Dietary Fatty Acids and the 10-Year Incidence of Age-Related Macular Degeneration

The Blue Mountains Eye Study

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Objective: To assess the relationship between baseline dietary fatty acids and 10-year incident age-related macular degeneration (AMD).

Methods: In an elderly Australian cohort, 3654 participants were examined at baseline and 2454 were examined 5 and/or 10 years later. We assessed AMD from retinal photographs. Participants completed a semiquantitative food frequency questionnaire.

Results: After adjusting for age, sex, and smoking, 1 serving of fish per week was associated with reduced risk of incident early AMD (relative risk, 0.69 [95% confidence interval, 0.49-0.98]), primarily among participants with less than the median linoleic acid consumption (0.57 [0.36-0.89]). Findings were similar for intake of long-chain ω-3 polyunsaturated fatty acids. One to 2 servings of nuts per week was associated with reduced risk of incident early AMD (relative risk, 0.65 [95% confidence interval, 0.47-0.91]). Protective associations between the intake of nuts and reduced risk of pigmentary abnormalities were seen among nonsmokers, participants with less than the median ratio of serum total to high-density lipoprotein cholesterol, and those with beta carotene intake greater than the median level.

Conclusions: This study provides evidence of protection against early AMD from regularly eating fish, greater consumption of ω-3 polyunsaturated fatty acids, and low intakes of foods rich in linoleic acid. Regular consumption of nuts may also reduce AMD risk. Joint effects from multiple factors are suggested.

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THE POTENTIAL INFLUENCE OF diet on the risk or the progression of age-related macular degeneration (AMD), a major cause of blindness,[1] has gained increasing interest. Management of AMD has been influenced by evidence from the Age-Related Eye Disease Study (AREDS) that a high-dose supplement of zinc and antioxidant vitamins (ascorbic acid [vitamin C], vitamin E, and beta carotene) slowed AMD progression by about 25% in relatively advanced early AMD.[2] A new AREDS trial is assessing an alternative supplement that includes long-chain ω-3 polyunsaturated fatty acids (PUFAs) and replaces beta carotene with lutein.[3]

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The role of dietary fatty acids in AMD was initially examined because of the hypothesis that AMD and cardiovascular disease may share a similar pathogenesis,[4] and fat intake has been associated with atherosclerosis and cardiovascular disease.[5] There is increasing evidence of a benefit from regular dietary fish and ω-3 PUFA intake on the risk of AMD,[6-10] particularly in people with a lower ratio of ω-6 to ω-3 PUFAs.[6,8,10] However, evidence of the association between AMD and total fat or other fat types, such as saturated and monounsaturated fatty acids, is inconsistent.[6-13]

Our group previously reported the association between dietary fatty acids and AMD observed in the Blue Mountains Eye Study cohort at baseline[11] and after the 5-year follow-up.[9] In those reports, regular consumption of fish was associated with a reduced risk of late[9,11] and early[9] AMD. In light of the continued and increasing interest in the link between dietary fatty acids (particularly fish and long-chain ω-3 PUFAs) and AMD, we aimed to examine the association between the consumption of dietary fats (total fat, PUFAs, and saturated, monounsaturated, and *trans*-unsaturated fatty acids), specific PUFA components and foods contributing to fat

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intake, and 10-year incident AMD in the same cohort. We also explored the possible effects of the ω-6 to ω-3 PUFA ratio[14] and the joint effect of dietary fats with other modifiable AMD-related factors, such as smoking and antioxidant intake.

METHODS

STUDY SUBJECTS

The Blue Mountains Eye Study is a population-based cohort study of vision, common eye diseases, and other health outcomes in an urban, predominantly white, Australian population west of Sydney. Study methods and procedures have been reported elsewhere.[15] Baseline (1992-1994) eye examinations of 3654 residents 49 years or older were conducted (82.4% participation). Of the baseline participants, 2335 (75.1% of survivors) returned for the 5-year follow-up examinations (1997-1999), and 1952 participants (53.4% of the original cohort, or 76.6% of survivors) returned for the 10-year follow-up examinations (2002-2004). At the baseline and 5- and 10-year examinations, photographs of both eyes were obtained in 97.5%, 97.6%, and 84.5% of participants, respectively, and photographs of at least 1 eye were obtained in 98.0%, 98.8%, and 86.5% of participants, respectively. Of those seen at the 5- or 10-year follow-up examination, 2454 (67.2% of the original cohort) had stereoscopic retinal photographs taken to assess the 10-year incidence of AMD.[16] This study followed the recommendations of the Declaration of Helsinki and was approved by the Western Sydney Area Human Research Ethics Committee. Written, informed consent was obtained from all participants.

DIETARY ASSESSMENT

Participants completed a 145-item, semiquantitative food frequency questionnaire (FFQ) modified from an early FFQ by Willett et al[17] for Australian diet and vernacular. Dietary data collected included portion sizes, frequency estimates, and details about margarines, butters, oils, and supplements to permit more detailed analysis of fatty acid intake. The FFQ was attempted and returned by 3267 participants at baseline (89.4%), with 2900 (88.8% of those who attempted the FFQ and 79.4% of those who attended the examination) usable FFQs after excluding those considered unreliable. Characteristics of the FFQ respondents and exclusion criteria have been reported.[18,19] Briefly, subjects were excluded if more than 12 FFQ questions or an entire page remained blank, or if daily energy intakes were less than 597 kilocalories (2500 kJ) or greater than 4300 kilocalories (18 000 kJ). The FFQ was found to be reliable in the population and to have reasonable concurrent validity compared with weighed food records collected for 1 year (total fat, $r=0.68$; saturated fatty acids, $r=0.67$; monounsaturated fatty acids, $r=0.54$; and PUFAs, $r=0.44$).[19] The electronic version of the Australian Tables of Food Composition 1990[20] was used to calculate the intake of most nutrients, with additional fatty acid composition of foods obtained from the Royal Melbourne Institute of Technology database.[21]

The intake of long-chain ω-3 PUFAs was calculated by adding dietary consumption of eicosapentaenoic (20:5, n-3), docosapentaenoic (22:5, n-3), and docosahexaenoic (22:6, n-3) fatty acids. The total ω-3 PUFA consumption was calculated by adding the intakes of long-chain ω-3 PUFAs and linolenic acid. The total ω-6 PUFA consumption was calculated by adding the intakes of linoleic and arachidonic acid. Comparisons of fatty acid intake in our cohort with those of other population dietary studies has been reported previously.[22]

AMD GRADING AND DEFINITION

At each examination, participants underwent a comprehensive eye examination after pupil dilation, and 30° stereoscopic retinal photographs were taken using a fundus camera (Zeiss FF3; Carl Zeiss, Oberkochen, Germany). Details of the photographic grading for AMD lesions performed in the Blue Mountains Eye Study were reported[15] and closely followed the Wisconsin Age-Related Maculopathy Grading System.[23] When any lesions were identified at follow-up, we performed side-by-side grading of the baseline and follow-up photographs. Assessments of intergrader and intragrader reliability showed good agreement for identifying AMD lesions.[15] Graders were unaware of the study question and were masked to the nutritional status of each participant.

Late AMD was defined to include neovascular AMD and geographic atrophy, as described in the international classification.[15,23] All detected late AMD cases were adjudicated and confirmed by a retinal specialist (P.M.). Incident late AMD was defined by the appearance at follow-up of neovascular AMD or geographic atrophy in either eye of persons without late AMD lesions in either eye at baseline. Incident neovascular AMD was defined after excluding baseline neovascular AMD cases. Cases with baseline geographic atrophy were not excluded, however, because we considered that neovascular AMD could still develop in eyes with geographic atrophy. Persons with both geographic atrophy and neovascular AMD at baseline or follow-up were not considered to have incident geographic atrophy.

Early AMD was defined as the presence at the macula[23] of large (diameter, >125 μm) indistinct soft or reticular drusen or combined large distinct soft drusen and retinal pigmentary abnormalities,[23] without late AMD signs. Incident early AMD was defined in persons without AMD at baseline by the appearance at follow-up of these lesions in either eye of persons without late AMD at follow-up. Incidence of the principal early AMD lesions, soft indistinct or reticular drusen, or retinal pigmentary abnormalities was defined by the appearance of these lesions at follow-up in either eye of persons without late or early AMD at baseline or follow-up and without corresponding lesions in either eye at baseline.

ASSESSMENT OF CONFOUNDERS

Information on potential confounders was collected at baseline. A standardized interviewer-administered questionnaire was used to ascertain demographic information, family history, medications taken, medical history (including self-reported diagnoses of diabetes mellitus, hypertension, acute myocardial infarction, angina, or stroke), and history of smoking and alcohol consumption. History of cardiovascular disease (ie, stroke, angina, and myocardial infarction) was combined as any cardiovascular disease. Weight, height, and blood pressure were measured by trained examiners. Hypertension was defined as use of antihypertensive medications, a systolic blood pressure of at least 160 mm Hg, or a diastolic blood pressure of at least 100 mm Hg at baseline (equivalent to hypertension grade 2 as per the World Health Organization definition[24]). Body mass index was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as a body mass index of at least 30. Fasting blood specimens were drawn for clinical biochemistry assessment. Diabetes was diagnosed from the medical history or from a fasting blood glucose level of at least 126 mg/dL (to convert to millimoles per liter, multiply by 0.05556). Total intake (from diet and supplements) of the micronutrients beta carotene, retinol equivalents, zinc, and vitamins C and E was calculated by adding the energy-adjusted dietary intake and intake from supplements. Micronutrient intake obtained from supplements was not energy adjusted.

STATISTICAL ANALYSES

We used commercially available software (SAS, version 9; SAS Institute Inc, Cary, North Carolina) for all analyses. We examined the association of baseline dietary fatty acid intake, the 10-year incidence of early or late AMD, and each specific lesion. The study factors included dietary intakes of total fat, PUFAs, and saturated, monounsaturated, and *trans*-unsaturated fatty acids. Intakes of the PUFA components of α-linolenic acid, linoleic acid, arachidonic acid, and total ω-3, long-chain ω-3, and total ω-6 PUFAs were analyzed separately. Specific foods that significantly contributed to fat intake, including fish, nuts, margarine, and butter[22] were also analyzed. Analyses of fish consumption and the risk of long-term incident late AMD have been reported separately[25] and will not be repeated herein. Dietary fatty acid intakes were energy adjusted using the residual method described by Willett and Stampfer.[26]

Relative risks (RRs) and 95% confidence intervals (CIs) were calculated using discrete linear logistic models initially adjusted for age, sex, and smoking (current vs never/past). Final multivariate models were also adjusted for other factors, including history of any cardiovascular disease and the combination of antioxidants evaluated in the AREDS (zinc, beta carotene, and vitamins C and E).[2] Fatty acid intakes were analyzed as quartiles. The lowest quartile was the reference group. Specific foods were analyzed by categorizing participants according to the frequency of consumption of standard serving sizes (fish, 145 g; nuts, 20 g; butter, 7 g; and margarine, 5 g). Those in the lowest category of consumption were the reference group. The servings for each category were less than 1, 1, and at least 2 per week for fish; less than 1, 1 to 2, and at least 3 per week for nuts; and less than 1, 1 to 6, and daily for butter and margarine. We calculated the trend in RR by modeling a variable corresponding to the median value for each group. Additional analyses of long-chain ω-3 PUFA intakes and fish consumption, stratified by linoleic acid intake (above or below the median linoleic acid intake of 6.9 g), were also performed because of the possible interrelationships between ω-3 and ω-6 PUFAs[6] and a possible joint effect of these fatty acids on AMD risk as reported in other studies.[6,8,10] Linoleic acid is the main contributor to ω-6 PUFA intake in our cohort.[22]

For the study factors with a significant major effect, we further examined the effect modification from modifiable cardiovascular and AMD risk factors, including smoking, diabetes mellitus, hypertension, obesity, the ratio of total to high-density lipoprotein cholesterol (HDL-C) levels, low-density lipoprotein cholesterol level, triglycerides level, statin use, and dietary intakes of zinc, beta carotene, vitamins C and E, lutein, and zeaxanthin. The joint effect of smoking and low fish consumption has been reported separately.[25] We also examined effect modification from high- and low-intake antioxidant groups that were created using the same methods described by van Leeuwen et al,[27] in which the median intake of total beta carotene, zinc, and vitamins C and E, based on the total sample, was used as the cutoff value. The high-intake group was defined as participants with an above-median intake of each of the 4 nutrients, whereas the low-intake group had a below-median intake of each nutrient. Participants with intakes between these values were considered the reference group. Interaction was assessed by including product terms in the multivariate models.

RESULTS

The mean follow-up intervals were 5.1 and 10.5 years for the 5- and 10-year examinations, respectively. Of the 2454 participants who were followed up and had retinal photographs for AMD assessment, 2083 had completed an FFQ at baseline. Compared with participants who were followed up and had baseline FFQ data (n=2083), those alive but lost to or unavailable for follow-up or with missing FFQ data (n=800) were significantly more likely to have been current smokers (16.9% vs 12.5%) and to have had diabetes mellitus (8.6% vs 6.1%). For those with baseline FFQ data, the mean intake of the fatty acids or specific foods examined in this study was not significantly different between those who were and were not followed up (data not shown). Those who died were more likely to have a reduced daily intake of PUFAs (12.2 vs 12.8 g), total ω-3 (0.90 vs 0.94 g) and total ω-6 (7.2 vs 7.7 g) PUFAs, linolenic acid (0.67 vs 0.70 g), and nuts (6.1 vs 7.4 g).

Total fat intake varied at baseline in the study population from an average of 58 and 93 g in the lowest and highest quartiles, respectively (**Table 1** and **Table 2**). Participants with the highest compared with the lowest quartiles of total fat intake generally consumed more protein and less alcohol, carbohydrates, lutein, zeaxanthin, beta carotene, and vitamins C and E. They were also younger and more likely to be obese and to have been smokers, but less likely to have a history of cardiovascular disease.

ASSOCIATIONS WITH THE MAIN FAT TYPES

In analyses of the main dietary fat types, only those in the second compared with the lowest quartile of total fat intake had a significantly increased risk of developing neovascular AMD (RR, 3.82 [95% CI, 1.41-10.35]) (*P* value for trend, .98). No other significant associations were found between the intake of total fat, PUFAs, or saturated, monounsaturated, or *trans*-unsaturated fatty acids and early or late AMD (**Table 3**) or any specific AMD subtype (data not shown).

ASSOCIATIONS WITH ω-3 PUFAs

When different components of dietary PUFA were analyzed separately, increasing intake of total ω-3 PUFAs was associated with a borderline reduced risk of early AMD (Table 3). A similar association was found between increasing total ω-3 PUFA intake and indistinct soft or reticular drusen (quartiles 4 vs 1 RR, 0.64 [95% CI, 0.41-0.99]) (*P* value for trend, .08). No other significant associations were found between the intake of other PUFAs and early or late AMD (Table 3).

However, increasing intakes of long-chain ω-3 PUFAs among participants with less than the median of linoleic acid intake was associated with a significantly reduced risk of incident early AMD or indistinct soft or reticular drusen (**Table 4**). In addition, a protective association was seen for pigmentary abnormalities for quartiles 2 and 3 compared with quartile 1 among participants with less than the median intake of linoleic acid. However, there was no significant association for quartile 4, and the trend across quartiles was also not significant. Conversely, among subjects with a greater than median level of linoleic acid intake, no association was found between intake of long-chain ω-3 PUFAs and incident early AMD. The interaction terms between linoleic acid and long-chain ω-3 PUFA intakes were not significant (data not shown).

Table 1. Baseline Characteristics According to Intake of Specific Types of Fat in the BMES

	Quartile Group[a]															
	Total Fat				Saturated Fatty Acids				Monounsaturated Fatty Acids				PUFAs			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Quartile score[b]	58	72	80	93	20.1	27.1	31.7	39.9	20.1	25.4	28.5	33.7	7.7	11.0	13.7	18.2
Mean age, y	64.7	64.3	64.1	63.0	64.5	64.3	63.4	63.8	65.0	63.8	64.0	63.2[c]	64.7	63.5	63.9	64.0
Women, %	51.9	59.1	57.0	59.3	52.3	60.5	59.1	55.5[c]	54.0	58.4	57.4	57.6	50.0	59.7	58.7	58.9[c]
Daily dietary intake[d]																
Total energy, kcal	2122	1993	1931	2122	2187	1934	1898	2151	2131	1988	1949	2100	2149	1890	2027	2102
Beta carotene, µg	8944	7793	6876	6416	8991	7722	7009	6308[c]	8856	7758	6828	6588[c]	7440	7880	7482	7224
Vitamin C, mg	409	377	312	279	419	380	304	275[c]	408	379	304	287[c]	337	363	345	333
Vitamin E, mg	51	41	32	34	52	40	34	33[c]	47	46	35	31[c]	40	45	35	39
Zinc, mg	12.9	13.2	12.6	13.7	13.2	12.7	12.8	13.6	12.8	13.0	13.1	13.5	12.9	13.3	13.4	12.8
Lutein and zeaxanthin, µg	942	842	779	747	968	836	792	714[c]	936	824	786	765[c]	834	835	845	797
Vegetables, g	499	445	412	419[c]	512	442	414	406[c]	501	434	414	425[c]	457	426	437	453
Fruit, g	502	367	290	252[c]	510	334	307	259[c]	501	359	291	259[c]	399	339	363	307[c]
Alcohol, g	14.7	11.6	8.7	7.2	14.0	11.9	8.5	7.8[c]	12.5	11.2	10.2	8.4[c]	14.2	10.4	8.8	8.8[c]
Protein, g	88	88	89	91	89	89	89	90	88	87	89	92[c]	89	89	91	88
Carbohydrate, g	269	244	230	205	265	240	232	211[c]	273	244	228	203[c]	245	240	238	225[c]
Current smoker, %	9.3	12.4	9.8	18.4	8.5	11.6	12.1	17.9[c]	9.8	10.1	12.2	17.8[c]	14.7	14.6	9.4	11.1[c]
History of CVD, %	22.1	17.8	14.4	9.8	22.1	16.9	14.0	11.1[c]	21.7	16.3	15.6	10.6[c]	18.5	14.6	16.5	14.6
Hypertension, %	47	42	44	38	47	46	43	36[c]	45	45	44	39	42	44	44	43
Diabetes, %	5.2	4.6	7.3	7.5	6.1	3.6	5.9	8.8[c]	5.6	4.8	5.9	8.2	5.8	5.0	5.9	7.9
Obesity, %	14.5	15.3	21.7	19.5	14.9	16.3	20.7	19.1	14.3	15.6	19.8	21.2[c]	15.5	19.6	18.7	17.2
Total cholesterol level, mg/dL	235	235	235	232	232	235	235	232	235	235	232	232	235	235	232	232

Abbreviations: BMES, Blue Mountains Eye Study; CVD, cardiovascular disease; PUFAs, polyunsaturated fatty acids.
SI conversion factors: To convert kilocalories to kilojoules, multiply by 4.186; total cholesterol to millimoles per liter, multiply by 0.259.
[a] For each quartile, n=520.
[b] Reported as mean amount in grams.
[c] $P \leq .05$ for trend. The Mantel-Haenszel χ^2 test was used to compute P values for discrete variables, and general linear models were used for continuous variables by modeling a variable corresponding to the median value for each quartile.
[d] Energy adjusted except for total energy intake and alcohol.

Table 2. Baseline Characteristics According to Intake of Specific Types of Fat and Fish in the BMES

	Quartile or Serving Group[a]														
	Trans-Unsaturated Fatty Acids				Total ω-3 PUFAs				Linoleic Acid				Fish Intake, Servings/wk		
	1	2	3	4	1	2	3	4	1	2	3	4	<1	1	≥2
Quartile score[b]	0.0	0.1	0.2	0.8	0.52	0.77	0.97	1.48	4.1	6.2	7.9	12.4	0.2	1.0	2.6
Mean age, y	65.1	63.6	63.5	63.9	65.0	63.7	63.6	63.7[c]	65.3	64.1	63.5	63.2[c]	64.6	63.6	64.2
Women, %	46.1	65.3	62.6	53.4[c]	51.5	58.5	60.5	56.8[c]	46.0	60.8	63.1	57.4[c]	58.1	56.7	56.0
Daily dietary intake[d]															
Total energy, kcal	2495	1773	1735	2166	2234	1918	1893	2123	2285	1892	1853	2139	1862	2016	2237[c]
Beta carotene, µg	7654	7752	7448	7172[c]	7776	7337	7800	7113	7445	7332	7514	7735	7183	7325	8074[c]
Vitamin C, mg	323	369	378	308	331	323	374	350	311	332	373	361[c]	300	329	407[c]
Vitamin E, mg	34	35	58	32	34	36	42	48[c]	30	34	46	49[c]	36	42	39
Zinc, mg	13.1	13.1	13.4	12.7	12.6	13.1	13.1	13.5	12.5	12.8	13.4	13.6[c]	13.3	12.9	13.2
Lutein and zeaxanthin, µg	836	866	826	783[c]	813	836	839	822	824	810	836	840	735	809	936[c]
Vegetables, g	519	417	397	441[c]	478	427	430	438[c]	469	418	427	459	399	433	498[c]
Fruit, g	422	348	310	329[c]	416	320	329	344[c]	398	333	329	350[c]	295	342	417[c]
Alcohol, g	12.6	7.2	10.0	12.4	11.5	10.7	9.9	10.1	13.8	9.8	8.0	10.6[c]	8.8	11.2	11.0
Protein, g	91	93	88	85[c]	86	90	89	92[c]	89	90	90	87	85	88	94[c]
Carbohydrate, g	245	241	235	227[c]	253	237	233	224[c]	245	240	235	227[c]	241	235	236
Current smoker, %	10.6	9.0	15.1	15.3[c]	11.7	14.0	12.6	11.7	12.7	13.3	11.3	12.6	16.7	12.8	8.4[c]
History of CVD, %	18.3	17.7	15.2	13.0	19.0	16.0	14.0	15.0	19.6	17.7	14.2	12.7[c]	15.7	15.5	17.3
Hypertension, %	46	45	43	39	45	44	44	40	47	41	42	40	43	41	44
Diabetes, %	6.3	5.9	6.1	6.1	5.2	6.7	6.7	5.9	5.2	6.9	5.8	6.7	6.8	6.5	5
Obesity, %	17.5	20.2	18.3	15.0	15.9	21.3	16.5	17.2	17.6	17.6	21.8	14.1[c]	19.4	17.3	17.1
Total cholesterol, mg/dL	232	232	239	232	232	236	236	232	232	236	236	232	232	232	236

Abbreviations: BMES, Blue Mountains Eye Study; CVD, cardiovascular disease; PUFAs, polyunsaturated fatty acids.
SI conversion factors: To convert kilocalories to kilojoules, multiply by 4.186; total cholesterol to millimoles per liter, multiply by 0.259.
[a] For each quartile, n=520. Fish intake groups had the following sample sizes: 511 for less than 1 serving/wk; 970 for 1 serving/wk; and 602 for at least 2 servings/wk.
[b] Reported as mean servings in grams except for fish, which is expressed in number of servings per week (1 serving=145 g).
[c] $P \leq .05$ for trend. The Mantel-Haenszel χ^2 test was used to compute P values for discrete variables, and general linear models were used for continuous variables by modeling a variable corresponding to the median value for each quartile.
[d] Energy adjusted except for total energy intake and alcohol.

Table 3. Associations Between Baseline Dietary Intake of Fatty Acids and 10-Year Incident Early and Late AMD in the BMES

	Early AMD		Late AMD	
Nutrient, Quartiles	No. of Cases/ No. at Risk	Adjusted RR (95% CI)[a]	No. of Cases/ No. at Risk	Adjusted RR (95% CI)[a]
Total fat				
1	59/483	1 [Reference]	15/510	1 [Reference]
2	57/479	0.95 (0.64-1.40)	21/508	1.56 (0.77-1.46)
3	51/478	0.84 (0.56-1.25)	10/506	0.62 (0.26-1.46)
4	53/485	0.86 (0.58-1.29)	13/511	0.83 (0.37-1.87)
P value for trend		.39		.29
Saturated fatty acids				
1	58/480	1 [Reference]	19/512	1 [Reference]
2	62/486	1.01 (0.69-1.48)	12/508	0.60 (0.28-1.29)
3	47/476	0.82 (0.54-1.23)	16/507	0.80 (0.38-1.66)
4	53/483	0.86 (0.57-1.28)	12/508	0.60 (0.28-1.29)
P value for trend		.32		.27
Monounsaturated fatty acids				
1	65/481	1 [Reference]	18/510	1 [Reference]
2	49/486	0.72 (0.48-1.07)	13/509	0.80 (0.38-1.71)
3	53/473	0.80 (0.54-1.18)	18/506	0.97 (0.48-1.96)
4	53/485	0.77 (0.52-1.14)	10/510	0.53 (0.23-1.23)
P value for trend		.22		.21
PUFAs				
1	61/476	1 [Reference]	18/506	1 [Reference]
2	50/476	0.82 (0.55-1.23)	16/506	1.16 (0.56-2.38)
3	51/488	0.76 (0.51-1.13)	11/510	0.62 (0.27-1.39)
4	58/485	0.89 (0.60-1.31)	14/513	0.84 (0.39-1.79)
P value for trend		.53		.39
Trans-unsaturated fatty acids				
1	59/481	1 [Reference]	13/507	1 [Reference]
2	53/486	0.92 (0.61-1.37)	14/513	1.33 (0.59-2.98)
3	62/478	1.13 (0.77-1.66)	18/506	1.35 (0.62-2.94)
4	46/480	0.78 (0.51-1.17)	14/509	0.96 (0.42-2.20)
P value for trend		.23		.64
Total ω-3 PUFAs				
1	68/484	1 [Reference]	15/511	1 [Reference]
2	51/479	0.78 (0.53-1.15)	19/511	1.20 (0.59-2.47)
3	57/478	0.85 (0.58-1.24)	16/506	1.01 (0.48-2.14)
4	44/484	0.63 (0.42-0.95)	9/507	0.54 (0.22-1.31)
P value for trend		.04		.14
Long-chain ω-3 PUFAs				
1	57/483	1 [Reference]	13/512	1 [Reference]
2	62/486	0.99 (0.67-1.46)	23/515	1.83 (0.88-3.80)
3	52/477	0.80 (0.53-1.20)	13/500	0.96 (0.42-2.19)
4	49/479	0.76 (0.50-1.14)	10/508	0.61 (0.25-1.50)
P value for trend		.12		.06
α-Linolenic acid				
1	62/478	1 [Reference]	14/509	1 [Reference]
2	58/480	1.01 (0.69-1.49)	21/511	1.76 (0.85-3.67)
3	53/476	0.84 (0.57-1.25)	17/503	1.47 (0.69-3.12)
4	47/491	0.80 (0.53-1.20)	7/512	0.54 (0.20-1.46)
P value for trend		.21		.15
Total ω-6 PUFAs				
1	51/476	1 [Reference]	15/506	1 [Reference]
2	69/479	1.35 (0.91-1.99)	22/511	1.57 (0.77-3.19)
3	53/487	1.04 (0.68-1.57)	13/509	1.00 (0.45-2.25)
4	47/483	0.94 (0.61-1.43)	9/509	0.63 (0.26-1.55)
P value for trend		.40		.16
Linoleic acid				
1	51/476	1 [Reference]	15/506	1 [Reference]
2	69/478	1.35 (0.91-1.99)	23/511	1.56 (0.77-3.18)
3	53/488	1.03 (0.68-1.56)	12/509	1.00 (0.44-2.24)
4	47/483	0.94 (0.61-1.43)	9/509	0.63 (0.26-1.55)
P value for trend		.40		.16
Arachidonic acid				
1	61/487	1 [Reference]	12/512	1 [Reference]
2	59/487	0.93 (0.63-1.36)	17/514	1.38 (0.64-2.99)
3	44/479	0.70 (0.46-1.06)	14/505	1.06 (0.46-2.44)
4	56/472	0.90 (0.61-1.32)	16/504	1.25 (0.56-2.76)
P value for trend		.49		.75

Abbreviations: AMD, age-related macular degeneration; BMES, Blue Mountains Eye Study; CI, confidence interval; PUFAs, polyunsaturated fatty acids; RR, relative risk.

[a] Adjusted for age, sex, and smoking.

Table 4. Associations Between Baseline Dietary Intake of Long-Chain ω-3 PUFAs and 10-Year Incident Early AMD Within Strata of Linoleic Acid Intake in the BMES

Nutrient, Quartiles	Early AMD		Indistinct or Soft Drusen		Pigmentary Abnormality	
	No. of Cases/ No. at Risk	Adjusted RR (95% CI)[a]	No. of Cases/ No. at Risk	Adjusted RR (95% CI)[a]	No. of Cases/ No. at Risk	Adjusted RR (95% CI)[a]
Long-Chain ω-3 PUFA and Linoleic Acid (Unstratified)						
Long-chain ω-3 PUFAs						
1	57/483	1 [Reference]	46/488	1 [Reference]	90/454	1 [Reference]
2	62/486	0.99 (0.67-1.46)	51/486	1.01 (0.66-1.55)	78/449	0.80 (0.57-1.11)
3	52/477	0.80 (0.53-1.20)	46/479	0.88 (0.57-1.37)	85/456	0.86 (0.62-1.20)
4	49/479	0.76 (0.50-1.14)	40/484	0.76 (0.48-1.19)	91/454	0.95 (0.69-1.32)
P value for trend		.12		.17		.86
Linoleic acid						
1	51/476	1 [Reference]	41/479	1 [Reference]	84/444	1 [Reference]
2	69/478	1.35 (0.91-1.99)	60/480	1.46 (0.95-2.24)	92/443	1.08 (0.78-1.49)
3	53/488	1.03 (0.68-1.56)	44/491	1.07 (0.68-1.68)	90/471	1.05 (0.75-1.45)
4	47/483	0.94 (0.61-1.43)	38/487	0.93 (0.58-1.49)	78/455	0.92 (0.65-1.28)
P value for trend		.40		.36		.50
Linoleic Acid, Quartiles 1 and 2						
Long-chain ω-3 PUFAs						
1	39/236	1 [Reference]	32/238	1 [Reference]	61/225	1 [Reference]
2	35/243	0.76 (0.46-1.25)	28/243	0.75 (0.43-1.31)	35/218	**0.49 (0.31-0.77)**
3	24/237	**0.50 (0.29-0.86)**	23/239	0.60 (0.34-1.07)	34/220	**0.45 (0.29-0.72)**
4	22/238	**0.48 (0.27-0.83)**	18/239	**0.48 (0.26-0.89)**	46/224	0.69 (0.45-1.05)
P value for trend		.01		.02		.40
Linoleic Acid, Quartiles 3 and 4						
Long-chain ω-3 PUFAs						
1	22/247	1 [Reference]	17/250	1 [Reference]	33/228	1 [Reference]
2	28/240	1.30 (0.71-2.37)	25/240	1.51 (0.78-2.91)	44/234	1.37 (0.84-2.23)
3	24/245	0.98 (0.52-1.82)	18/245	0.92 (0.45-1.88)	52/239	1.57 (0.98-2.52)
4	26/239	1.08 (0.59-1.97)	22/243	1.17 (0.60-2.29)	39/225	1.13 (0.68-1.88)
P value for trend		.91		.96		.90

Abbreviations: AMD, age-related macular degeneration; BMES, Blue Mountains Eye Study; CI, confidence interval; PUFAs, polyunsaturated fatty acids; RR, relative risk.
[a]Adjusted for age, sex, and smoking. Boldface type indicates significant values.

Results were similar when long-chain ω-3 PUFA consumption was stratified by total ω-6 PUFA intake rather than linoleic acid intake alone. A harmful association between increasing total ω-6 to ω-3 PUFA ratio and early AMD was also suggested (quartile 2 RR, 1.63 [95% CI, 1.07-2.50]; quartile 3, 1.71 [1.12-2.63]; and quartile 4, 1.43 [0.93-2.20] [RR for quartile 1 is the reference]), although the trend across the quartiles was not significant ($P=.18$).

ASSOCIATIONS WITH REGULAR INTAKE OF FISH IN THE DIET

One serving of fish compared with less than 1 serving per week was associated with a significantly reduced risk of early AMD and pigmentary abnormalities (**Table 5**). After stratifying participants with greater and less than the median level of linoleic acid intake, these findings only persisted among participants with lower intakes of linoleic acid. The interaction terms between linoleic acid intake and fish consumption were not significant (data not shown). Results were similar when fish consumption was stratified by total ω-6 PUFAs rather than linoleic acid intake alone.

ASSOCIATIONS WITH REGULAR CONSUMPTION OF NUTS

One or two servings of nuts compared with less than 1 serving of nuts per week was associated with a reduced risk of early AMD, indistinct soft or reticular drusen, or pigmentary abnormality (**Table 6**). Participants consuming at least 3 servings per week of nuts also had a significantly reduced risk of incident indistinct soft or reticular drusen, suggesting a possible threshold effect at 1 serving per week of nuts on the risk of these early AMD lesions. No other significant associations were found between specific food groups assessed and AMD.

Interactions between nut consumption and the serum total cholesterol to HDL-C ratio (*P* value for interaction, .01), dietary beta carotene (*P* value for interaction, .03), and smoking (*P* value for interaction, .05) were found for the risk of pigmentary abnormalities. Among participants with less than the median (4.3) total cholesterol to HDL-C ratio, those who consumed at least 3 servings of nuts per week had a significantly reduced risk of incident pigmentary abnormalities (RR, 0.55 [95% CI, 0.35-0.87]) (*P* value for trend, .03) compared with those who consumed less

Table 5. Associations Between Baseline Dietary Intake of Fish and 10-Year Incident Early AMD Within Strata of Linoleic Acid Intake in the BMES

	Early AMD		Pigmentary Abnormality	
	No. of Cases/ No. at Risk	Adjusted RR (95% CI)[a]	No. of Cases/ No. at Risk	Adjusted RR (95% CI)[a]
Total Fish (Servings/wk) (Unstratified)				
Fish servings/wk[b]				
<1	66/460	1 [Reference]	98/438	1 [Reference]
1	94/907	**0.69 (0.49-0.98)**	151/850	**0.71 (0.53-0.94)**
≥2	60/558	0.71 (0.49-1.03)	95/525	0.75 (0.55-1.03)
P value for trend		.20		.24
Linoleic Acid Intake, Quartiles 1 and 2				
Fish servings/wk				
<1	45/251	1 [Reference]	56/236	1 [Reference]
1	47/444	**0.57 (0.36-0.89)**	74/411	**0.64 (0.43-0.94)**
≥2	28/259	0.59 (0.36-0.99)	46/240	0.77 (0.50-1.18)
P value for trend		.12		.55
Linoleic Acid Intake, Quartiles 3 and 4				
Fish servings/wk				
<1	21/209	1 [Reference]	42/202	1 [Reference]
1	47/463	0.95 (0.55-1.65)	77/439	0.80 (0.53-1.21)
≥2	32/299	0.94 (0.52-1.69)	49/285	0.75 (0.47-1.18)
P value for trend		.89		.33

Abbreviations: AMD, age-related macular degeneration; BMES, Blue Mountains Eye Study; CI, confidence interval; RR, relative risk.
[a] Adjusted for age, sex, and smoking. Boldface type indicates significant values.
[b] Median number of servings per week for each category was 0.2 serving/wk for less than 1; 1 serving/wk for 1; and 2.6 servings/wk for at least 2 (1 serving=145 g).

Table 6. Associations Between Baseline Dietary Intake of Nuts and 10-Year Incident Early AMD in the BMES

AMD Stage/Lesion	Servings per Week[a]	No. of Outcomes/ No. at Risk	Adjusted RR (95% CI)[b]
Early AMD	<1	85/517	1 [Reference]
	1-2	76/818	**0.65 (0.47-0.91)**
	≥3	59/590	0.73 (0.51-1.06)
P value for trend			.43
Indistinct soft or reticular drusen	<1	76/521	1 [Reference]
	1-2	61/821	**0.61 (0.42-0.87)**
	≥3	46/595	**0.66 (0.44-0.98)**
P value for trend			.23
Pigmentary abnormality	<1	114/483	1 [Reference]
	1-2	135/772	**0.74 (0.56-0.98)**
	≥3	95/558	0.75 (0.56-1.02)
P value for trend			.28

Abbreviations: AMD, age-related macular degeneration; BMES, Blue Mountains Eye Study; CI, confidence interval; RR, relative risk.
[a] Median number of servings per week for each category was 0.14 serving/wk for less than 1; 1 serving/wk for 1 to 2; and 5 servings/wk for at least 3.
[b] Adjusted for age, sex, and smoking. Boldface type indicates significant values.

than 1 serving of nuts per week. However, among participants with greater than the median total cholesterol to HDL-C ratio, no significant association was found between nuts in the diet and incident pigmentary abnormalities (RR, 1.08 [95% CI, 0.71-1.66]) (*P* value for trend, .32). Among participants with greater than the median intake (6836 µg) of beta carotene, those consuming at least 3 servings of nuts per week had a significantly reduced risk of incident pigmentary abnormalities (RR, 0.62 [95% CI, 0.40-0.96]) (*P* value for trend, .07) compared with those who consumed less than 1 serving per week. However, among participants with less than the median intakes of beta carotene, no significant association was found (RR, 0.90 [95% CI, 0.58-1.38]) (*P* value for trend, .77). Similarly, a reduced risk of incident pigmentary abnormalities was associated with 1 to 2 servings of nuts per week (RR, 0.73 [95% CI, 0.54-0.98]) or at least 3 servings of nuts per week (0.72 [0.52-0.99]) among nonsmokers but not smokers (1-2 servings/wk, 0.80 [0.34-1.88]; ≥3 servings/wk, 0.91 [0.38-2.20]).

There were no other significant interactions between any of the fatty acids found to be significantly associated with AMD and smoking, diabetes mellitus, hypertension, obesity, low-density lipoprotein cholesterol level, triglyceride level, statin use, and dietary antioxidant in-

take. All results were similar after further adjustment for cardiovascular disease and antioxidant intake. Results were also similar after further adjusting for intake of lutein and zeaxanthin or after substituting lutein and zeaxanthin for beta carotene in the multivariate models.

COMMENT

In this population-based longitudinal study, a weekly serving of fish was associated with a reduced risk of incident early AMD. This was primarily among participants with low linoleic acid intakes. Findings were similar between increasing intakes of long-chain ω-3 PUFA and incident early AMD. One to 2 servings of nuts per week were found to reduce risk of early AMD, including indistinct soft or reticular drusen and pigmentary abnormalities. We found little evidence of association between intakes of total fat, PUFAs, or saturated, monounsaturated, or *trans*-unsaturated fatty acids and AMD incidence.

Our findings that regular intake of ω-3 PUFAs and fish reduce AMD risk are supported by other studies,[6-8,10,12] including previous cross-sectional[11] and 5-year incidence[9] reports from our group. Fish consumption of more than 1 serving/wk did not significantly reduce AMD risk in our cohort. This finding could suggest a threshold effect at 1 serving of fish per week, with no increased protection at increased levels of intake. However, our findings may also result from small numbers or chance; thus, replication of our findings in other studies will be important.

These protective associations were mainly evident in those with a reduced ω-6 to ω-3 PUFA ratio. These results, however, should be interpreted with caution because we could not confirm the interaction statistically. Nevertheless, our findings are consistent with those of other studies[6,8,10] and are further supported by our finding that increasing the total ω-6 to ω-3 PUFA ratio increased the risk of early AMD. Higher ω-6 to ω-3 PUFA ratios in some developed countries[14] are driven by processed foods containing vegetable oils, which have been suggested to increase AMD risk in some studies.[8,10] In addition, diets with higher ω-6 to ω-3 PUFA ratios produce larger quantities of metabolic products that contribute to inflammation,[14] which has been implicated in AMD pathogenesis.[1] A higher ω-6 to ω-3 PUFA ratio has also been suggested to increase the risk of other diseases, including cardiovascular disease,[14] which has also been linked to AMD.[4]

A protective effect of increased consumption of ω-3 PUFAs or fish, the main source of long-chain ω-3 PUFAs in our cohort,[22] against AMD is biologically plausible. There may be an antiatherosclerotic effect of ω-3 PUFAs.[28] Fish oil may contribute to a number of antiangiogenic mechanisms in the retina.[29] Inflammation and oxidative stress have also been implicated in AMD pathogenesis.[1,27] Studies have shown that ω-3 PUFAs may protect against retinal inflammation, oxidation, and degeneration.[29] Given this newly emerging evidence, the AREDS extension trial[3] testing the role of ω-3 PUFA supplementation on AMD progression is pivotal.

Our finding that regular consumption of nuts significantly reduced early AMD risk was not shown at the 5-year follow-up.[9] Only a few studies have examined the influence of eating nuts on AMD.[8-10] A case-control study found no association between eating nuts and neovascular AMD.[10] A prospective cohort study found that nuts appeared to reduce the risk of progression from nonexudative AMD to neovascular AMD or geographic atrophy.[8] Although nuts are a major contributor to ω-6 PUFA levels in our cohort,[22] a beneficial effect of eating nuts on AMD risk is supported by studies showing that nuts may reduce the risk of cardiovascular disease and type 2 diabetes mellitus,[8] diseases linked to AMD.[4] In addition, nuts have been shown to have antioxidant and anti-inflammatory properties.[30] Given the inconsistency of results across these few studies, further longitudinal studies are needed to clarify the association between nuts and AMD.

Our findings also suggest that smoking, dietary beta carotene intake, or the serum total cholesterol to HDL-C ratio together with nut consumption may influence the risk of incident pigmentary abnormalities. Few studies have examined the interplay between dietary fat intake and other AMD risk factors. The Third National Health and Nutrition Examination Survey[13] categorized participants into high and low antioxidant status based on serum levels of beta carotene and vitamins E and C. No significant association was found between total fat or saturated fatty acid intake and AMD, and antioxidant status was not found to be an effect modifier. The AREDS[7] observed that increasing ω-3 long-chain PUFA and fish consumption reduced neovascular AMD risk without effect modification by other risk factors such as age, smoking, and education level. Our findings should therefore be interpreted with caution because chance findings cannot be excluded.

Joint effects on AMD risk between eating nuts and smoking, serum total cholesterol to HDL-C ratio, or dietary beta carotene intake are biologically plausible. Adverse effects from smoking, elevated total cholesterol to HDL-C ratio, or low beta carotene intake could have attenuated any protective effect against AMD conferred by regularly eating nuts. Smoking is an established AMD risk factor[25] and is known to accelerate atherosclerosis.[31] Cigarette smoke has also been shown to be proinflammatory,[32] to reduce plasma antioxidant levels,[33] and to increase oxidative stress.[34] Increased total cholesterol to HDL-C ratio, a consistent predictor of coronary heart disease,[35] may promote atherosclerosis.[35,36] A role for cholesterol in AMD pathogenesis and the possibility of joint effects with other AMD risk factors are also supported by animal model studies.[37,38] A high intake of beta carotene combined with zinc and vitamins C and E has been shown to slow AMD progression in relatively advanced early AMD cases[2] and to reduce late AMD incidence.[27] Reduced carotenoid levels in the serum[39] or the diet[40] and low antioxidant intake[41] have been associated with increased AMD risk. Low serum antioxidant levels have also been shown to increase endothelial damage after high-fat food.[42]

The strengths of our study include the prospective observation from a population-based sample, reasonable follow-up, and the use of criterion standard methods to assess AMD incidence, including photographic grading by the same personnel at all examinations and a detailed side-by-side comparison of the baseline and follow-up photographs to ensure negligible misclassification of in-

cident AMD. Although we had moderate losses to follow-up, the mean intake of the study factors was similar between those who were and were not followed up. Bias may be introduced if those lost to follow-up developed AMD at differential incident rates or did not return because they lost vision.

Because we have examined many associations, the possibility of chance findings cannot be excluded. Patients may also overestimate or have a greater recall of certain food groups if they have knowledge of the implications to eye disease. However, recall bias is unlikely to operate in a longitudinal study, and the dietary measurements were made before the possible health benefits of foods such as fish were common knowledge. It is possible that our results have been biased owing to selective survival. Because those who died consumed fewer PUFAs and nuts, such selective survival could have underestimated the associations observed and could explain the lack of an observed association between fatty acids and late AMD. Increasing fish consumption was associated with increasing intake of fruit and vegetables (Table 2). In addition, a high vegetable intake was associated with a significantly reduced risk of developing any AMD (early or late) and a borderline nonsignificant reduced risk of incident early AMD in the same cohort.[43] Our results could therefore reflect other aspects of healthy diets and healthy behaviors associated with frequent fish consumption, such as high fruit and vegetable intake, and should be interpreted with caution.

In conclusion, our findings support the hypothesis that increased intake of ω-3 PUFAs and regular consumption of fish and/or nuts in the diet may protect against the development of early AMD. Joint effects on AMD risk are suggested between the consumption of fish, nuts, or long-chain ω-3 PUFAs and other factors, including smoking, intake of ω-6 PUFAs or beta carotene, and the ratio of serum total cholesterol to HDL-C. These findings also suggest that an appropriate balance among various nutrients is essential for maximizing nutritional benefit. Further studies, particularly clinical trials such as the AREDS extension trial, should provide important evidence of whether dietary intervention or supplementation with long-chain ω-3 PUFAs could prevent or delay the development of this significant cause of blindness.

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From the Archives of the Archives

Dr G. T. Stevens, of New York, spoke on *A Suggestion Regarding An Element In The Ætiology Of Trachoma,* in which he supported the theory that an anomalous position of the horizontal plane of the eyes was the cause of trachoma, the eyes being elevated and the nervous force of the eyelids and eye muscles pressing the eyes downward so as to see well below the horizontal plane being the exciting cause of trachoma in which the eye affected deviated upward more than other, and consequently suffered from the trachomatous disease, and was cured by proper lenses and muscular correction. The real causation of the deviation of the horizontal plane of the eyes was the result of the malformation of the skull.

The discussion took a wide range, and, among others, Foucher, of Montreal, remarked that in Canada Indians there were very few cases of trachoma, but in Manitoba Indians it was not rare at all. He thought this might be due to excess of snow and glare on the ice and snow in the latter country.

Dr G. M. Gould was quite unable to see how eyelid-pressure could produce trachoma at all.

Dr Proudfoot remarked on the rarity of trachoma in native Indians.

Dr Lucien Howe spoke of variations in the direction of the orbital axis as a possible cause. He thought the histology of the Negro eyelid and that of the white man identical. He was quite sure that germs were the only cause of genuine trachoma. He had seen in Egypt epidemics of ophthalmia produced by flies carrying germs from diseased eyes to those that were healthy, and he had seen cultures made from the droppings of flies walking across a plate of clean glass. In Finland, smoky houses full of peat- and grass-smoke were a prevalent cause of trachomatous disease and of blindness.

Reference: *Arch Ophthalmol*. 1897;26:594.