Published in final edited form as:
Arch Ophthalmol. 2011 July ; 129(7): 921–929. doi:10.1001/archophthalmol.2011.34.

Dietary ω-3 Fatty Acid and Fish Intake and Incident Age-related Macular Degeneration in Women

William G. Christen, ScD, **Debra A. Schaumberg, ScD**, **Robert J. Glynn, ScD**, and **Julie E. Buring, ScD**
Divisions of Preventive Medicine (W.G.C., D.A.S., R.J.G., J.E.B.) and Aging (J.E.B.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; Department of Biostatistics (R.J.G.), Harvard School of Public Health; and the Department of Ambulatory Care and Prevention, Harvard Medical School (J.E.B); all in Boston, MA.

Abstract

Objective—To examine whether intake of ω-3 fatty acids and fish affect incidence of age-related macular degeneration (AMD) in women.

Design—A detailed food-frequency questionnaire was administered at baseline among 39,876 female health professionals (mean [SD] age: 54.6 [7.0] years). A total of 38,022 women completed the questionnaire and were free of a diagnosis of AMD.

Main Outcome Measure—Incident AMD responsible for a reduction in best-corrected visual acuity to 20/30 or worse based on self-report confirmed by medical record review.

Results—A total of 235 cases of AMD, most characterized by some combination of drusen and retinal pigment epithelial changes, were confirmed during an average of 10 years of follow-up. Women in the highest tertile of intake for docosahexaenoic acid (DHA), compared to those in the lowest, had a multivariate-adjusted relative risk (RR) of AMD of 0.62 (95% confidence interval [CI], 0.44–0.87). For eicosapentaenoic acid (EPA), women in the highest tertile of intake had a RR of 0.66 (CI, 0.48–0.92). Consistent with the findings for DHA and EPA, women who consumed 1 or more servings of fish per week, compared to those who consumed less than 1 serving per month, had a RR of AMD of 0.58 (CI, 0.38–0.87).

Conclusions—These prospective data from a large cohort of female health professionals without a diagnosis of AMD at baseline indicate that regular consumption of DHA and EPA and fish was associated with a significantly decreased risk of incident AMD, and may be of benefit in primary prevention of AMD.

An estimated 9 million U.S. adults aged 40 years and older show signs of age-related macular degeneration (AMD) (1). Most cases of severe vision loss associated with the disease are due to advanced AMD, either central geographic atrophy or neovascular AMD, which affects an estimated 1.7 million persons (1). An additional 7.3 million persons have early AMD which is usually associated with moderate or no vision loss (2,3), but does increase the risk of progression to advanced AMD (4–6). Current treatment options are limited to a minority of persons with late-stage neovascular AMD (7–12), or intermediate AMD (13). For the large majority of persons with early or no AMD, there is no recognized

Corresponding author: William G. Christen, Sc.D., 900 Commonwealth Avenue East, Boston, MA 02215-1204. (617) 278-0795; Fax: (617) 278-2030; wchristen@rics.bwh.harvard.edu. Reprints are not available from the author.

The authors have no proprietary or commercial interest in any materials discussed in this article.

Dr. Christen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

means of disease prevention other than avoiding cigarette smoking (14–16). Thus, the identification of means to prevent or delay the development of AMD would have marked public health significance.

Cardiovascular disease and AMD have been hypothesized to share similar mechanisms and risk factors (17). Dietary intake of fish, and specifically ω-3 fatty acids concentrated in fish (docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]), have been linked with reduced rates of cardiovascular events in epidemiologic studies (18–20), and could have a similar beneficial effect in AMD. ω-3 fatty acids are known to exert anti-inflammatory, anti-atherosclerotic, and anti-thrombotic effects on the vasculature (21–23), and may help to maintain or improve choroidal blood flow in the eye. The further observations that DHA and arachidonic acid (AA), an ω-6 fatty acid, are found in high concentrations in the retina (24), are modifiable by diet (25,26), and are important structural components of retinal photoreceptor outer segments and vascular tissue (27,28) further supports the potential importance of these nutrients in AMD.

Some evidence from observational epidemiologic studies suggests an inverse relation between regular dietary intake of fish and DHA and EPA and risks of advanced AMD (29,30). Indeed, the Age-related Eye Disease Study 2 is evaluating in a randomized trial whether supplemental DHA and EPA can reduce the risk of progression to advanced AMD (31). However, available data for early AMD are limited and inconsistent. Additional observational data, particularly from prospective cohorts, are needed to increase the evidence base regarding the potential benefits of consumption of DHA and EPA and fish in the primary prevention of AMD for the large majority of Americans who are at usual risk for the disease.

In this report, we examine in prospective data the relation of dietary intake of DHA and EPA and fish with visually-significant AMD during 10 years of follow-up in a large cohort of female health professionals who were free of a diagnosis of AMD at baseline.

Materials and Methods

Study participants were women enrolled in the Women's Health Study (WHS), a completed randomized trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. The methods and results of the WHS have been described in detail previously (32–34). Briefly, 39,876 apparently healthy female U.S. health professionals, 45 years or older at the beginning of 1993, who did not have a history of cardiovascular disease, cancer (except nonmelanoma skin cancer), or other major illnesses were randomly assigned to receive aspirin (100 mg on alternate days), vitamin E (600 IU on alternate days), both active agents, or both placebos. The women completed a baseline questionnaire on which they provided information on possible risk factors for AMD, and whether they had previously been diagnosed with AMD. The women also completed annual questionnaires on which they provided information on their compliance with pill-taking and the occurrence of any relevant events including AMD. Pill-taking and endpoint ascertainment were continued in a blinded fashion through the scheduled end of the trial on March 31, 2004. Morbidity and mortality follow-up were 97.2% and 99.4% complete, respectively. This study was conducted according to the ethical guidelines of Brigham and Women's Hospital.

Dietary assessment

At baseline in 1993, 39,310 (99%) of the randomized participants completed a 131-item semiquantitative food-frequency questionnaire (SFFQ) (35) on which they indicated their average consumption over the past year of various types of food with a typical portion size

specified for each food. The SFFQ included questions on the intake of canned tuna fish (3–4 oz, 85–113 g) ; dark meat fish such as mackerel, salmon, sardines, bluefish, and swordfish (3–5 oz, 85–142 g); other fish (3–5 oz, 85–142 g); and shrimp, lobster, and scallops as a main dish. For each food item, women were asked to indicate how often, on average, they had consumed that amount over the past year. There were nine possible responses ranging from "never or less than once per month" to "six or more times per day". The calculation of ω-3 and ω-6 fatty acid intake has been described in detail elsewhere (36,37). The average daily intake of other nutrients was calculated by multiplying the frequency of consumption of each item by its nutrient content per serving and totaling the nutrient intake for all food items. In this report, intake of ω-3 fatty acids was based on data for DHA (22:6), EPA (20:5), docosapentaenoic acid (DPA, 22:5), and ∀-linolenic acid (ALA, 18:3). Intake of ω-6 fatty acids was based on data for linoleic acid (LA, 18:2) and arachidonic acid (AA, 20:4). Details on the reliability and validity of these estimates of fish and ω-3 and ω-6 fatty acid intake have been previously published (38–40).

Ascertainment and definition of endpoints

We excluded women who reported a prior diagnosis of AMD at baseline. Annual questionnaires asked about any new diagnoses in the past year including "macular degeneration right eye" and "macular degeneration left eye". Women who responded affirmatively were asked to provide the month and year of the diagnosis and to complete and sign a consent form granting permission to examine medical records pertaining to the diagnosis. Eye doctors were contacted by mail and asked to complete an AMD questionnaire. The questionnaire requested information on the date of initial diagnosis of AMD, the best-corrected visual acuity at the time of diagnosis, and the date when best-corrected visual acuity reached 20/30 or worse (if different from the date of initial diagnosis). The questionnaire also asked about signs of AMD observed (drusen, retinal pigment epithelium [RPE] hypo/hyperpigmentation, geographic atrophy, RPE detachment, subretinal neovascular membrane, or disciform scar) when visual acuity was first noted to be 20/30 or worse, and the date when exudative neovascular disease, if present, was first noted (defined by presence of RPE detachment, subretinal neovascular membrane, or disciform scar). The questionnaire further asked about other ocular abnormalities that could explain or contribute to the patient's vision loss. If other ocular abnormalities were noted, the eye doctor was asked to indicate whether the AMD, by itself, was significant enough to cause the best-corrected visual acuity to be reduced to 20/30 or worse. Eye doctors could also provide the requested information by supplying photocopies of the relevant medical records which then underwent expert review. Medical record data were obtained for 85.2% of participants reporting AMD.

The primary study endpoint was visually-significant AMD defined as a self-report confirmed by medical record evidence of an initial diagnosis made after randomization but on or before March 31, 2004 (the last day of randomized treatment), with best-corrected visual acuity reduced to 20/30 or worse attributable to AMD.

Data analysis

For this analysis we excluded participants who reported total energy intake less than 600 kcal/d or greater than 3500 kcal/d, or who had more than 70 blanks on the SFFQ. Of the remainder, 38,022 participants were without a diagnosis of AMD at baseline and were included in the analysis.

Intakes of ω-3 and ω-6 fatty acids and other dietary fats were adjusted for total energy intake using the residual method (41). Intakes were categorized into tertiles (rather than quartiles or quintiles) in order to enhance the stability of estimates, and categories were based on the

overall distribution of nutrient intakes in all women. We examined the baseline distribution of known and possible AMD risk factors according to tertiles of ω-3 long chain fatty acids and ω-6 fatty acids and the ω-6:ω-3 ratio. Cox proportional hazards regression models were used to estimate relative risk (RR) and 95% confidence interval (CI) for AMD, comparing the incidence rate for a specific tertile of intake with the rate in the lowest tertile (reference) (42). Crude RR estimates were obtained by adjusting for age (in years) and randomized treatment assignment. Multivariate RRs were obtained by further adjusting for smoking, alcohol use, body mass index (BMI), postmenopausal hormone use, history of hypertension, history of high cholesterol, history of diabetes, multivitamin use, and history of an eye exam in the last 2 years. In some analyses, we further adjusted for tertiles of saturated fat, monounsaturated fat, and trans unsaturated fats. For each RR, two-sided P values and 95 percent CIs were calculated (43). We tested for a linear trend across tertiles of nutrient intake using category medians modeled as a continuous variable. We also examined possible modification of the association between ω-3 fatty acids and AMD by conducting stratified analyses within strata of participants above and below the median intake for LA, AA, and total ω-6 fatty acids (LA plus AA). Tests of interaction were performed to evaluate the null hypothesis of no difference in the association of ω-3 fatty acids with AMD across strata of ω-6 fatty acids. Because fish and seafood intakes account for most of the total ω-3 long chain fatty acid intake, we also examined the association of fish and seafood intakes with AMD. We classified average daily consumption into 3 categories: <1 serving/month, 1–3 servings/month, and ≥1 servings/week, and tested for a linear trend across categories of intake using category medians modeled as a continuous variable

The unit of analysis was individuals, rather than eyes, because eyes were not examined independently, and participants were classified according to the status of the worse eye based on disease severity.

RESULTS

Table 1 shows the distribution of baseline characteristics according to tertiles of ω-3 long chain and ω-6 fatty acid intake. Older women, and women who reported a history of hypertension, high cholesterol, and diabetes were more likely to report higher intakes of ω-3 and ω-6 fatty acids. Daily users of alcohol, current multivitamin users, and those who reported an eye exam in the past 2 years also reported higher intakes of ω-3 fatty acids, but lower intakes of ω-6 fatty acids. Current smokers reported lower intake of ω-3 fatty acids, but higher intake of ω-6 fatty acids. Women with a higher ω-6:ω-3 were younger, more likely to smoke but less likely to use alcohol, and had higher BMI. These women were also less likely to report current hormone use, hypertension, high cholesterol, diabetes, current multivitamin use, and an eye exam in the past 2 years.

Among 38,022 participants who completed an SFFQ at baseline and were without a prior diagnosis of AMD, a total of 235 cases of visually-significant AMD were documented during 10 years of follow-up. Most of these cases were characterized by some combination of drusen and RPE changes when vision was first noted to be 20/30 or worse (drusen only, 33 [14.0%]; RPE changes only, 56 [23.8%]; drusen and RPE changes, 81 [34.5%]) indicating an early stage of AMD development.

Relative risks for AMD according to tertiles of ω-3 and ω-6 fatty acid intake are presented in Table 2. In analyses adjusted for age and treatment assignment, women in the highest tertile of DHA intake, compared to the lowest, had a 38% lower risk of AMD (RR, 0.62; 95% confidence interval [CI], 0.45–0.85; p, test for trend, 0.003). Similar inverse associations with AMD were observed for higher intake of EPA (RR, 0.64; CI, 0.46–0.88; p, test for trend, 0.004) and for DHA+EPA (RR, 0.62; CI, 0.45–0.86; p, test for trend, 0.004). Higher

intake of DPA, an intermediary between EPA and DHA, was associated with a 25% reduced risk of AMD that was of borderline significance (RR, 0.75; CI, 0.55–1.02; p, test for trend, 0.06). There was no association between ALA intake and AMD. These RR estimates were not materially altered after further adjustment for other possible risk factors for AMD, and for tertiles of saturated fat, monounsaturated fat, and trans unsaturated fats (Table 2). For ω-6 fatty acids, higher intake of LA, but not AA, was associated with an increased risk of AMD. Women in the highest tertile of LA intake, relative to the lowest, had an age- and treatment-adjusted RR of 1.41 (CI, 1.03–1.94; p, test for trend, 0.028). However, the RR was attenuated and no longer significant after additional adjustment for AMD risk factors and other fats. The ratio of ω-6 to ω-3 fatty acids was directly associated with the risk of AMD, and the association was strengthened when the denominator term for ω-3 fatty acids included only DHA and EPA (Table 2).

We also examined the relation between DHA and EPA intake and incident AMD within strata of ω-6 fatty acid intake. Table 3 presents the results stratified by intake of LA. The inverse relation between DHA and EPA intake and AMD appeared stronger among participants with intake of LA above, as opposed to below, the median level although the tests of interaction were not significant. Findings were similar when models were fit above and below the median intake level for AA and total ω-6 fatty acids (LA + AA) (data not shown).

The results for fish intake and AMD are shown in Table 4. Consumption of one or more servings of fish per week, compared to less than one per month, was associated with a 42% lower risk of AMD (RR, 0.58; CI, 0.38–0.87; p, test for trend, 0.001). This lower risk appeared to be due primarily to consumption of canned tuna fish (RR, 0.56; CI, 0.40–0.80; p, test for trend, 0.001) and dark meat fish (RR, 0.56; CI, 0.32–0.99; p, test for trend, 0.014).

DISCUSSION

In this large prospective cohort study of female health professionals, regular consumption of DHA and EPA and fish was associated with a 35%–45% lower risk of visually-significant AMD during 10 years of follow-up. This inverse association was independent of other AMD risk factors, and was not materially altered after adjustment for saturated, monounsaturated, and trans unsaturated fat intake. The study population was comprised of women without a prior diagnosis of AMD, and the large majority of cases documented during follow-up were characterized by some combination of drusen and RPE changes signifying an early stage of disease development. Thus, these findings suggest that dietary intake of DHA and EPA and fish may be beneficial in the primary prevention of AMD.

Previous observational studies (44–57), including 5 prospective studies (48,49,53,55,56), are suggestive of an inverse association between fish and ω-3 long chain fatty acid intake and risks of advanced AMD (ie. neovascular AMD or central geographic atrophy). For example, recent prospective data from AREDS indicated that those with the highest consumption of DHA and EPA, compared to the lowest, had an approximate 30% lower risk of progression to advanced AMD that was apparent even after 12 years of follow-up (56). However, the data for early AMD are more limited and inconsistent. Of 5 cross-sectional studies that included cases of early AMD, 3 reported an inverse relation with advanced AMD only (45,46,51), and 2 reported no association with either early or advanced AMD (44,54). Interestingly, recent cross-sectional data from the Carotenoids in Age-Related Eye Disease Study indicated an increased risk of intermediate AMD for those with high intake of DHA and EPA (58). Data from three previous prospective studies provide only modest support for an inverse link between early AMD and fish and ω-3 long chain fatty acid intake. A report based on 567 cases of visually-significant (20/30 or worse) AMD identified during 10 to 12

years of follow-up of 42,000 women in the Nurses Health Study (NHS) and 30,000 men in the Health Professionals Follow-up Study (HPFS), aged 50 years and older, found that higher intake of DHA was associated with a 30% lower risk of AMD (multivariable RR [high vs. low quintile]; 0.70, CI, 0.52–0.93) (59). However, the RR was attenuated and no longer significant after further adjustment for other fats. A similar non significant inverse relation was observed for EPA in that study, while intake of ALA was directly related to risks of AMD in a fully adjusted model (RR, 1.41; CI, 1.00–1.98). That study also found that men and women who reported eating fish 4 or more times per week, compared to those who ate fish less than 4 times a month, had a 35% lower risk of AMD (RR, 0.65; CI, 0.46–0.91). This lower risk appeared to be due largely to intake of canned tuna fish (RR, 0.61; CI, 0.45–0.83); no association was observed for intake of dark- or white-meat fish in that study (59). In the Blue Mountains Eye Study, a repeat eye exam at 5 years for 2,335 men and women aged 49 years and older documented 130 new cases of early AMD and 22 cases of late AMD (49). Participants in the highest quintile of intake for ω-3 long chain fatty acids (DHA, DPA, EPA), compared to the lowest quintile, had a significantly lower risk of early AMD (OR, 0.41; CI, 0.22–0.75). Consumption of fish was also associated with significantly lower risks of early AMD (and late AMD) at the 5 year follow-up (49). However, at 10 years, the inverse relation between early AMD and intake of ω-3 long chain fatty acids (DHA, DPA, EPA) and fish was attenuated and no longer significant (55). In a third study, conducted among 846 men and women in Reykjavik, Iceland, aged 50 years and older, a repeat eye exam at 5 years of follow-up documented 126 new cases of early AMD. Those who reported eating herring 2 times per week or more, versus less than once a month, had a 39% lower risk of early AMD (RR, 0.61, CI, 0.37–1.00) (60). Our data, based on 10 years of follow-up of a large cohort of female health professionals, are broadly consistent with these earlier findings, and appear to be the strongest observational evidence to date in support of a possible role for intake of ω-3 long chain fatty acids and fish in the primary prevention of AMD. Moreover, because early AMD is associated with an increased risk of developing advanced AMD (eg. one study showed that eyes with soft indistinct drusen or RPE abnormalities were approximately 20 to 40 times more likely to develop late AMD than were eyes without these lesions [4]), our data further suggest that dietary intake of ω-3 long chain fatty acids and fish by persons at usual risk may ultimately reduce the number of persons who suffer from advanced AMD.

There is strong biologic plausibility for an association of DHA and EPA intake with AMD, and multiple mechanisms have been described (61). DHA and EPA could affect AMD occurrence by modulating inflammatory and immune processes thought to play a role in AMD pathogenesis (62,63). ω-3 and ω-6 fatty acids compete both for enzymes that convert essential fatty acids ALA and LA to longer chain DHA, EPA, and AA (64), and for enzymes that initiate conversion of these long-chain fatty acids to eicosanoids, locally-acting lipids more immediately involved in the control of inflammatory and immune processes (65–67). Higher intake of ω-3 fatty acids reduces production of AA-derived eicosanoids which are generally proinflammatory, and increases levels of EPA-derived eicosanoids which are 10–100 fold less active (68). Our observation in the present study that the ratio of ω-6 to ω-3 fatty acids (DHA plus EPA) was strongly predictive of early AMD is consistent with similar findings for advanced AMD in prior studies (47,51,69), and supports the conclusion that both the level of ω-3 fatty acids and its ratio to ω-6 fatty acids are important in determining risks of AMD (70). We also observed that the inverse relation of DHA and EPA with AMD was more apparent in participants reporting higher levels of ω-6 fatty acid intake although tests of interaction were not significant. This finding appears consistent with subgroup findings for LA intake in the AREDS population (51), but seems to conflict with two previous reports indicating a benefit primarily among participants with the lowest levels of LA intake (47,48). The reasons for these somewhat different findings are unclear and require further investigation. Other mechanisms through which DHA and EPA may contribute to a

reduced risk of AMD include enhanced production of resolvins and neuroprotectins, which are thought to dampen and resolve inflammatory responses (71–73), and the modulation of expression of signal transduction genes and genes for proinflammatory cytokines (74–76).

The study had several strengths and limitations that need to be considered. The prospective design of the study precluded the possibility of recall bias, and the high follow-up rate minimized the possibility of selection bias. The nutritional estimates were derived from a validated food frequency questionnaire which has been shown to reflect long-term dietary intake (77). Moreover, because women with a previous history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illnesses were excluded, misclassification due to recent changes in dietary intake prior to baseline was less likely in this population. Nonetheless, estimates of nutrient intake from dietary self-reports are prone to measurement error which would tend to underestimate any association of diet with risk of AMD. In addition, any changes in dietary intake during follow-up, which would likely be nondifferential with respect to the AMD endpoint, would also attenuate the true associations. We collected information on a range of known or potential risk factors for AMD at baseline and this enabled adjustment for these variables in the analyses. However, residual or unmeasured confounding remains a possibility in our analyses. It seems unlikely though that residual or unmeasured confounding had a major effect on these analyses since observed associations were not materially changed after adjustment for a range of measured confounders. With respect to the generalizability of our findings, participants are female health professionals, thus the findings may not be generalizable to other populations. It is also important to consider limitations of our methodology of disease ascertainment. Our study endpoint was based on participant self report, thus, some degree of underascertainment of AMD is plausible. Random misclassification of AMD, which would tend to shift the RR estimate toward the null, was reduced by the use of medical records to confirm the self reports, and by the use of strict diagnostic criteria that included reduction in best-corrected visual acuity to 20/30 or worse due to AMD. Surveillance bias was a possibility since women who reported higher intake of ω-3 fatty acids were more likely to report an eye exam in the past 2 years, and thus may have been more likely to have existing AMD diagnosed. However, the likely effect of such bias would be to underestimate any reduction in risk of AMD associated with ω-3 fatty acid intake. We controlled for possible surveillance bias by including a term for a baseline report of an eye exam in the past 2 years in multivariate analyses. Finally, it should be noted that this methodology has identified important risk factors for AMD such as cigarette smoking (14), body weight (78), and genetic variants (79–81), associations also demonstrated in examined populations with fundus photographs, providing reassuring evidence for the construct validity of this methodology.

In summary, these prospective data from a large population of women with no prior diagnosis of AMD indicate that regular consumption of DHA and EPA and fish significantly reduced the risk of incident AMD. These data appear to be the strongest evidence to date to support a role for ω-3 long chain fatty acids in the primary prevention of AMD, and perhaps a reduction in the number of persons who ultimately suffer from advanced AMD, and need to be confirmed in randomized trials.

Acknowledgments

Supported by research grants CA 47988, HL 43851, and EY 06633 from the National Institutes of Health, Bethesda, Md. Pills and packaging were provided by Bayer Healthcare and the Natural Source Vitamin E Association.

REFERENCES

1. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. 2004; 122(4):564–572. [PubMed: 15078675]
2. Klein R, Wang Q, Klein BE, et al. The relationship of age-related maculopathy, cataract, and glaucoma to visual acuity. Invest Ophthalmol Vis Sci. 1995; 36(1):182–191. [PubMed: 7822146]
3. Hogg RE, Chakravarthy U. Visual function and dysfunction in early and late age-related maculopathy. Prog Retin Eye Res. 2006; 25(3):249–276. [PubMed: 16580242]
4. Klein R, Klein BE, Tomany SC, et al. Ten-year incidence and progression of age-related maculopathy: The Beaver Dam eye study. Ophthalmology. 2002; 109(10):1767–1779. [PubMed: 12359593]
5. Ferris FL, Davis MD, Clemons TE, et al. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. Arch Ophthalmol. 2005; 123(11):1570–1574. [PubMed: 16286620]
6. van Leeuwen R, Klaver CC, Vingerling JR, et al. The risk and natural course of age-related maculopathy: follow-up at 6 1/2 years in the Rotterdam study. Arch Ophthalmol. 2003; 121(4):519–526. [PubMed: 12695249]
7. Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group. Arch Ophthalmol. 1991; 109(8):1109–1114. [PubMed: 1714270]
8. Laser photocoagulation of subfoveal neovascular lesions of age-related macular degeneration. Updated findings from two clinical trials. Macular Photocoagulation Study Group. Arch Ophthalmol. 1993; 111(9):1200–1209. [PubMed: 7689827]
9. Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. Arch Ophthalmol. 2001; 119(2):198–207. [PubMed: 11176980]
10. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization--verteporfin in photodynamic therapy report 2. Am J Ophthalmol. 2001; 131(5):541–560. [PubMed: 11336929]
11. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med. 2004; 351(27):2805–2816. [PubMed: 15625332]
12. Michels S, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology. 2005; 112(6):1035–1047. [PubMed: 15936441]
13. 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. Arch Ophthalmol. 2001; 119(10):1417–1436. [PubMed: 11594942]
14. Christen WG, Glynn RJ, Manson JE, et al. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. Jama. 1996; 276(14):1147–1151. [PubMed: 8827967]
15. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. Jama. 1996; 276(14):1141–1146. [PubMed: 8827966]
16. Klein R, Klein BE, Moss SE. Relation of smoking to the incidence of age-related maculopathy. The Beaver Dam Eye Study. Am J Epidemiol. 1998; 147(2):103–110. [PubMed: 9456998]
17. Snow KK, Seddon JM. Do age-related macular degeneration and cardiovascular disease share common antecedents? Ophthalmic Epidemiol. 1999; 6(2):125–143. [PubMed: 10420212]
18. He K, Song Y, Daviglus ML, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation. 2004; 109(22):2705–2711. [PubMed: 15184295]
19. Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. Am J Cardiol. 2004; 93(9):1119–1123. [PubMed: 15110203]
20. Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. J Am Coll Cardiol. 2009; 54(7):585–594. [PubMed: 19660687]

21. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002; 106(21):2747–2757. [PubMed: 12438303]
22. Robinson JG, Stone NJ. Antiatherosclerotic and antithrombotic effects of omega-3 fatty acids. Am J Cardiol. 2006; 98(4A):39i–49i.
23. Harris WS, Miller M, Tighe AP, et al. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. Atherosclerosis. 2008; 197(1):12–24. [PubMed: 18160071]
24. Anderson RE. Lipids of ocular tissues. IV. A comparison of the phospholipids from the retina of six mammalian species. Exp Eye Res. 1970; 10(2):339–344. [PubMed: 4320824]
25. Neuringer M, Connor WE, Lin DS, et al. Biochemical and functional effects of prenatal and postnatal omega 3 fatty acid deficiency on retina and brain in rhesus monkeys. Proc Natl Acad Sci U S A. 1986; 83(11):4021–4025. [PubMed: 3459166]
26. Sanders TA, Hinds A, Pereira CC. Influence of n-3 fatty acids on blood lipids in normal subjects. J Intern Med Suppl. 1989; 731:99–104. [PubMed: 2539838]
27. Fliesler SJ, Anderson RE. Chemistry and metabolism of lipids in the vertebrate retina. Prog Lipid Res. 1983; 22(2):79–131. [PubMed: 6348799]
28. Lecomte M, Paget C, Ruggiero D, et al. Docosahexaenoic acid is a major n-3 polyunsaturated fatty acid in bovine retinal microvessels. J Neurochem. 1996; 66(5):2160–2167. [PubMed: 8780049]
29. Hodge WG, Schachter HM, Barnes D, et al. Efficacy of omega-3 fatty acids in preventing age-related macular degeneration: a systematic review. Ophthalmology. 2006; 113(7):1165–1172. quiz 72-3, 78. [PubMed: 16815401]
30. Chong EW, Kreis AJ, Wong TY, et al. Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis. Arch Ophthalmol. 2008; 126(6):826–833. [PubMed: 18541848]
31. Age-Related Eye Disease Study 2 Investigators. Age-Related Eye Disease Study 2. ClinicalTrials.gov identifier: NCT00345176. [Accessed June 14, 2010]. Available at: http://clinicaltrials.gov/ct2/show/NCT00345176?term=AREDS2&rank=1
32. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005; 352(13):1293–1304. [PubMed: 15753114]
33. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. Jama. 2005; 294(1):47–55. [PubMed: 15998890]
34. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. Jama. 2005; 294(1): 56–65. [PubMed: 15998891]
35. Christen WG, Liu S, Schaumberg DA, Buring JE. Fruit and vegetable intake and the risk of cataract in women. Am J Clin Nutr. 2005; 81(6):1417–1422. [PubMed: 15941896]
36. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. Jama. 2002; 287(14):1815–1821. [PubMed: 11939867]
37. Miljanovic B, Trivedi KA, Dana MR, et al. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. Am J Clin Nutr. 2005; 82(4):887–893. [PubMed: 16210721]
38. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc. 1993; 93(7):790–796. [PubMed: 8320406]
39. Hunter DJ, Rimm EB, Sacks FM, et al. Comparison of measures of fatty acid intake by subcutaneous fat aspirate, food frequency questionnaire, and diet records in a free-living population of US men. Am J Epidemiol. 1992; 135(4):418–427. [PubMed: 1550093]
40. Baylin A, Kim MK, Donovan-Palmer A, et al. Fasting whole blood as a biomarker of essential fatty acid intake in epidemiologic studies: comparison with adipose tissue and plasma. Am J Epidemiol. 2005; 162(4):373–381. [PubMed: 16014782]
41. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol. 1986; 124(1):17–27. [PubMed: 3521261]
42. Cox D. Regression models and life-tables. J. R. Stat Soc Ser B. 1972; 34:187–220.

43. Kleinbaum, DGKL.; Morgenstern, H. Epidemiologic research: principles and quantitative methods. Belmont, CA: Lifetime Learning Publications; 1982.
44. Mares-Perlman JA, Brady WE, Klein R, et al. Dietary fat and age-related maculopathy. Arch Ophthalmol. 1995; 113(6):743–748. [PubMed: 7786215]
45. Smith W, Mitchell P, Leeder SR. Dietary fat and fish intake and age-related maculopathy. Arch Ophthalmol. 2000; 118(3):401–404. [PubMed: 10721964]
46. Heuberger RA, Mares-Perlman JA, Klein R, et al. Relationship of dietary fat to age-related maculopathy in the Third National Health and Nutrition Examination Survey. Arch Ophthalmol. 2001; 119(12):1833–1838. [PubMed: 11735796]
47. Seddon JM, Rosner B, Sperduto RD, et al. Dietary fat and risk for advanced age-related macular degeneration. Arch Ophthalmol. 2001; 119(8):1191–1199. [PubMed: 11483088]
48. Seddon JM, Cote J, Rosner B. Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake. Arch Ophthalmol. 2003; 121(12):1728–1737. [PubMed: 14662593]
49. Chua B, Flood V, Rochtchina E, et al. Dietary fatty acids and the 5-year incidence of age-related maculopathy. Arch Ophthalmol. 2006; 124(7):981–986. [PubMed: 16832021]
50. Delcourt C, Carriere I, Cristol JP, et al. Dietary fat and the risk of age-related maculopathy: the POLANUT study. Eur J Clin Nutr. 2007; 61(11):1341–1344. [PubMed: 17299457]
51. SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS Report No. 20. Arch Ophthalmol. 2007; 125(5):671–679. [PubMed: 17502507]
52. Augood C, Chakravarthy U, Young I, et al. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. Am J Clin Nutr. 2008; 88(2):398–406. [PubMed: 18689376]
53. SanGiovanni JP, Chew EY, Agron E, et al. The relationship of dietary omega-3 long-chain polyunsaturated fatty acid intake with incident age-related macular degeneration: AREDS report no. 23. Arch Ophthalmol. 2008; 126(9):1274–1279. [PubMed: 18779490]
54. Chong EW, Robman LD, Simpson JA, et al. Fat consumption and its association with age-related macular degeneration. Arch Ophthalmol. 2009; 127(5):674–680. [PubMed: 19433719]
55. Tan JS, Wang JJ, Flood V, Mitchell P. Dietary fatty acids and the 10-year incidence of age-related macular degeneration: the Blue Mountains Eye Study. Arch Ophthalmol. 2009; 127(5):656–665. [PubMed: 19433717]
56. Sangiovanni JP, Agron E, Meleth AD, et al. {omega}-3 Long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy: AREDS report 30, a prospective cohort study from the Age-Related Eye Disease Study. Am J Clin Nutr. 2009; 90(6):1601–1607. [PubMed: 19812176]
57. Swenor BK, Bressler S, Caulfield L, West SK. The Impact of Fish and Shellfish Consumption on Age-Related Macular Degeneration. Ophthalmology. 2010 [Epub ahead of print].
58. Parekh N, Voland RP, Moeller SM, et al. Association between dietary fat intake and age-related macular degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS): an ancillary study of the Women's Health Initiative. Arch Ophthalmol. 2009; 127(11):1483–1493. [PubMed: 19901214]
59. Cho E, Hung S, Willett WC, et al. Prospective study of dietary fat and the risk of age-related macular degeneration. Am J Clin Nutr. 2001; 73(2):209–218. [PubMed: 11157315]
60. Arnarsson A, Sverrisson T, Stefansson E, et al. Risk factors for five-year incident age-related macular degeneration: the Reykjavik Eye Study. Am J Ophthalmol. 2006; 142(3):419–428. [PubMed: 16935586]
61. SanGiovanni JP, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. Prog Retin Eye Res. 2005; 24(1):87–138. [PubMed: 15555528]
62. Hageman GS, Luthert PJ, Victor Chong NH, et al. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. Prog Retin Eye Res. 2001; 20(6):705–732. [PubMed: 11587915]

63. Hollyfield JG. Age-related macular degeneration: the molecular link between oxidative damage, tissue-specific inflammation and outer retinal disease: the Proctor lecture. Invest Ophthalmol Vis Sci. 2010; 51(3):1275–1281. [PubMed: 20185837]
64. Gerster H. Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? Int J Vitam Nutr Res. 1998; 68(3):159–173. [PubMed: 9637947]
65. Culp BR, Titus BG, Lands WE. Inhibition of prostaglandin biosynthesis by eicosapentaenoic acid. Prostaglandins Med. 1979; 3(5):269–278. [PubMed: 121610]
66. Corey EJ, Shih C, Cashman JR. Docosahexaenoic acid is a strong inhibitor of prostaglandin but not leukotriene biosynthesis. Proc Natl Acad Sci U S A. 1983; 80(12):3581–3584. [PubMed: 6304720]
67. Marshall LA, Johnston PV. Modulation of tissue prostaglandin synthesizing capacity by increased ratios of dietary alpha-linolenic acid to linoleic acid. Lipids. 1982; 17(12):905–913. [PubMed: 6298554]
68. Alexander JW. Immunonutrition: the role of omega-3 fatty acids. Nutrition. 1998; 14(7–8):627–633. [PubMed: 9684267]
69. Seddon JM, George S, Rosner B. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US.
70. Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed Pharmacother. 2002; 56(8):365–379. [PubMed: 12442909]
71. Serhan CN, Hong S, Gronert K, et al. Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J Exp Med. 2002; 196(8):1025–1037. [PubMed: 12391014]
72. Tian H, Lu Y, Sherwood AM, et al. Resolvins E1 and D1 in choroid-retinal endothelial cells and leukocytes: biosynthesis and mechanisms of anti-inflammatory actions. Invest Ophthalmol Vis Sci. 2009; 50(8):3613–3620. [PubMed: 19443724]
73. Mukherjee PK, Marcheselli VL, Serhan CN, Bazan NG. Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. Proc Natl Acad Sci U S A. 2004; 101(22):8491–8496. [PubMed: 15152078]
74. Calder PC. Dietary modification of inflammation with lipids. Proc Nutr Soc. 2002; 61(3):345–358. [PubMed: 12296294]
75. Weaver KL, Ivester P, Seeds M, et al. Effect of dietary fatty acids on inflammatory gene expression in healthy humans. J Biol Chem. 2009; 284(23):15400–15407. [PubMed: 19359242]
76. Connor KM, SanGiovanni JP, Lofqvist C, et al. Increased dietary intake of omega-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. Nat Med. 2007; 13(7):868–873. [PubMed: 17589522]
77. Willett, W. Nutritional Epidemiology. New York, NY: Oxford University Press; 1998.
78. Schaumberg DA, Christen WG, Hankinson SE, Glynn RJ. Body mass index and the incidence of visually significant age-related maculopathy in men. Arch Ophthalmol. 2001; 119(9):1259–1265. [PubMed: 11545630]
79. Schaumberg DA, Christen WG, Kozlowski P, et al. A prospective assessment of the Y402H variant in complement factor H, genetic variants in C-reactive protein, and risk of age-related macular degeneration. Invest Ophthalmol Vis Sci. 2006; 47(6):2336–2340. [PubMed: 16723442]
80. Schaumberg DA, Hankinson SE, Guo Q, et al. A prospective study of 2 major age-related macular degeneration susceptibility alleles and interactions with modifiable risk factors. Arch Ophthalmol. 2007; 125(1):55–62. [PubMed: 17210852]
81. Schaumberg DA, Christen WG, DeAngelis MM, Chasman DI. Novel associations of SNPs on chromosomes 2 and 16 and risk of incident neovascular age-related macular degeneration in the Women's Genome Health Study. Association for Research in Vision and Ophthalmology. 2010 Abstract no. 1623.

Table 1

Distribution of baseline characteristics that are possible risk factors for age-related macular degeneration according to tertiles of ω-3 and ω-6 fatty acid intake in the Women's Health Study.[a]

	Tertile of intake			
	1	2	3	p-trend
ω–3 long chain fatty acid intake[b]	n=12,638	n=13,119	n=12,265	
Range (gm)	0.0–0.11	0.12–0.23	0-24-3.43	
Median (gm)	0.08	0.16	0.33	
Mean age (y)	54.4 ∀ 7.1	54.4 ∀ 6.9	54.9 ∀ 6.9	<.0001
Current smoking	14.2	13.5	11.5	<.0001
Daily alcohol use	8.4	10.0	12.7	<.0001
Body mass index (kg/m^2)	26.0 ∀ 5.1	26.1 ∀ 5.0	25.9 ∀ 5.0	0.02
Current hormone use	28.8	30.1	31.4	<.0001
History of hypertension[d]	24.2	25.8	26.9	<.0001
History of high cholesterol[e]	28.0	29.6	30.3	<.0001
History of diabetes	2.2	2.5	2.8	.004
Current multivitamin use	34.8	36.4	40.0	<.0001
Eye exam in past 2 years	80.8	82.9	84.5	<.0001
ω–6 fatty acid intake[c]	n=12,650	n=12,675	n=12,697	
Range (gm)	1.89–9.35	9.36–11.70	11.71–38.98	
Median (gm)	8.07	10.47	13.41	
Mean age (y)	54.4 ∀ 6.9	54.5 ∀ 7.0	54.8 ∀ 7.0	<.0001
Current smoking	11.7	12.6	15.0	<.0001
Daily alcohol use	12.1	10.0	8.9	<.0001
Body mass index (kg/m^2)	25.6 ∀ 4.8	26.1 ∀ 5.0	26.3 ∀ 5.2	<.0001
Current hormone use	29.6	30.2	30.6	0.08
History of hypertension[d]	24.4	25.8	26.5	.0001
History of high cholesterol[e]	28.5	29.3	30.1	.005
History of diabetes	2.2	2.4	2.8	.001
Current multivitamin use	39.5	36.8	34.4	<.0001
Eye exam in past 2 years	83.5	82.5	82.2	.004
ω-6:ω–3 long chain fatty acid intake	n=12,673	n=12,674	n=12,673	
Range	1.21–45.17	45.18-93-55	93.56–3239.00	
Median	30.00	64.54	149.33	
Mean age (y)	54.8 ∀ 6.9	54.4 ∀ 6.9	54.4 ∀ 7.1	<.0001
Current smoking	11.5	13.0	14.7	<.0001
Daily alcohol use	12.9	10.1	7.9	<.0001
Body mass index (kg/m^2)	25.8 ∀ 4.9	26.1 ∀ 5.0	26.1 ∀ 5.2	<.0001
Current hormone use	31.4	29.9	29.1	<.0001

	Tertile of intake			
	1	2	3	p-trend
History of hypertension[d]	26.5	25.5	24.8	.003
History of high cholesterol[e]	30.1	29.5	28.3	.001
History of diabetes	2.7	2.5	2.3	.05
Current multivitamin use	40.1	36.7	34.0	<.0001
Eye exam in past 2 years	84.4	82.7	81.1	<.0001

[a] Data are given as percentage of participants unless otherwise noted.

[b] Docosahexaenoic acid plus eicosapentaenoic acid.

[c] Linoleic acid plus arachidonic acid.

[d] Hypertension was defined as a self-reported systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or self-reported physician-diagnosed hypertension or current treatment.

[e] High cholesterol was defined as a self-reported total cholesterol of at least 240 mg/dL, or self-reported physician-diagnosed high cholesterol levels or current treatment.

Arch Ophthalmol. Author manuscript; available in PMC 2012 July 1.

Table 2

RRs and 95% CIs for diagnosis of visually-significant age-related macular degeneration according to tertiles of ω-3 and ω-6 fatty acid intake.in the Women's Health Study.

Tertile of dietary intake (median, gr/d)	No. of subjects	No. with AMD	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)	Model 3[c] RR (95% CI)
Docosahexaenoic acid					
Tertile 1 (0.06)	13,600	103	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (0.13)	11,923	72	0.82 (0.61–1.11)	0.83 (0.61–1.12)	0.85 (0.63–1.16)
Tertile 3 (0.23)	12,499	60	0.62 (0.45–0.85)	0.59 (0.42–0.81)	0.62 (0.44–0.87)
P for trend			0.003	0.001	0.005
Eicosapentaenoic acid					
Tertile 1 (0.01)	13,716	98	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (0.04)	11,412	75	0.97 (0.72–1.31)	0.95 (0.70–1.29)	0.98 (0.72–1.33)
Tertile 3 (0.10)	12,894	62	0.64 (0.46–0.88)	0.63 (0.46–0.88)	0.66 (0.48–0.92)
P for trend			0.004	0.005	0.012
Docosapentaenoic acid					
Tertile 1 (0.01)	12,267	92	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (0.02)	10,743	67	0.92 (0.67–1.26)	0.95 (0.69–1.31)	0.98 (0.71–1.35)
Tertile 3 (0.03)	15,012	76	0.75 (0.55–1.02)	0.74 (0.54–1.01)	0.79 (0.57–1.09)
P for trend			0.06	0.06	0.16
∀-linolenic acid					
Tertile 1 (0.85)	12,557	68	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (1.11)	12,784	76	1.06 (0.76–1.47)	1.06 (0.76–1.47)	1.03 (0.74–1.44)
Tertile 3 (1.46)	12,681	91	1.11 (0.81–1.52)	1.07 (0.78–1.47)	1.04 (0.75–1.44)
P for trend			0.52	0.69	0.83
Total ω-3 fatty acids					
Tertile 1 (1.04)	12,856	74	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (1.35)	12,594	76	0.99 (0.72–1.36)	1.00 (0.72–1.38)	0.99 (0.72–1.37)
Tertile 3 (1.73)	12,572	85	0.98 (0.72–1.34)	0.95 (0.69–1.30)	0.95 (0.68–1.31)
P for trend			0.92	0.73	0.74
ω-3 long chain fatty acids (DHA + EPA)					
Tertile 1 (0.08)	12,638	96	1.00 (ref)	1.00 (ref)	1.00 (ref)

Tertile of dietary intake (median, gr/d)	No. of subjects	No. with AMD	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)	Model 3[c] RR (95% CI)
Tertile 2 (0.16)	13,119	79	0.83 (0.62–1.12)	0.83 (0.62–1.13)	0.86 (0.63–1.16)
Tertile 3 (0.33)	12,265	60	0.62 (0.45–0.86)	0.59 (0.42–0.83)	0.63 (0.45–0.88)
P for trend			0.004	0.002	0.007
Linoleic acid					
Tertile 1 (7.92)	12,658	63	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (10.33)	12,685	75	1.13 (0.81–1.58)	1.11 (0.80–1.56)	1.07 (0.75–1.51)
Tertile 3 (13.27)	12,679	97	1.41 (1.03–1.94)	1.32 (0.96–1.82)	1.20 (0.84–1.72)
P for trend			0.028	0.08	0.31
Arachidonic acid					
Tertile 1 (0.09)	12,366	87	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (0.14)	13,919	77	0.99 (0.72–1.34)	0.97 (0.71–1.32)	0.94 (0.69–1.28)
Tertile 3 (0.20)	11,737	71	1.10 (0.80–1.51)	1.01 (0.73–1.40)	1.01 (0.73–1.40)
P for trend			0.56	0.93	0.94
ω-6 fatty acids					
Tertile 1 (8.07)	12,650	64	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (10.47)	12,675	75	1.11 (0.80–1.56)	1.10 (0.78–1.53)	1.05 (0.74–1.48)
Tertile 3 (13.41)	12,697	96	1.38 (1.01–1.89)	1.28 (0.93–1.77)	1.16 (0.81–1.66)
P for trend			0.040	0.12	0.40
ω-6 fatty acids :total ω–3 fatty acids[d]					
Tertile 1 (6.40)	12,674	63	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (7.80)	12,675	88	1.50 (1.08–2.07)	1.53 (1.10–2.13)	1.43 (1.01–2.01)
Tertile 3 (9.41)	12,673	84	1.54 (1.11–2.14)	1.55 (1.11–2.16)	1.37 (0.95–1.96)
P for trend			0.012	0.014	.13
ω-6 fatty acids: ω-3 long chain fatty acids[e]					
Tertile 1 (30.00)	12,673	58	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2 (64.54)	12,674	78	1.41 (1.00–1.98)	1.41 (1.00–1.99)	1.35 (0.95–1.92)
Tertile 3 (149.33)	12,673	99	1.75 (1.27–2.42)	1.77 (1.27–2.47)	1.64 (1.16–2.31)
P for trend			0.001	0.001	0.008

Abbreviations: RR, relative risk; CI, confidence interval; AMD, age-related macular degeneration.

[a]Adjusted for age and randomized treatment assignment.

[b] Adjusted for age, aspirin and vitamin E treatment assignment, smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), menopausal status and use of HT (premenopausal, uncertain, postmenopausal and current HT, postmenopausal and no HT), history of hypertension (self-reported systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or self-reported physician-diagnosed hypertension or current treatment; yes or no), history of high cholesterol (self-reported total cholesterol of at least 240 mg/dL, or self-reported physician-diagnosed high cholesterol levels or current treatment; yes or no), history of diabetes (yes or no), multivitamin use (current, past/never), history of eye exam in the last 2 years (yes or no).

[c] Adjusted as in model 2 but including tertiles of saturated fat, monounsaturated fat, and trans unsaturated fats.

[d] LA+AA / DHA+EPA+DPA+ALA

[e] LA+AA / DHA+EPA

Percentage of total energy intake (median) for increasing tertiles: DHA (0.03, 0.07, 0.13); EPA (0.01, 0.02, 0.06); DPA (0.01, 0.01, 0.02); ALA (0.45, 0.59, 0.81); total ω-3 fatty acids (0.55, 0.71, 0.97); marine ω-3 fatty acids (DHA + EPA) (0.04, 0.09, 0.19); LA (4.16, 5.49, 7.39); AA (0.05, 0.07, 0.12); total ω-6 fatty acids (4.23, 5.57, 7.47).

Table 3

RRs and 95% CIs for diagnosis of visually-significant age-related macular degeneration according to tertiles of ω-3 fatty acid intake stratified by linoleic acid intake in the Women's Health Study.

	Linoleic acid[a]						
	Below median			Above median			
Tertile of dietary intake	No. of subjects	No. with AMD	RR[b] (95% CI)	No. of subjects	No. with AMD	RR[b] (95% CI)	P-Interaction
Docosahexaenoic acid							
Tertile 1	6,394	32	1.0 (ref)	6,000	65	1.0 (ref)	
Tertile 2	6,531	30	0.92 (0.56–1.52)	6,575	47	0.72 (0.49–1.05)	0.55
Tertile 3	6,072	25	0.92 (0.56–1.52)	6,450	36	0.48 (0.31–0.74)	
P for trend			0.30			0.001	
Eicosapentaenoic acid							
Tertile 1	6,449	30	1.0 (ref)	7	68	1.0 (ref)	
Tertile 2	6,276	29	0.96 (0.57–1.61)	5	43	1.00 (0.67–1.48)	0.39
Tertile 3	6,272	28	0.85 (0.51–1.44)	6	37	0.57 (0.38–0.86)	
P for trend			0.54			0.005	
Marine ω-3 fatty acids							
Tertile 1	6,697	30	1.0 (ref)	6	68	1.0 (ref)	
Tertile 2	5,992	31	1.15 (0.69–1.91)	5	44	0.80 (0.55–1.18)	0.41
Tertile 3	6,308	26	0.83 (0.49–1.42)	6	36	0.51 (0.33–0.77)	
P for trend			0.40			0.002	

Abbreviations: RR, relative risk; CI, confidence interval; AMD, age-related macular degeneration.

[a] Median intake: 10.33 gr/d; range: 1.86–38.79 gr/d.

[b] Adjusted for age, randomized treatment assignment, smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), menopausal status and use of HT (premenopausal, uncertain, postmenopausal and current HT, postmenopausal and no HT), history of hypertension (self-reported systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or self-reported physician-diagnosed hypertension or current treatment; yes or no), history of high cholesterol (self-reported total cholesterol of at least 240 mg/dL, or self-reported physician-diagnosed high cholesterol levels or current treatment; yes or no), history of diabetes (yes or no), multivitamin use (current, past/never), history of eye exam in the last 2 years (yes or no).

Table 4

RRs and 95% CIs for diagnosis of visually-significant age-related macular degeneration according to categories of fish intake in the Women's Health Study.

Intake of fish (no. of servings)	No. of subjects	No. with AMD	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)
Total fish				
<1/month	2,970	28	1.00 (ref)	1.00 (ref)
1–3/month	10,793	83	0.90 (0.59–1.38)	0.88 (0.57–1.35)
∃1/week	24,218	124	0.61 (0.40–0.92)	0.58 (0.38–0.87)
P for trend			.002	.001
Dark meat fish				
<1/month	25,230	170	1.00 (ref)	1.00 (ref)
1–3/month	9,398	50	0.73 (0.53–0.99)	0.76 (0.55–1.05)
∃1/week	3,163	13	0.52 (0.30–0.92)	0.56 (0.32–0.99)
P for trend			.004	.014
Canned tuna fish				
<1/month	8,340	73	1.00 (ref)	1.00 (ref)
1–3/month	15,775	97	0.78 (0.58–1.06)	0.76 (0.56–1.03)
∃1/week	13,570	61	0.60 (0.43–0.84)	0.56 (0.40–0.80)
P for trend			.003	.001
Shrimp/lobster/scallops				
<1/month	22,005	144	1.00 (ref)	1.00 (ref)
1–3/month	13,251	72	0.98 (0.74–1.30)	0.94 (0.70–1.27)
∃1/week	2,587	17	1.26 (0.76–2.08)	1.28 (0.77–2.13)
P for trend			.62	.69
Other fish (not canned tuna/dark)				
<1/month	12,064	88	1.00 (ref)	1.00 (ref)
1–3/month	15,551	89	0.86 (0.64–1.15)	0.85 (0.63–1.14)
∃1/week	10,102	56	0.72 (0.52–1.01)	0.72 (0.51–1.01)
P for trend			.054	.06

Abbreviations: RR, relative risk; CI, confidence interval; AMD, age-related macular degeneration.

[a] Adjusted for age and randomized treatment assignment.

[b] Adjusted for age, randomized treatment assignment, smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), menopausal status and use of HT (premenopausal, uncertain, postmenopausal and current HT, postmenopausal and no HT), history of hypertension (self-reported systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or self-reported physician-diagnosed hypertension or current treatment; yes or no), history of high cholesterol (self-reported total cholesterol of at least 240 mg/dL, or self-reported physician-diagnosed high cholesterol levels or current treatment; yes or no), history of diabetes (yes or no), multivitamin use (current, past/never), history of eye exam in the last 2 years (yes or no).