

ONLINE FIRST

Dietary • -3 Fatty Acid and Fish Intake and Incident Age-Related Macular Degeneration in Women

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Objective: To examine whether intake of • -3 fatty acids and fish affects 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. The main outcome measure was 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, compared with those in the lowest, had a multivariate-adjusted relative risk of AMD of 0.62 (95% confidence interval, 0.44-

0.87). For eicosapentaenoic acid, women in the highest tertile of intake had a relative risk of 0.66 (95% confidence interval, 0.48-0.92). Consistent with the findings for docosahexaenoic acid and eicosapentaenoic acid, women who consumed 1 or more servings of fish per week, compared with those who consumed less than 1 serving per month, had a relative risk of AMD of 0.58 (95% confidence interval, 0.38-0.87).

Conclusion: These prospective data from a large cohort of female health professionals without a diagnosis of AMD at baseline indicate that regular consumption of docosahexaenoic acid and eicosapentaenoic acid and fish was associated with a significantly decreased risk of incident AMD and may be of benefit in primary prevention of AMD.

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AN ESTIMATED 9 MILLION US 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 AMD⁷⁻¹² or intermediate AMD.¹³ For the large majority of persons with early or no AMD, there is no recognized 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 • -3 fatty acids concentrated in fish (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]), has been linked with reduced rates of cardiovascular events in epidemiologic studies¹⁸⁻²⁰ and could have a similar beneficial effect in AMD. • -3 Fatty acids are known to exert anti-inflammatory, anti-atherosclerotic, and antithrombotic effects on the vasculature²¹⁻²³ and may help to maintain or improve choroidal blood flow in the eye. The further observations that DHA and arachidonic acid (AA), an • -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 support the potential importance of these nutrients in AMD.

Some evidence from observational epidemiologic studies suggests an inverse re-

lation 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.

METHODS

Study participants were women enrolled in the Women's Health Study, 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 Women's Health Study have been described in detail previously.³²⁻³⁴ Briefly, 39 876 apparently healthy female US 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 end point ascertainment were continued in a masked 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 questionnaire³⁵ 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 semiquantitative food-frequency questionnaire 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 9 possible responses ranging from "never or less than once per month" to "6 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 (22:5), and ω -linolenic acid (18:3). Intake of ω -6 fatty

acids was based on data for linoleic acid (LA) (18:2) and 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 END POINTS

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. Ophthalmologists and optometrists 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] hypopigmentation or 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 ophthalmologist and optometrist 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. Ophthalmologists and optometrists 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 end point 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 semiquantitative food-frequency questionnaire. 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) 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 smok-

Table 1. Distribution of Baseline Characteristics That Are Possible Risk Factors for Age-Related Macular Degeneration According to Tertiles of • -3 and • -6 Fatty Acid Intake in the Women's Health Study

	%			P Value for Trend
	Tertile of Intake			
	1	2	3	
• -3 Long-chain fatty acid intake ^a	n=12 638	n=13 119	n=12 265	
Median (range), g	0.08 (0.0-0.11)	0.16 (0.12-0.23)	0.33 (0.24-3.43)	
Age, mean (SD), y	54.4 (7.1)	54.4 (6.9)	54.9 (6.9)	.001
Current smoking	14.2	13.5	11.5	.001
Daily alcohol use	8.4	10.0	12.7	.001
BMI, mean (SD)	26.0 (5.1)	26.1 (5.0)	25.9 (5.0)	.02
Current hormone use	28.8	30.1	31.4	.001
History of hypertension ^b	24.2	25.8	26.9	.001
History of high cholesterol ^c	28.0	29.6	30.3	.001
History of diabetes	2.2	2.5	2.8	.004
Current multivitamin use	34.8	36.4	40.0	.001
Eye examination in past 2 y	80.8	82.9	84.5	.001
• -6 Fatty acid intake ^d	n=12 650	n=12 675	n=12 697	
Median (range), g	8.07 (1.89-9.35)	10.47 (9.36-11.70)	13.41 (11.71-38.98)	
Age, mean (SD), y	54.4 (6.9)	54.5 (7.0)	54.8 (7.0)	.001
Current smoking	11.7	12.6	15.0	.001
Daily alcohol use	12.1	10.0	8.9	.001
BMI, mean (SD)	25.6 (4.8)	26.1 (5.0)	26.3 (5.2)	.001
Current hormone use	29.6	30.2	30.6	.08
History of hypertension ^b	24.4	25.8	26.5	.001
History of high cholesterol ^c	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	.001
Eye examination in past 2 y	83.5	82.5	82.2	.004
• -6 • -3 Long-chain fatty acid intake	n=12 673	n=12 674	n=12 673	
Median (range)	30.00 (1.27-45.17)	64.54 (45.18-93.55)	149.33 (93.56-3239.00)	
Age, mean (SD), y	54.8 (6.9)	54.4 (6.9)	54.4 (7.1)	.001
Current smoking	11.5	13.0	14.7	.001
Daily alcohol use	12.9	10.1	7.9	.001
BMI, mean (SD)	25.8 (4.9)	26.1 (5.0)	26.1 (5.2)	.001
Current hormone use	31.4	29.9	29.1	.001
History of hypertension ^b	26.5	25.5	24.8	.003
History of high cholesterol ^c	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	.001
Eye examination in past 2 y	84.4	82.7	81.1	.001

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factor: To convert total cholesterol to millimoles per liter, multiply by 0.0259.

^aDocosahexaenoic acid plus eicosapentaenoic acid.

^bHypertension was defined as a self-reported systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension or current treatment.

^cHigh cholesterol was defined as a self-reported total cholesterol level of at least 240 mg/dL or self-reported physician-diagnosed high cholesterol levels or current treatment.

^dLinoleic acid plus arachidonic acid.

ing, alcohol use, body mass index, postmenopausal hormone use, history of hypertension, history of high cholesterol, history of diabetes mellitus, multivitamin use, and history of an eye examination 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, 2-sided P values and 95% 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 • -3 fatty acids and AMD by conducting stratified analyses within strata of participants higher than and lower than the median intake for LA, AA, and total • -6 fatty acids (LA plus AA). Tests of interaction were performed to evaluate the null hypothesis of no difference in the association of • -3 fatty acids with AMD across strata of • -6 fatty acids. Because fish and seafood intakes account for most of the total • -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, less than 1 serving per month, 1 to 3 servings per month, and 1 or more servings per 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 • -3 long-chain and • -6 fatty

acid intake. Older women and women who reported a history of hypertension, high cholesterol level, 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 examination 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 ratio were younger, more likely to smoke but less likely to use alcohol, and had a higher body mass index. These women were also less likely to report current hormone use, hypertension, high cholesterol level, diabetes, current multivitamin use, and an eye examination in the past 2 years.

Among 38 022 participants who completed a semi-quantitative food-frequency questionnaire 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 visual acuity was first noted to be 20/30 or worse (drusen only, $n=33$ [14.0%]; RPE changes only, $n=56$ [23.8%]; drusen and RPE changes, $n=81$ [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 with the lowest, had a 38% lower risk of AMD (RR, 0.62; 95% CI, 0.45-0.85; P for trend = .003). Similar inverse associations with AMD were observed for higher intake of EPA (RR, 0.64; 95% CI, 0.46-0.88; P for trend = .004) and for DHA plus EPA (RR, 0.62; 95% CI, 0.45-0.86; P for trend = .004). Higher intake of docosapentaenoic acid, an intermediary between EPA and DHA, was associated with a 25% reduced risk of AMD that was of borderline significance (RR, 0.75; 95% CI, 0.55-1.02; P for trend = .06). There was no association between ω -linolenic acid 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 (95% CI, 1.03-1.94; P for trend = .03). 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 higher than, as opposed to lower than, the median level, although the tests of interaction were not significant. Findings were similar when models were fit

higher than and lower than the median intake level for AA and total ω -6 fatty acids (LA plus AA) (data not shown).

The results for fish intake and AMD are shown in Table 4. Consumption of 1 or more servings of fish per week, compared with less than 1 per month, was associated with a 42% lower risk of AMD (RR, 0.58; 95% CI, 0.38-0.87; P for trend = .001). This lower risk appeared to be due primarily to consumption of canned tuna fish (RR, 0.56; 95% CI, 0.40-0.80; P for trend = .001) and dark-meat fish (RR, 0.56; 95% CI, 0.32-0.99; P for trend = .01).

COMMENT

In this large prospective cohort study of female health professionals, regular consumption of DHA and EPA and fish was associated with a 35% to 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 comprised 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 the Age-Related Eye Disease Study indicated that those with the highest consumption of DHA and EPA, compared with 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 3 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 (visual acuity 20/30 or worse) AMD identified during 10 to 12 years of follow-up of 42 000 women in the Nurses' Health Study and 30 000 men 50 years and older in the Health Professionals Follow-up Study found that higher intake of DHA was associated with a 30% lower risk of AMD (multivariable RR [high vs low quintile], 0.70; 95% CI, 0.52-0.93).⁵⁹ However, the RR was attenuated and no longer significant after further adjustment for other fats. A similar nonsignificant inverse relation was observed for EPA in that study, while intake of ω -linolenic acid was directly related to risks of AMD in a fully adjusted

Table 2. Diagnosis of Visually Significant Age-Related Macular Degeneration According to Tertiles of • -3 and • -6 Fatty Acid Intake in the Women's Health Study^a

Tertile of Dietary Intake (Median, g/d)	No. of Subjects	No. With AMD	RR (95% CI)		
			Model 1 ^b	Model 2 ^c	Model 3 ^d
DHA					
Tertile 1 (0.06)	13 600	103	1 [Reference]	1 [Reference]	1 [Reference]
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)	0.52 (0.44-0.87)
P value for trend			.003	.001	.005
EPA					
Tertile 1 (0.01)	13 716	98	1 [Reference]	1 [Reference]	1 [Reference]
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 (0.48-0.82)
P value for trend			.004	.005	.01
DPA					
Tertile 1 (0.01)	12 267	92	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.06	.06	.16
ALA					
Tertile 1 (0.85)	12 557	68	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.52	.69	.83
Total • -3 fatty acids					
Tertile 1 (1.04)	12 856	74	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.92	.73	.74
• -3 Long-chain fatty acids (DHA • EPA)					
Tertile 1 (0.08)	12 638	96	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.004	.002	.007
LA					
Tertile 1 (7.92)	12 658	63	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.03	.08	.31
AA					
Tertile 1 (0.09)	12 366	87	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.56	.93	.94
• -6 Fatty acids					
Tertile 1 (8.07)	12 650	84	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.04	.12	.40
• -6 Fatty acids:total • -3 fatty acids^e					
Tertile 1 (6.40)	12 674	63	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.01	.01	.13
• -6 Fatty acids • -3 long-chain fatty acids^f					
Tertile 1 (30.00)	12 673	58	1 [Reference]	1 [Reference]	1 [Reference]
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 value for trend			.001	.001	.008

Abbreviations: AA, arachidonic acid; ALA, • -linolenic acid; AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; HT, hormone therapy; LA, linoleic acid; RR, relative risk.

^aSI conversion factor: To convert total cholesterol to millimoles per liter, multiply by 0.0259.

^bPercentage 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 • -3 fatty acids (0.55, 0.71, 0.97); marine • -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 • -6 fatty acids (4.23, 5.57, 7.47).

^cAdjusted for age and randomized treatment assignment.

^dAdjusted for age, aspirin and vitamin E treatment assignment, smoking (current, past, never), alcohol use (rarely/never, 1-3 drinks/mo, 1-6 drinks/wk, and • 1 drinks/d), 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 mm Hg, diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension or current treatment; yes or no), history of high cholesterol (self-reported total cholesterol level 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), and history of eye examination in the last 2 years (yes or no).

^eAdjusted as in model 2 but including tertiles of saturated fat, monounsaturated fat, and trans unsaturated fats.

^fLA • AA/DHA • EPA • DPA • ALA.

^gLA • AA/DHA • EPA.

Table 3. 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

Tertile of Dietary Intake	Linoleic Acid Intake ^a						P Value Interaction
	Lower Than the Median			Higher Than the Median			
	No. of Subjects	No. With AMD	RR (95% CI) ^b	No. of Subjects	No. With AMD	RR (95% CI) ^b	
Docosahexaenoic acid							
Tertile 1	6394	32	1 [Reference]	6000	65	1 [Reference]	55
Tertile 2	6531	30	0.92 (0.56-1.52)	6575	47	0.72 (0.49-1.05)	
Tertile 3	6072	25	0.92 (0.56-1.52)	6450	36	0.48 (0.31-0.74)	
P value for trend			.30			.001	
Eicosapentaenoic acid							
Tertile 1	6449	30	1 [Reference]	7267	68	1 [Reference]	39
Tertile 2	6276	29	0.96 (0.57-1.61)	5112	43	1.00 (0.67-1.48)	
Tertile 3	6272	28	0.85 (0.51-1.44)	6646	37	0.57 (0.38-0.86)	
P value for trend			.54			.005	
Marine ω-3 fatty acids							
Tertile 1	6697	30	1 [Reference]	6725	68	1 [Reference]	41
Tertile 2	5992	31	1.15 (0.69-1.91)	5855	44	0.80 (0.55-1.18)	
Tertile 3	6308	26	0.83 (0.49-1.42)	6445	36	0.51 (0.33-0.77)	
P value for trend			.40			.002	

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HT, hormone therapy; RR, relative risk.

SI conversion factor: To convert total cholesterol to millimoles per liter, multiply by 0.0259.

^aMedian intake: 10.33 g/d; range: 1.86 to 38.79 g/d.

^bAdjusted for age, randomized treatment assignment, smoking (current, past, never), alcohol use (rarely/never, 1-3 drinks/mo, 1-6 drinks/wk, and ≥ 1 drinks/d), 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 mm Hg, diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension or current treatment; yes or no), history of high cholesterol (self-reported total cholesterol level 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), and history of eye examination in the last 2 years (yes or no).

model (RR, 1.41; 95% CI, 1.00-1.98). That study also found that men and women who reported eating fish 4 or more times per week, compared with those who ate fish less than 4 times a month, had a 35% lower risk of AMD (RR, 0.65; 95% CI, 0.46-0.91). This lower risk appeared to be due largely to intake of canned tuna fish (RR, 0.61; 95% 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 repeated eye examination at 5 years for 2335 men and women 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, docosapentaenoic acid, and EPA), compared with the lowest quintile, had a significantly lower risk of early AMD (odds ratio, 0.41; 95% 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, docosapentaenoic acid, and EPA) and fish was attenuated and no longer significant.⁵⁵ In a third study, conducted among 846 men and women in Reykjavik, Iceland, 50 years and older, a repeated eye examination at 5 years of follow-up documented 126 new cases of early AMD. Those who reported eating herring 2 times per week or more, vs less than once a month, had a 39% lower risk of early AMD (RR, 0.61; 95% 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 find-

ings 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, 1 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 lesions⁴), 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 have advanced AMD.

There is strong biologic plausibility for an association of DHA and EPA intake with AMD, and multiple mechanisms have been described.⁶¹ Docosahexaenoic acid 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 ω -linolenic acid and LA to longer-chain DHA, EPA, and AA⁶⁴ 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- to 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

Table 4. 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	RR (95% CI)	
			Model 1 ^a	Model 2 ^b
Total fish				
• 1 mo	2970	28	1 [Reference]	1 [Reference]
1-3 mo	10 793	83	0.90 (0.59-1.38)	0.88 (0.57-1.35)
• 1 wk	24 218	124	0.61 (0.40-0.92)	0.58 (0.38-0.87)
P value for trend			.002	.001
Dark-meat fish				
• 1 mo	25 230	170	1 [Reference]	1 [Reference]
1-3 mo	9398	50	0.73 (0.53-0.99)	0.76 (0.55-1.05)
• 1 wk	3163	13	0.52 (0.30-0.92)	0.56 (0.32-0.99)
P value for trend			.004	.01
Canned tuna fish				
• 1 mo	8340	73	1 [Reference]	1 [Reference]
1-3 mo	15 775	97	0.78 (0.58-1.06)	0.76 (0.56-1.03)
• 1 wk	13 570	61	0.60 (0.43-0.84)	0.56 (0.40-0.80)
P value for trend			.003	.001
Shrimp/lobster/scallops				
• 1 mo	22 005	144	1 [Reference]	1 [Reference]
1-3 mo	13 251	72	0.98 (0.74-1.30)	0.94 (0.70-1.27)
• 1 wk	2587	17	1.26 (0.76-2.08)	1.28 (0.77-2.13)
P value for trend			.62	.69
Other fish (not canned tuna/dark meat)				
• 1 mo	12 064	88	1 [Reference]	1 [Reference]
1-3 mo	15 551	89	0.86 (0.64-1.15)	0.85 (0.63-1.14)
• 1 wk	10 102	56	0.72 (0.52-1.01)	0.72 (0.51-1.01)
P value for trend			.05	.06

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; mo, months; HT, hormone therapy; RR, relative risk.

SI conversion factor: To convert total cholesterol to millimoles per liter, multiply by 0.0259.

^aAdjusted for age and randomized treatment assignment.

^bAdjusted for age, randomized treatment assignment, smoking (current, past, never), alcohol use (rarely/never, 1-3 drinks/mo, 1-6 drinks/wk, and • 1 drinks/d), 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 mm Hg, diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension or current treatment; yes or no), history of high cholesterol (self-reported total cholesterol level 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), and history of eye examination in the last 2 years (yes or no).

with similar findings for advanced AMD in prior studies^{47,51,69} and supports the conclusion that both the level of • -3 fatty acids and its ratio to • -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 • -6 fatty acid intake, although tests of interaction were not significant. This finding appears consistent with subgroup findings for LA intake in the Age-Related Eye Disease Study population⁵¹ but seems to conflict with 2 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 has 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 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 end point, 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 method of disease ascertainment. Our study end point 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 examination 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 examination in the past 2 years in multivariate analyses. Finally, this method 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 method.

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 have advanced AMD, and need to be confirmed in randomized trials.

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