who participated in the 1991 Sante Quebec Health Survey</p>	<p>Examine the profile of plasma phospholipids concentrations of n-3 (EPA and DHA) among the James Bay Cree to verify the relationship between these concentrations and CVD risk factors</p>	<p>Results: The mean fish consumption on the day before the survey was 60 g among the adult Cree population. Expressed as a percentage of total fatty acid, relative concentrations of EPA and DHA were 0.65% and 2.80% respectively. N-3 fatty acid was higher among coastal residents than among inland residents. A positive association was observed between plasma HDL and n-3 fatty acids. EPA and EPA+DHA were inversely associated with triacylglycerols. Among subjects aged 50-74 y, an inverse association between EPA and EPA:AA and total HDL cholesterol was observed. Conclusion: n-3 Fatty acid may favorably influence some CVD risk factors. The Cree population must be encouraged to maintain their traditional fish-based diet, which may be one of the factors protecting them against mortality from CVD.</p>
<p>Kris-Etherton PM, Harris WS, Appel LJ; Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2003 Feb 1; 23(2):e20-30.</p>	<p>Review</p>	<p>n/a</p>	<p>n/a</p>	<p>RCTs have demonstrated that omega-3 fatty acid supplements can reduce cardiac events (eg, death, nonfatal MI, nonfatal stroke) and decrease progression of atherosclerosis in coronary patients. However, additional studies are needed to confirm and further define the health benefits of omega-3 fatty acid supplements for both primary and secondary prevention. For example, placebo-controlled, double-blind RCTs are needed to document both the safety and efficacy of omega-3 fatty acid supplements in both high-risk patients (e.g., patients with type 2 diabetes, dyslipidemia, and hypertension, and smokers) and coronary patients on drug therapy. Mechanistic studies on their apparent effects on sudden death are also needed. A dietary (ie, food-based) approach to increasing omega-3 fatty acid intake is preferable. Still, for patients with coronary artery disease, the dose of omega-3 (1 g/d) may be greater than what can readily be achieved through diet alone. These individuals, in consultation with their physician, could consider supplements for CHD risk reduction. Supplements also could be a component of the medical management of hypertriglyceridemia, a setting in which even larger doses (2 to 4 g/d) are required. The availability of high-quality omega-3 fatty acid supplements, free of contaminants, is an important.</p>

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Leaf A. <i>"The role of Omega 3 Fatty Acids in the Prevention and Rehabilitation of Coronary Artery Disease"</i> . Ann Acad Med Singapore. 1992 Jan; 21(1):132-6.	Review	n/a	n/a	Coronary artery disease, the leading cause of death in the world, poses a major socioeconomic problem which has prompted extensive research into both preventive and therapeutic measures. Among the former are dietary modifications, including fish oil supplements which have been strongly advocated to prevent the development of atherosclerosis. This article reviews the pathophysiological basis of the evidence for recommending fish and fish oil supplement in the prevention of atherosclerosis.
Ballard-Barbash R, Callaway CW., <i>"Marine Fish Oils: Role in Prevention of Coronary Artery Disease"</i> . Mayo Clin Proc. 1987 Feb; 62(2):113-8.	Review	n/a	Outcome: prevention of CAD.	Since the early 1970s, investigators have been interested in the relationship between dietary marine fish oils and plasma lipoproteins. Previous studies have shown that consumption of a diet rich in marine fatty acids results in altered lipid profiles, prolonged bleeding times, reduced platelet aggregation, and decreased blood pressure, but the precise mechanisms of action must be examined further. These findings, however, have led to the conclusion that dietary marine fish oils may be of benefit in the prevention of coronary artery disease. Before specific recommendations can be made about their general use, further studies of their long-term efficacy and toxicity must be conducted.
Bucher HC, Hengstler P, Schindler C, Meier G. <i>"N-3 Polyunsaturated Fatty Acids in Coronary Heart Disease: A Meta-analysis of Randomized Controlled Trials"</i> . Am J Med. 2002 Mar; 112(4):298-304.	Review/Meta-Analysis	11 trials which included 7,951 patients with interventions and 7855 control patients.	Dietary and supplemental intake of n-3 polyunsaturated fatty acids; Outcomes: overall mortality, mortality due to myocardial infarction, sudden death in patients with coronary heart disease.	RESULTS: The risk ratio of nonfatal myocardial infarction in patients who were on n-3 polyunsaturated fatty acid-enriched diets compared with control diets or placebo was 0.8 (95% confidence interval [CI]: 0.5 to 1.2, P = 0.16; Breslow-Day test for heterogeneity, P = 0.01), and the risk ratio of fatal myocardial infarction was 0.7 (95% CI: 0.6 to 0.8, P <0.001; heterogeneity P >0.20). In 5 trials, sudden death was associated with a risk ratio of 0.7 (95% CI: 0.6 to 0.9, P <0.01; heterogeneity P >0.20), whereas the risk ratio of overall mortality was 0.8 (95% CI: 0.7 to 0.9, P <0.001; heterogeneity P >0.20). There was no difference in summary estimates between dietary and non-dietary interventions of n-3 polyunsaturated fatty acids for all endpoints. CONCLUSION: This meta-analysis suggests that dietary and non-dietary intake of n-3 polyunsaturated fatty acids reduces overall mortality, mortality due to myocardial infarction, and sudden death in patients with coronary heart disease.

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<p>Appel LJ, Miller ER 3rd, Seidler AJ, Whelton PK., "Does Supplementation of Diet with 'Fish Oil' Reduce Blood Pressure? A Meta-analysis of Controlled Clinical Trials". Arch Intern Med. 1993 Jun 28; 153(12):1429-38.</p>	<p>Review/Meta-Analysis</p>	<p>17 controlled clinical trials of omega-3 PUFA supplementation</p>	<p>Outcome: Blood pressure.</p>	<p>RESULTS: In the 11 trials that enrolled normotensive individuals (n = 728), omega-3 PUFA supplementation led to significant reductions of systolic BP (SBP) and diastolic BP (DBP) in two and one trials, respectively. In the six studies that enrolled untreated hypertensives (n = 291), significant reductions of SBP and DBP were present in two and four trials, respectively. Weighted, pooled estimates of SBP and DBP change (mm Hg) with 95% confidence intervals were -1.0 (-2.0 to 0.0) and -0.5 (-1.2 to +0.2) in the trials of normotensives, and -5.5 (-8.1 to -2.9) and -3.5 (-5.0 to -2.1) in the trials of untreated hypertensives. In 13 of 17 studies, trial duration was less than 3 months. Doses of omega-3 PUFA tended to be high (average dose > 3 g/d in 11 trials). The magnitude of BP reduction was greatest at high BP but was not significantly associated with dose of omega-3 PUFA. Side effects, most commonly eructation and a fishy taste, occurred more frequently in omega-3 PUFA participants than in control participants (28% vs 13%, P < .001). CONCLUSIONS: Our analyses indicate that diet supplementation with a relatively high dose of omega-3 PUFA, generally more than 3 g/d, can lead to clinically relevant BP reductions in individuals with untreated hypertension. However, use of omega-3 PUFA as antihypertensive therapy will require demonstration of long-term efficacy and patient acceptability of lower doses.</p>
<p>Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS, "Preventing Restenosis with Fish Oils Following Coronary Angioplasty. A Meta-analysis". Arch Intern Med. 1993 Jul 12; 153(13):1595-601.</p>	<p>Review/Meta-Analysis</p>	<p>Studies about the use of omega-3 fatty acids to reduce the rate of restenosis following PTCA.</p>	<p>Outcome: restenosis after PTCA.</p>	<p>RESULTS: For four studies that used angiography to define coronary restenosis, the absolute difference in restenosis rates between treatment and control groups was 13.9% (95% confidence interval [CI], 3.2% to 24.5%). Furthermore, regression analysis revealed a positive linear relationship between the dose of omega-3 fatty acids used and the absolute difference in restenosis rates (r = .99, P < .03). When three studies that used stress testing as a means of determining restenosis rates were added to the four studies that used angiography, the risk difference was 5.1% (95% CI, -3.8% to 13.9%). CONCLUSIONS: Restenosis after coronary angioplasty is reduced by supplemental fish oils, and the extent of the observed benefit may be dependent on the dose of omega-3 fatty acids used.</p>

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<p>Morris MC, Sacks F, Rosner B., <i>"Does Fish Oil Lower Blood Pressure? A Meta-analysis of Controlled Trials"</i>. Circulation. 1993 Aug; 88(2):523-33.</p>	<p>Review/Meta-Analysis</p>	<p>31 placebo-controlled trials on 1356 subjects.</p>	<p>Outcome: blood pressure response.</p>	<p>The mean reduction in blood pressure caused by fish oil for the 31 studies was -3.0/-1.5 mm Hg (95% confidence intervals: systolic blood pressure: -4.5, -1.5; diastolic blood pressure: -2.2, -0.8). There was a statistically significant dose-response effect when studies were grouped by omega-3 fatty acid dose: -1.3/-0.7 mm Hg at doses < or = 3 g/d, -2.9/-1.6 mm Hg at 3.3 to 7 g/d, and -8.1/-5.8 mm Hg at 15 g/d. Both eicosapentaenoic acid and docosahexaenoic acid were significantly related to blood pressure response. There was no effect on blood pressure in eight studies of "healthy" persons (mean reduction, -0.4/-0.7 mm Hg) at an overall mean dose of 4.2 g omega-3 fatty acids/d. By contrast, there was a significant effect of -3.4/-2.0 mm Hg in the group of hypertensive studies with a mean fish oil dose of 5.6 g/d and on systolic blood pressure only in six studies of hypercholesterolemic patients (-4.4/-1.1 mm Hg) with a mean dose of 4.0 g/d. A nonsignificant decrease in blood pressure was observed in four studies of patients with atherosclerotic cardiovascular disease (-6.3/-2.9 mm Hg). Variations in the length of treatment (from 3 to 24 weeks), type of placebo, and study design (crossover or parallel groups) did not appear to account for inconsistent findings among studies. CONCLUSIONS. There is a dose-response effect of fish oil on blood pressure of -0.66/-0.35 mm Hg/g omega-3 fatty acids. The hypotensive effect may be strongest in hypertensive subjects and those with clinical atherosclerotic disease or hypercholesterolemia.</p>
<p>O'Connor GT, Malenka DJ, Olmstead EM, Johnson PS, Hennekens CH., <i>"A Meta-analysis of Randomized Trials of Fish Oil in Prevention of Restenosis Following Coronary Angioplasty"</i>. Am J Prev Med. 1992 May-Jun; 8(3):186-92.</p>	<p>Review/Meta-Analysis</p>	<p>Randomized trials concerning use of fish oil in prevention of restenosis following PTCA.</p>	<p>Outcome: rates of restenosis two to 12 months after PTCA.</p>	<p>We evaluated rates of restenosis two to 12 months after PTCA and calculated an estimate of the overall effect and 95% confidence interval (CI). The typical odds ratio (treatment versus control) was 0.71 (95% CI 0.54, 0.94), P = 0.016 (two-tailed). The data show a strong and highly significant (P less than .0001) relationship between daily fish oil dose and gastrointestinal side effects. While compatible with a small to moderate benefit of fish oil on rates of restenosis, these results require confirmation in a randomized clinical trial large enough to distinguish reliably between a clinically meaningful benefit and a null result.</p>

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Radack K, Deck C., <i>"The Effects of Omega-3 Polyunsaturated Fatty Acids on Blood Pressure: A Methodological Analysis of the Evidence"</i> . J Am Coll Nutr. 1989 Oct;8(5):376-85.	Review/Meta-Analysis	RCTs that studied the effect of omega-3 PUFA on BP response (6 studies included).	Outcome: Blood pressure response.	There was no statistically significant difference between the omega-3-PUFA groups and the control groups, possibly because of failure to include hypertensive subjects in all but one trial. Despite the positive effects in two studies, little scientifically valid evidence is available to demonstrate a significant BP-lowering effect of omega-3-PUFAs. Areas needing more attention in future research are identified and methods to improve study designs are suggested.
Holub, Bruce J., "Clinical Nutrition: 4. Omega – 3 Fatty Acids in Cardiovascular Care". JAMC, 5 Mars 2002, 166(5): 608 – 615.	Review / Synthese	various		Studies of the use of omega-3 fatty acids found in fish oils for the prevention and management of cardiovascular disease. In particular studies of EPA and DHA indicating that increased consumption of fish as a source of omega-3 fatty acids is often associated with decreased mortality for cardiovascular disease.
Balk E, Chung M, Lichtenstein A, Chew P, Kupelnick B, Lawrence A, DeVine D, Lau J, <i>"Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease"</i> , Summary, Evidence Report / Technology Assessment, No. 93, (Prepared by the Tufts-New England Medical Center Evidence-based Practice Center, Boston, MA) AHRQ Publication No. 04-E010-1.March 2004.	Meta-analysis	various	23 CVD risk factors and intermediate markers of CVD	Researchers screened 7,464 abstracts. 807 full articles were reviewed of which 344 reported on CVD risk factors and met initial eligibility criteria. Ultimately 123 articles met the final eligibility criteria for 23 potential risk factors and use of omega-3 fatty acids.

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<p>Laidlaw, Maggie and Holub, Bruce J., "Effects of Supplemental Fish Oil – Derived n-3 Fatty Acids and Alpha-linolenic Acid on Circulating Plasma Lipids and Fatty Acid Profiles in Women" Am J Clin Nutr, 2003; 77: 37-42.</p> <p>Daviglus ML, Stamler J, Orenca AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB. <i>Fish Consumption and the 30-year Risk of Fatal Myocardial Infarction.</i> NEJM April 10, 1997; 1046-1053.</p>	<p>RTC</p> <p>30-year cohort study</p>	<p>Thirty-one women were assigned to 1 of 4 groups, equalized on the basis of their fasting triacylglycerol concentrations. Supplements of 4g EPA+DHA (4:0), 4g EPA-DHA plus 1g GLA (4:1), 2g GLA (4:2) or 4gGLA (4:4) daily for 28 days.</p> <p>1822 men free of CVD at baseline</p>	<p>Plasma lipids and fatty acids of serum phospholipids were measured on days 0 and 28.</p> <p>Fish consumption and mortality from coronary heart disease.</p>	<p>Results: Plasma triacylglycerol concentrations were significantly lower on day 28 than on day 0 in the 4:0, 4:1 and 4:2 groups. LDL cholesterol decreased significantly (by 11.3%) in the 4:2 group. Dihomo-alpha-linolenic acid increased significantly in serum phospholipids only in the 4:2 and 4:4 groups; however, total n-3 fatty acids increased in all 4 groups. Conclusion: A mixture of 4g EPA+DHA and 2g GLA favorably altered blood lipid and fatty acid profiles in healthy women. On the basis of calculated PROCAM values, the 4:2 group was estimated to have a 43% reduction in the 10-y risk of myocardial infarction.</p> <p>RESULTS: During 47,153 person-years of follow-up, there were 430 deaths from coronary heart disease; 293 were due to myocardial infarctions. Cox proportional-hazards regression showed that for men who consumed 35 g or more of fish daily as compared with those who consumed none, the relative risks of death from coronary heart disease and from sudden or nonsudden myocardial infarction were .62 and .56, respectively, with a graded relation between the relative risks and the strata of fish consumption. These findings were accounted for by the relation of fish consumption to nonsudden death from myocardial infarction. CONCLUSIONS: These data show an inverse association between fish consumption and death from coronary heart disease, especially nonsudden death from myocardial infarction.</p>