Prospective study of dietary fat and the risk of age-related macular degeneration[1–3]

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ABSTRACT

Background: The relation between intakes of total fat and specific types of fat and age-related macular degeneration (AMD) remains unclear.

Objective: Our objective was to examine prospectively the association between fat intake and AMD.

Design: We conducted a prospective follow-up study of participants in the Nurses' Health Study and the Health Professionals Follow-up Study. At baseline (1984 for women and 1986 for men), the study included 42 743 women and 29 746 men aged ≥50 y with no diagnosis of AMD who were followed until 1996. Fat intake was assessed with a food-frequency questionnaire.

Results: We accrued 567 patients with AMD with a visual loss of 20/30 or worse. The pooled multivariate relative risk (RR) for the highest compared with the lowest quintile of total fat intake was 1.54 (95% CI: 1.17, 2.01; *P* for trend = 0.008). Linolenic acid was positively associated with risk of AMD (top versus bottom quintile of RR: 1.49; 95% CI: 1.15, 1.94; *P* for trend = 0.0009). Docosahexaenoic acid had a modest inverse relation with AMD (top versus bottom quintile of RR: 0.70; 95% CI: 0.52, 0.93; *P* for trend = 0.05), and >4 servings of fish/wk was associated with a 35% lower risk of AMD compared with ≤3 servings/mo (RR: 0.65; 95% CI: 0.46, 0.91; *P* for trend = 0.009).

Conclusions: Total fat intake was positively associated with risk of AMD, which may have been due to intakes of individual fatty acids, such as linolenic acid, rather than to total fat intakes per se. A high intake of fish may reduce the risk of AMD. *Am J Clin Nutr* 2001;73:209–18.

KEY WORDS Age-related macular degeneration, diet, fats, fatty acids, fish, food-frequency questionnaire, Health Professionals Follow-up Study, men, Nurses' Health Study, prospective studies, women

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of vision loss for which treatment options are limited. Because of the increasing size of the elderly population in the United States, the effect of this disease continues to grow. The macula is the area located at the center of the retina and is responsible for detailed, fine central vision. AMD involves degenerative changes such as drusen, changes in the retinal pigment epithelium, and subretinal neovascular membranes in the macular region.

It has been hypothesized that atherosclerosis of the blood vessels that supply the retina contributes to the risk of AMD, analogous to the mechanism underlying coronary heart disease (CHD) (1, 2). According to this hypothesis, dietary fat components related to CHD may also be related to AMD (3, 4). Dietary saturated fat, cholesterol, and *trans* unsaturated fats were shown to be positively related to the risk of CHD; *cis*-, mono-, and polyunsaturated fatty acids were shown to be inversely related to the risk of CHD (5, 6). Thus, these specific types of fat may have similar associations with AMD. Long-chain n−3 fatty acids, especially docosahexaenoic acid (DHA), are abundant in the retina (7) and play an essential role in the development of vision (8). Blood DHA concentrations were shown to be inversely related to other degenerative diseases of the retina, such as retinitis pigmentosa (9–11). However, a high intake of polyunsaturated fatty acids may also increase the degree of unsaturation in the macular structures and increase susceptibility to oxidative stress. Because few studies have assessed the associations between specific types of fat and risk of AMD (12, 13), we examined these relations in 2 large prospective cohorts of women and men.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study (NHS) enrolled 121 700 female registered nurses aged 30–55 y in 1976. The Health Professionals Follow-up Study (HPFS) included 51 529 male health

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professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists) aged 40–75 y in 1986. We sent follow-up questionnaires to both cohorts biennially to update information regarding diet and lifestyle and to ascertain new diagnoses of AMD.

Ascertainment of fat intake

A semiquantitative food-frequency questionnaire (FFQ) with ≈130 food items was sent to women in 1984, 1986, and 1990 to assess usual dietary intakes in the previous year. A similar FFQ was administered to men in 1986 and 1990. Participants were asked how often, on average, they had consumed each type of food or beverage during the previous year. The questionnaire had 9 possible responses ranging from never or <1 time/mo to ≥6 times/d. For this analysis, we began follow-up in the NHS in 1984 because the shorter FFQ collected in 1980 did not have the detailed questions needed for calculation of n−3 fatty acids. Fat intake per individual was calculated as the sum of the contributions from all foods based on US Department of Agriculture food-composition data (14), taking into account types of margarine and fats used in cooking and baking.

The reproducibility and validity of fat intake was assessed previously in both cohorts (15, 16). The Pearson correlation coefficients between energy-adjusted fat intakes from the average of two 1-wk diet records and from the FFQ varied from 0.48 to 0.73 (0.57 for total fat and 0.68 for saturated fat) in women and from 0.37 to 0.75 (0.67 for total fat and 0.75 for saturated fat) in men, with correction for attenuation due to random error in diet records. Spearman correlation coefficients between the percentage of fat intake calculated from the FFQ and the fatty acid composition of subcutaneous fat aspirates also confirmed that the FFQ measured specific fatty acids from exogenous sources reasonably well [r = 0.51 (women) and 0.34 (men) for *trans* unsaturated fat, r = 0.35 (women) and 0.37 (men) for linoleic acid, and r = 0.48 (women) and 0.49 (men) for long-chain n−3 fatty acids] (17, 18). The reproducibility and validity of individual fat-contributing foods was also evaluated previously (19, 20). The correlation coefficients for intake of meat and fish between diet records and the FFQ were 0.46 and 0.66, respectively, in women and varied from 0.58 to 0.73 in men after correction for attenuation due to random error in diet records.

Population analyzed

Because AMD is rare in young populations, we restricted the baseline population for this study to women aged ≥50 y in 1984 and to men aged ≥50 y in 1986 (55 865 women and 33 357 men) and excluded those who did not complete a baseline FFQ, who had implausible energy intakes (<2510 or >14 644 kJ/d for women and <3347 or >17 573 kJ/d for men), or who left >70 items blank on the FFQ (9353 women and 1138 men). Participants who reported a diagnosis of AMD or cancer (except nonmelanoma skin cancer) at baseline were excluded (3346 women and 1756 men); these exclusions were updated every 2 y. We also excluded participants who did not respond to any of the follow-up questionnaires about a diagnosis of AMD (1986–1996 in the NHS and 1988–1996 in the HPFS; 423 women and 717 men). A total of 42 743 women and 29 746 men were included in the analysis at baseline and additional participants were added every 2 y as they reached 50 y of age. By 1994, 71 486 women and 41 474 men contributed to the analyses. Of the eligible participants, including those who did not respond to any follow-up questionnaires, the follow-up rates calculated with person-time of follow-up were 98% for women and 96% for men.

Endpoints

The endpoint for this analysis was incident AMD with visual loss of 20/30 or worse [ie, a person with AMD could recognize at 20 ft (6.1 m) a symbol that could be recognized by a person with normal acuity at ≥30 ft (9.1 m)] due primarily to AMD in at least one eye. We obtained data on the diagnosis of AMD beginning in 1986 for women and in 1988 for men. Of the eligible participants, a total of 2706 women and 1205 men reported a diagnosis of AMD during follow-up. For these participants, we requested permission to review medical records. A total of 564 women and 285 men responded that their initial report of AMD was in error, and 242 women and 146 men did not grant us permission to contact their ophthalmologists. We asked the remaining participants' ophthalmologists to either complete a standardized questionnaire or to send us copies of ocular records to confirm the diagnosis. The questionnaire asked for the date of initial diagnosis, the best corrected visual acuity, and signs of AMD (drusen, retinal pigment epithelial hypo- or hyperpigmentation, geographic atrophy, retinal pigment epithelial detachment, subretinal neovascular membrane, or disciform scar) and asked whether the visual loss was due mainly to AMD. A diagnosis of AMD was not confirmed by the ophthalmologist in 626 women and 218 men. In a substantial proportion of these cases, other maculopathies (eg, macular hole) or other eye diseases (eg, cataract or diabetic retinopathy) were noted instead. Of the confirmed cases of AMD (964 women and 452 men), we excluded patients who did not have a visual loss of 20/30 or worse (480 women and 178 men) or whose visual loss was not attributable to AMD (133 women and 57 men). Thus, 351 women and 216 men participated in the analysis.

We included all 567 patients in the primary analysis and conducted additional analyses based on subgroups of AMD [ie, early and dry AMD, wet AMD, and AMD with visual acuity 20/50 or worse—a person with AMD can recognize at 20 ft (6.1 m) a symbol that those with normal acuity can recognize at ≥50 ft (15.2 m)]. The early and dry form of AMD is defined as the presence of drusen, retinal pigment epithelial changes, or geographic atrophy. The wet form of AMD, usually associated with greater visual impairment, included retinal pigment epithelial detachment, choroidal neovascular membrane, or disciform scar. The person was used as the unit of analysis, and, if a participant had bilateral AMD with different degrees of progression, the more severe status was used.

Our definition of AMD was validated by 2 retinal specialists who conducted a standardized review of fundus slides in a subset of cases (those ascertained from the 1990 follow-up in the NHS) (21). Among cases with photographs of sufficient quality to grade, 86% (36 of 42) were classified as having definite signs of AMD and 93% (39 of 42) were classified as having definite or probable AMD by both readers. Regarding the classification of subtypes of AMD (early and dry compared with wet), there was 100% (23 of 23) concordance between the retinal specialist and the reporting ophthalmologist for early and dry AMD and 86% (12 of 14) for wet AMD.

Data analysis

To calculate the percentage of energy contributed by each type of fat, we divided energy intake from each fat by total energy intake. Participants were divided into quintiles according to this

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TABLE 1
Baseline characteristics of the cohorts according to total fat intake of participants who were aged ≥50 y at baseline (1984 in women and 1986 in men)[1]

Variable	Quintile of fat intake 1	2	3	4	5
Women					
Median total fat (% of energy)	27	32	35	38	42
Age (y)	57 ± 4[2]	56 ± 4	56 ± 4	56 ± 4	56 ± 4
Current smokers (%)	22	22	23	25	30
Body mass index (kg/m^2)	25 ± 4	25 ± 4	26 ± 5	26 ± 5	26 ± 5
Vigorous exercise >1 time/wk (%)	47	44	40	39	36
Postmenopausal hormone use (%)	18	17	16	17	16
Alcohol (g/d)	10 ± 16	8 ± 12	7 ± 10	6 ± 9	4 ± 8
Energy (kJ/d)	6847 ± 2098	7204 ± 2144	7324 ± 2171	7392 ± 2229	7230 ± 2296
Zinc from food and supplements (mg/d)[3]	17 ± 18	16 ± 15	15 ± 14	16 ± 15	16 ± 14
Vitamin E from food and supplements (IU/d)[3]	123 ± 224	101 ± 195	90 ± 187	87 ± 184	85 ± 188
Lutein and zeaxanthin (μg/d)[3]	4533 ± 3689	3902 ± 2651	3512 ± 2411	3301 ± 2216	2940 ± 2133
Men					
Median total fat (% of energy)	24	29	32	35	40
Age (y)	61 ± 7	61 ± 7	60 ± 7	60 ± 7	60 ± 7
Current smokers (%)	6	8	10	11	14
Body mass index (kg/m^2)	25 ± 3	25 ± 3	26 ± 3	26 ± 3	26 ± 3
Physical activity (METs/wk)	27 ± 72	24 ± 71	22 ± 70	22 ± 78	21 ± 80
Alcohol (g/d)	15 ± 21	13 ± 17	12 ± 15	10 ± 14	8 ± 11
Energy (kJ/d)	7731 ± 2445	7937 ± 2372	8306 ± 2505	8505 ± 2616	8614 ± 2733
Zinc from food and supplements (mg/d)[3]	24 ± 30	22 ± 25	21 ± 23	21 ± 22	22 ± 23
Vitamin E from food and supplements (IU/d)[3]	148 ± 252	122 ± 223	109 ± 208	99 ± 201	96 ± 200
Lutein and zeaxanthin (μg/d)[3]	4803 ± 3854	4194 ± 3061	3862 ± 2780	3577 ± 2507	3163 ± 2674

[1] Because of the large sample size, all variables except postmenopausal hormone use showed a significant test for trend ($P < 0.05$). METs, metabolic equivalents.
[2] $\bar{x}$ ± SD.
[3] Energy-adjusted intake.

percentage. The quintiles were updated according to the cumulative average intake over the follow-up period examined. For example, in women, the intake in 1984 was used for the 1984–1986 follow-up and the average of the 1984 and 1986 intakes was used for the 1986–1990 follow-up. In addition, the participants were classified according to their responses to individual fat-contributing foods, which were also updated according to average frequencies of intake over the follow-up period. Study participants contributed person-time in each 2-y interval from the time the baseline FFQ was returned or from 50 y of age until a diagnosis of AMD or cancer, death, the time that the last questionnaire was returned, or the end of the follow-up period (1 June 1996 for women and 1 January 1996 for men), whichever came first.

To examine the associations between total fat intake and other risk factors for AMD, we used ordinal logistic regression, with quintile of total fat intake as the outcome and age and other risk factors as the predictors.

Age-adjusted rates were calculated with age in 5-y categories. Analyses that controlled for other potential confounders were conducted with pooled multivariate logistic regression (22). The models included potential risk factors for AMD such as age, smoking, body mass index, energy and lutein and zeaxanthin intakes, alcohol intake, physical activity [quintiles of metabolic equivalents (METs) per week in men, vigorous activity more than once per week in women], postmenopausal hormone use (in women), and occupation (in men). To adjust for smoking, pack-years of smoking (the number of years of smoking multiplied by the average number of packs of cigarettes smoked per day) was used because this best reflects the cumulative effect of smoking and is more strongly associated with AMD than is current smoking status (21). Of these covariates, age, pack-years of smoking, body mass index, and postmenopausal hormone use were updated in every 2-y period. Dietary covariates were updated in the same manner as was fat intake. For all RRs, 95% CIs were calculated. Tests for trend across categories of fat intake were conducted by using the medians within each category as a continuous variable. All P values are 2-sided.

We conducted separate analyses for each cohort and pooled the 2 study groups to achieve maximum statistical power. Tests for heterogeneity between the 2 study groups were conducted, and meta-analytic methods with use of a random-effects model were used to pool the RRs from the 2 cohorts (23).

After the primary analyses with use of cumulative updated fat intakes, we performed alternate analyses using baseline intakes and the most recent intakes. To confirm the results of the primary analyses, we conducted additional restricted analyses in participants without cardiovascular disease (angina, myocardial infarction, stroke, or coronary bypass or angioplasty in men, and angina, myocardial infarction, or stroke in women) or diabetes at baseline or during follow-up and in participants who reported having had an eye examination during follow-up.

RESULTS

We documented 567 cases of AMD (351 women and 216 men) during 12 y of follow-up in women (635 873 person-years) and 10 y of follow-up in men (300 242 person-years).

Participants with a high total fat intake were more likely to smoke cigarettes, to have a higher body mass index, and to exercise less (**Table 1**). Total fat intake was inversely related to alcohol,

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TABLE 2
Relative risk of age-related macular degeneration according to quintile of fat intake[1]

Nutrient	Quintile of fat intake 1	2	3	4	5	*P* for trend[2]	*P* for heterogeneity[3]
Total fat							
Women (*n*)	71	69	87	47	77	—	—
Median intake (% of energy)	27	32	35	38	42	—	—
Age-adjusted RR (95% CI)	1.00	1.12	1.51	0.87	1.63	0.02	—
Multivariate RR (95% CI)[4]	1.00	1.14	1.57	0.89	1.61	0.03	—
Men (*n*)	44	45	38	42	47	—	—
Median intake (% of energy)	24	29	32	35	40	—	—
Age-adjusted RR (95% CI)	1.00	1.10	1.02	1.20	1.36	0.12	—
Multivariate RR (95% CI)[5]	1.00	1.09	1.01	1.20	1.42	0.11	—
Pooled multivariate RR (95% CI)	1.00	1.12 (0.86, 1.45)	1.29 (0.84, 2.00)	1.01 (0.76, 1.35)	1.54 (1.17, 2.01)	0.008	0.91
Animal fat							
Women (*n*)	68	73	75	73	62	—	—
Median intake (% of energy)	13	17	19	22	26	—	—
Age-adjusted RR (95% CI)	1.00	1.24	1.38	1.46	1.28	0.08	—
Multivariate RR (95% CI)[4]	1.00	1.25	1.38	1.41	1.25	0.14	—
Men (*n*)	45	34	50	49	38	—	—
Median intake (% of energy)	11	15	18	21	26	—	—
Age-adjusted RR (95% CI)	1.00	0.84	1.29	1.37	1.10	0.22	—
Multivariate RR (95% CI)[5]	1.00	0.82	1.26	1.32	1.07	0.30	—
Pooled multivariate RR (95% CI)	1.00	1.04 (0.69, 1.56)	1.33 (1.03, 1.73)	1.37 (1.06, 1.78)	1.18 (0.89, 1.56)	0.07	0.84
Pooled multivariate + vegetable fat + *trans* unsaturated fat	1.00	1.02 (0.67, 1.54)	1.31 (1.00, 1.71)	1.36 (1.03, 1.79)	1.19 (0.87, 1.62)	0.10	—
Vegetable fat							
Women (*n*)	67	76	65	69	74	—	—
Median intake (% of energy)	9	12	15	17	21	—	—
Age-adjusted RR (95% CI)	1.00	1.21	1.07	1.16	1.26	0.27	—
Multivariate RR (95% CI)[4]	1.00	1.24	1.11	1.18	1.28	0.24	—
Men (*n*)	37	47	39	44	49	—	—
Median intake (% of energy)	8	11	13	15	19	—	—
Age-adjusted RR (95% CI)	1.00	1.37	1.21	1.34	1.41	0.15	—
Multivariate RR (95% CI)[5]	1.00	1.39	1.20	1.37	1.48	0.11	—
Pooled multivariate RR (95% CI)	1.00	1.29 (0.99, 1.68)	1.14 (0.87, 1.51)	1.25 (0.95, 1.64)	1.35 (1.04, 1.77)	0.06	0.54
Pooled multivariate + animal fat + *trans* unsaturated fat	1.00	1.22 (0.93, 1.61)	1.06 (0.79, 1.43)	1.17 (0.86, 1.59)	1.33 (0.95, 1.87)	0.22	0.23
Cholesterol							
Women (*n*)	83	68	59	77	64	—	—
Median intake (% of energy)	113	146	170	196	246	—	—
Age-adjusted RR (95% CI)	1.00	0.93	0.82	1.10	0.97	0.81	—
Multivariate RR (95% CI)[4]	1.00	0.91	0.82	1.12	0.98	0.76	—
Men (*n*)	36	44	39	49	48	—	—
Median intake (% of energy)	95	123	145	170	214	—	—
Age-adjusted RR (95% CI)	1.00	1.28	1.12	1.39	1.32	0.21	—
Multivariate RR (95% CI)[5]	1.00	1.27	1.12	1.40	1.37	0.16	—
Pooled multivariate RR (95% CI)	1.00	1.04 (0.76, 1.42)	0.92 (0.69, 1.23)	1.21 (0.94, 1.56)	1.12 (0.81, 1.55)	0.29	0.34
Pooled multivariate + vegetable fat + *trans* unsaturated fat	1.00	1.12 (0.73, 1.42)	0.91 (0.65, 1.27)	1.19 (0.92, 1.55)	1.13 (0.76, 1.69)	0.35	0.23

[1] Values for intake were computed as the cumulative updated average. All nutrient variables were included as quintiles in models. RR, relative risk.

[2] Calculated with median intakes of fat in each category as a continuous variable.

[3] Test for between-study heterogeneity for test for trend.

[4] Multivariate model controlling for 2-y period (6 periods), age (50–54, 55–59, 60–64, 65–69, and ≥70 y), pack-years of smoking (never and 1–9, 10–24, 25–44, 45–64, and ≥65 y), energy and lutein and zeaxanthin intakes (all quintiles), body mass index (kg/m^2; <21, 21–22.9, 23–24.9, 25.0–28.9, and ≥29.0), postmenopausal hormone use (premenopausal and never, current, and past user), vigorous exercise more than once per week (yes or no), and alcohol intake (0, 0.1–4.9, 5–14.9, 15–29.9, and ≥30 g/d).

[5] Multivariate model controlling for 2-y period (5 periods), age 50–59, 60–64, 65–69, 70–74, and ≥75 y), pack-years of smoking (never and 1–9, 10–24, 25–44, 45–64, and ≥65 y), energy and lutein and zeaxanthin intakes (all quintiles), body mass index (kg/m^2; <21, 21–22.9, 23–24.9, 25.0–28.9, and ≥29.0), profession (dentist, pharmacist, optometrist, podiatrist, or veterinarian), physical activity (metabolic equivalent quintiles), and alcohol intake (0, 0.1–4.9, 5–14.9, 15–29.9, and ≥30 g/d).

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TABLE 3
Multivariate relative risk of age-related macular degeneration according to quintile of each type of fat intake[1]

Nutrient	Quintile of fat intake 1	2	3	4	5	*P* for trend[2]	*P* for heterogeneity[3]
Saturated fat							
Women (*n*)	68	94	55	68	66	—	—
Median intake (% of energy)	9.3	11.1	12.3	13.6	15.7	—	—
RR (95% CI)	1.00	1.65	1.09	1.44	1.53	0.07	—
Men (*n*)	48	37	50	41	40	—	—
Median intake (% of energy)	7.4	9.5	10.9	12.2	14.4	—	—
RR (95% CI)	1.00	0.81	1.22	1.09	1.14	0.34	—
Pooled RR (95% CI)	1.00	1.18 (0.59, 2.35)	1.14 (0.87, 1.50)	1.29 (0.98, 1.70)	1.36 (1.03, 1.80)	0.04	0.65
Pooled additional adjustment[4]	1.00	1.07 (0.48, 2.41)	1.02 (0.73, 1.42)	1.11 (0.62, 2.01)	1.17 (0.57, 2.41)	0.60	0.15
Monounsaturated fat							
Women (*n*)	72	67	81	65	66	—	—
Median intake (% of energy)	9.5	11.4	12.6	13.9	15.7	—	—
RR (95% CI)	1.00	1.09	1.41	1.22	1.29	0.12	—
Men (*n*)	42	40	45	44	45	—	—
Median intake (% of energy)	8.6	10.8	12.2	13.6	15.5	—	—
RR (95% CI)	1.00	1.01	1.20	1.26	1.32	0.14	—
Pooled RR (95% CI)	1.00	1.06 (0.81, 1.38)	1.33 (1.03, 1.72)	1.23 (0.94, 1.62)	1.30 (0.98, 1.71)	0.03	0.93
Pooled additional adjustment[4]	1.00	0.92 (0.67, 1.25)	1.07 (0.75, 1.52)	0.95 (0.62, 1.47)	0.97 (0.51, 1.87)	0.97	0.13
Polyunsaturated fat							
Women (*n*)	81	47	66	73	84	—	—
Median intake (% of energy)	4.5	5.6	6.5	7.3	8.8	—	—
RR (95% CI)	1.00	0.63	0.93	1.03	1.19	0.04	—
Men (*n*)	47	43	36	48	42	—	—
Median intake (% of energy)	4.2	5.1	5.8	6.5	7.9	—	—
RR (95% CI)	1.00	0.96	0.85	1.15	1.02	0.69	—
Pooled RR (95% CI)	1.00	0.77 (0.51, 1.16)	0.90 (0.69, 1.17)	1.07 (0.83, 1.38)	1.13 (0.88, 1.44)	0.06	0.43
Pooled additional adjustment[4]	1.00	0.72 (0.48, 1.09)	0.82 (0.62, 1.09)	0.97 (0.73, 1.29)	1.02 (0.74, 1.39)	0.36	0.30
trans Unsaturated fat							
Women (*n*)	67	66	73	74	71	—	—
Median intake (% of energy)	1.2	1.6	1.9	2.2	2.7	—	—
RR (95% CI)	1.00	1.13	1.36	1.45	1.44	0.02	—
Men (*n*)	36	41	56	45	38	—	—
Median intake (% of energy)	0.7	1.0	1.2	1.5	1.9	—	—
RR (95% CI)	1.00	1.20	1.70	1.40	1.21	0.46	—
Pooled RR (95% CI)	1.00	1.16 (0.88, 1.52)	1.48 (1.14, 1.94)	1.43 (1.09, 1.88)	1.35 (1.02, 1.80)	0.02	0.50
Pooled additional adjustment[4]	1.00	1.16 (0.86, 1.54)	1.46 (1.09, 1.97)	1.38 (1.00, 1.90)	1.26 (0.89, 1.79)	0.22	0.36

[1] Values for intake were computed as the cumulative updated average. All values were controlled for the variables listed for women and men separately in footnotes 4 and 5 of Table 2. RR, relative risk.

[2] Test for trend calculated with median intakes of fat in each category as a continuous variable.

[3] Test for between-study heterogeneity for test for trend.

[4] Additional adjustment for quintiles of other fats in the table simultaneously.

zinc, vitamin E, and lutein and zeaxanthin intakes and positively to energy intake.

Total fat intake was associated with an increased risk of AMD in both women and men (**Table 2**). In women, the age-adjusted RR for the fifth quintile of intake compared with the first quintile was 1.63 (95% CI: 1.19, 2.24) and did not materially change after other risk factors were controlled for. In men, the RR for the same comparison of intake was 1.36 (95% CI: 0.90, 2.06) and, again, was not altered in the multivariate analysis. The corresponding pooled multivariate RR was 1.54 (95% CI: 1.17, 2.01). Intakes of animal and vegetable fats were both associated with modest increases in risk of AMD. In a multivariate model including both sources of fat as well as *trans* unsaturated fat simultaneously, the weak positive associations did not change materially. Cholesterol intake was not related to AMD risk.

Saturated, monounsaturated, and *trans* unsaturated fats were each associated with a modest, marginally significant increase in risk of AMD (**Table 3**). Polyunsaturated fat had a nonlinear, nonsignificant positive association with AMD. We adjusted further for the percentage of energy from protein (in quintiles) so that the coefficients for fats could be interpreted as the estimated effect of substituting a specific percentage of energy from fat for the same percentage of energy from carbohydrate. This additional adjustment resulted in a modest attenuation of the effect of *trans* unsaturated fatty acids only (data not shown). The risks were attenuated (and were no longer significant) after adjustment for quintiles of all fats simultaneously (Table 3).

Polyunsaturated fat consists of several fatty acids that may differently affect the development of AMD. Of these, linolenic acid was positively associated with risk of AMD in both women and men (**Table 4**); the highest quintile of intake was associated with a 49% increased risk compared with the lowest quintile (95% CI: 1.15, 1.94). With adjustment for quintiles of linolenic acid, polyunsaturated fat intake became slightly inversely related

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TABLE 4
Multivariate relative risk of age-related macular degeneration according to quintile of polyunsaturated fatty acid intake[1]

Nutrient	Quintile of fat intake 1	2	3	4	5	*P* for trend[2]	*P* for heterogeneity[3]
Linoleic acid							
Women (*n*)	79	49	69	72	82	—	—
Median intake (% of energy)	3.7	4.8	5.6	6.4	7.7	—	—
RR (95% CI)	1.00	0.68	1.00	1.06	1.22	0.05	—
Men (*n*)	47	41	39	48	41	—	—
Median intake (% of energy)	3.4	4.3	4.9	5.7	7.0	—	—
RR (95% CI)	1.00	0.94	0.95	1.18	1.03	0.60	—
Pooled RR (95% CI)	1.00	0.78 (0.58, 1.07)	0.98 (0.76, 1.27)	1.10 (0.86, 1.42)	1.15 (0.89, 1.47)	0.05	0.47
Pooled additional adjustment[4]	1.00	0.71 (0.50, 1.02)	0.82 (0.61, 1.11)	0.88 (0.64, 1.21)	0.84 (0.58, 1.22)	0.73	0.37
Linolenic acid							
Women (*n*)	58	57	69	75	92	—	—
Median intake (% of energy)	0.41	0.50	0.57	0.65	0.78	—	—
RR (95% CI)	1.00	1.01	1.23	1.29	1.54	0.003	—
Men (*n*)	42	45	34	42	53	—	—
Median intake (% of energy)	0.35	0.43	0.48	0.55	0.66	—	—
RR (95% CI)	1.00	1.14	0.87	1.09	1.41	0.11	—
Pooled RR (95% CI)	1.00	1.06 (0.81, 1.41)	1.07 (0.76, 1.50)	1.21 (0.92, 1.58)	1.49 (1.15, 1.94)	0.0009	0.81
Pooled additional adjustment[4]	1.00	1.06 (0.79, 1.41)	1.06 (0.73, 1.54)	1.18 (0.86, 1.62)	1.41 (1.00, 1.98)	0.03	0.85
Arachidonic acid							
Women (*n*)	78	76	72	52	73	—	—
Median intake (% of energy)	0.04	0.06	0.07	0.08	0.10	—	—
RR (95% CI)	1.00	0.99	0.95	0.68	0.97	0.46	—
Men (*n*)	42	37	60	45	32	—	—
Median intake (% of energy)	0.04	0.06	0.07	0.09	0.11	—	—
RR (95% CI)	1.00	0.85	1.39	1.05	0.76	0.41	—
Pooled RR (95% CI)	1.00	0.94 (0.73, 1.22)	1.13 (0.77, 1.64)	0.83 (0.54, 1.27)	0.89 (0.68, 1.18)	0.27	0.95
Pooled additional adjustment[4]	1.00	0.97 (0.74, 1.26)	1.16 (0.88, 1.54)	0.87 (0.64, 1.17)	0.96 (0.63, 1.48)	0.71	0.41
Eicosapentaenoic acid							
Women (*n*)	80	65	65	66	75	—	—
Median intake (% of energy)	0.007	0.015	0.024	0.041	0.073	—	—
RR (95% CI)	1.00	0.79	0.73	0.71	0.74	0.19	—
Men (*n*)	40	43	47	42	44	—	—
Median intake (% of energy)	0.007	0.019	0.034	0.051	0.092	—	—
RR (95% CI)	1.00	0.95	0.97	0.87	0.84	0.38	—
Pooled RR (95% CI)	1.00	0.85 (0.65, 1.11)	0.81 (0.63, 1.06)	0.76 (0.58, 1.00)	0.77 (0.59, 1.01)	0.12	0.75
Pooled additional adjustment[4]	1.00	0.86 (0.66, 1.12)	0.84 (0.64, 1.10)	0.80 (0.60, 1.06)	0.84 (0.62, 1.14)	0.48	0.88
Docosahexaenoic acid							
Women (*n*)	79	67	59	83	63	—	—
Median intake (% of energy)	0.021	0.038	0.056	0.084	0.141	—	—
RR (95% CI)	1.00	0.81	0.66	0.89	0.62	0.05	—
Men (*n*)	42	45	44	39	46	—	—
Median intake (% of energy)	0.024	0.048	0.075	0.109	0.186	—	—
RR (95% CI)	1.00	0.96	0.88	0.78	0.83	0.37	—
Pooled RR (95% CI)	1.00	0.86 (0.66, 1.12)	0.74 (0.56, 0.97)	0.85 (0.65, 1.11)	0.70 (0.52, 0.93)	0.05	0.41
Pooled additional adjustment[4]	1.00	0.86 (0.66, 1.13)	0.75 (0.57, 1.00)	0.89 (0.67, 1.18)	0.75 (0.54, 1.05)	0.27	0.44

[1] Values for intake were computed as the cumulative updated average. All values were controlled for the variables listed for women and men separately in footnotes 4 and 5 of Table 2. RR, relative risk.

[2] Test for trend calculated with median intakes of fat in each category as a continuous variable.

[3] Test for between-study heterogeneity for test for trend.

[4] Additional adjustment for quintiles of other fats in the table as well as quintiles of saturated fat, monounsaturated fat, and *trans* unsaturated fat simultaneously.

to AMD (data not shown). This relation represents the association of polyunsaturated fatty acids other than linolenic acid (mostly linoleic acid) with AMD.

To evaluate further the association with linolenic acid, the major food sources of this fatty acid were examined (**Table 5**). These foods provided 38% of linolenic acid intake in women and 46% in men at baseline. Of the food sources of linolenic acid, intake of beef, pork, or lamb as a main dish appeared strongly positively related to AMD. More than 1 serving/wk of beef, pork, or lamb as a main dish was associated with a 35% increased risk of AMD compared with <3 servings/mo (pooled RR: 1.35; 95% CI: 1.07, 1.69). A high intake of margarine was also significantly related to an increased risk of AMD. Because these food items were also major contributors of *trans* unsaturated fat, we adjusted further for quintiles of *trans* unsaturated and other fats in models with linolenic acid; the relation with linolenic acid was slightly

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TABLE 5
Relative risk of age-related macular degeneration according to food contributors of linolenic acid[1]

Food	Frequency of intake (times per week or month)					*P* for trend[2]	*P* for heterogeneity[3]
	≤3/mo	>3/mo–1/wk	>1/wk–4/wk	>4/wk–6/wk	≥6/wk		
Mayonnaise or other creamy salad dressings							
Women (*n*)	100	47	153	51		—	—
Age-adjusted RR (95% CI)	1.00	0.84	0.95	1.16		0.58	—
Multivariate RR (95% CI)	1.00	0.83	0.95	1.13		0.68	—
Men (*n*)	93	34	60	29		—	—
Age-adjusted RR (95% CI)	1.00	0.85	1.00	1.50		0.20	—
Multivariate RR (95% CI)	1.00	0.80	0.93	1.39		0.45	—
Pooled multivariate RR (95% CI)	1.00	0.82 (0.63, 1.06)	0.94 (0.77, 1.16)	1.22 (0.93, 1.61)		0.42	0.75
Oil and vinegar dressing							
Women (*n*)	136	28	17	70		—	—
Age-adjusted RR (95% CI)	1.00	0.89	0.94	1.32		0.24	—
Multivariate RR (95% CI)	1.00	0.89	0.99	1.37		0.16	—
Men (*n*)	83	40	64	29		—	—
Age-adjusted RR (95% CI)	1.00	1.65	1.31	1.18		0.20	—
Multivariate RR (95% CI)	1.00	1.62	1.30	1.13		0.30	—
Pooled multivariate RR (95% CI)	1.00	1.21 (0.67, 2.17)	1.11 (0.85, 1.45)	1.29 (1.00, 1.66)		0.08	0.94
Margarine							
Women (*n*)	57	9	73	51	161	—	—
Age-adjusted RR (95% CI)	1.00	1.54	1.02	1.03	1.13	0.42	—
Multivariate RR (95% CI)	1.00	1.59	1.05	1.10	1.21	0.26	—
Men (*n*)	45	11	48	22	90	—	—
Age-adjusted RR (95% CI)	1.00	1.69	1.41	1.00	1.84	0.004	—
Multivariate RR (95% CI)	1.00	1.67	1.43	0.96	1.72	0.02	—
Pooled multivariate RR (95% CI)	1.00	1.64 (1.01, 2.65)	1.20 (0.90, 1.62)	1.05 (0.77, 1.43)	1.42 (1.01, 2.00)	0.03	0.26
Beef, pork, or lamb as a main dish							
Women (*n*)	68	111		172		—	—
Age-adjusted RR (95% CI)	1.00	1.44		1.38		0.05	—
Multivariate RR (95% CI)	1.00	1.44		1.47		0.02	—
Men (*n*)	57	54		105		—	—
Age-adjusted RR (95% CI)	1.00	0.98		1.36		0.04	—
Multivariate RR (95% CI)	1.00	0.91		1.20		0.25	—
Pooled multivariate RR (95% CI)	1.00	1.16 (0.75, 1.82)		1.35 (1.07, 1.69)		0.01	0.56
Other cheese (eg, American or cheddar)							
Women (*n*)	52	43	71	85		—	—
Age-adjusted RR (95% CI)	1.00	1.16	0.99	1.25		0.36	—
Multivariate RR (95% CI)	1.00	1.12	1.04	1.29		0.27	—
Men (*n*)	57	30	87	42		—	—
Age-adjusted RR (95% CI)	1.00	0.89	0.99	1.14		0.57	—
Multivariate RR (95% CI)	1.00	0.84	0.89	0.96		0.80	—
Pooled multivariate RR (95% CI)	1.00	0.98 (0.73, 1.33)	0.97 (0.77, 1.22)	1.14 (0.86, 1.51)		0.50	0.36

[1] Values for intake were computed as the cumulative updated average. All values were controlled for the variables listed for women and men separately in footnotes 4 and 5 of Table 2. RR, relative risk.

[2] Calculated by using each category as a continuous variable with the same increment (1, 2, 3, 4).

[3] Test for between-study heterogeneity for test for trend.

attenuated but remained significant (Table 4). Other high-fat foods were not associated with risk of AMD (data not shown).

DHA intake had a modest inverse relation with AMD (Table 4). The pooled multivariate RR for the highest quintile of DHA intake compared with the lowest was 0.70 (95% CI: 0.52, 0.93). Further adjustment for quintile of protein intake attenuated the association (data not shown). Simultaneous control for quintiles of other fat components attenuated the RR as well.

Because fish is a major source of DHA, we examined the associations of total and types of fish intake with AMD risk (**Table 6**). Fish intake contributed 77% of DHA intake in women and 80% in men. Participants who ate fish >4 times/wk had a lower risk of AMD than did those who consumed it ≤3 times/mo (RR: 0.65; 95% CI: 0.46, 0.91) in pooled multivariate analysis. This inverse association was consistent in women and men. Of the individual fish items examined, a significant inverse association was found only with tuna intake. The pooled RR of participants who ate canned tuna more than once per week compared with those who consumed it less than once per month was 0.61 (95% CI: 0.45, 0.83).

To examine whether the positive association of total fat with AMD represented a generic effect of total fat or an effect of one or more specific components of fat, we conducted multivariate analyses including total fat with each fat component, one at a time (data not shown). Adjustment for quintiles of linolenic acid had the greatest effect on the RR for total fat. The pooled RR for the highest quintile of total fat intake compared with the lowest quintile decreased from 1.54 to 1.30 (95% CI: 0.95, 1.78). Further

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TABLE 6
Relative risk of age-related macular degeneration according to fish intake[1]

Food	Frequency of fish intake (times per week or month)					*P* for trend[2]	*P* for heterogeneity[3]
	≤1/mo	>1/mo–3/mo	>3/mo–1/wk	>1/wk–4/wk	≥4/wk		
Canned tuna fish							
Women (*n*)	39	157	88	67		—	—
Age-adjusted RR (95% CI)	1.00	0.90	0.75	0.61		0.002	—
Multivariate RR (95% CI)	1.00	0.92	0.77	0.64		0.007	—
Men (*n*)	49	73	63			31	—
Age-adjusted RR (95% CI)	1.00	0.77	0.80	0.56		0.03	—
Multivariate RR (95% CI)	1.00	0.78	0.79	0.58		0.04	—
Pooled multivariate RR (95% CI)	1.00	0.85 (0.66, 1.09)	0.78 (0.60, 1.03)	0.61(0.45, 0.83)		0.0007	0.86
Dark-meat fish (eg, mackerel, salmon, sardines, bluefish, and swordfish)							
Women (*n*)	205	112		34		—	—
Age-adjusted RR (95% CI)	1.00	0.71		0.93		0.06	—
Multivariate RR (95% CI)	1.00	0.75		0.96		0.12	—
Men (*n*)	80	74		62		—	—
Age-adjusted RR (95% CI)	1.00	0.90		0.94		0.69	—
Multivariate RR (95% CI)	1.00	0.92		0.97		0.83	—
Pooled multivariate RR (95% CI)	1.00	0.80 (0.67, 0.97)		0.96 (0.75, 1.24)		0.21	0.34
Other fish (white-meat fish)							
Women (*n*)	57	130	101	63		—	—
Age-adjusted RR (95% CI)	1.00	0.70	0.91	0.78		0.78	—
Multivariate RR (95% CI)	1.00	0.73	0.96	0.84		0.88	—
Men (*n*)	28	75	71	42		—	—
Age-adjusted RR (95% CI)	1.00	1.29	1.19	1.04		0.83	—
Multivariate RR (95% CI)	1.00	1.26	1.16	1.04		0.82	—
Pooled multivariate RR (95% CI)	1.00	0.94 (0.55, 1.60)	1.03 (0.78, 1.34)	0.91 (0.67, 1.23)		0.98	0.78
Total fish (sum of all fish)							
Women (*n*)	61		54	203	33	—	—
Age-adjusted RR (95% CI)	1.00		0.77	0.72	0.64	0.02	—
Multivariate RR (95% CI)	1.00		0.78	0.75	0.66	0.05	—
Men (*n*)	31		34	113	38	—	—
Age-adjusted RR (95% CI)	1.00		0.87	0.84	0.67	0.11	—
Multivariate RR (95% CI)	1.00		0.84	0.80	0.64	0.08	—
Pooled multivariate RR (95% CI)	1.00		0.80 (0.60, 1.07)	0.77 (0.60, 0.98)	0.65 (0.46, 0.91)	0.009	0.94

[1] Values for intake were computed as the cumulative updated average. All values were controlled for the variables listed for women and men separately in footnotes 4 and 5 of Table 2. RR, relative risk.

[2] Calculated by using each category as a continuous variable with the same increment (1, 2, 3, 4).

[3] Test for between-study heterogeneity for test for trend.

adjustment for *trans* unsaturated fat attenuated the RR for total fat to 1.16 (95% CI: 0.83, 1.63). In this model, intakes of linolenic acid and *trans* unsaturated fatty acid had nonsignificant positive associations with AMD, independent of total fat [pooled RRs for the fifth compared with the first quintiles = 1.32 (95% CI: 0.97, 1.80) for linolenic acid and 1.20 (95% CI: 0.86, 1.67) for *trans* unsaturated fat]. We also used the same models with the fat variables in a continuous scale to minimize residual confounding due to a categoric scale. Adjustment for linolenic acid attenuated the RR for total fat more substantially; the RR for each increase of 10% of energy from total fat was reduced from 1.20 (95% CI: 1.02, 1.40) to 1.04 (95% CI: 0.86, 1.26). In this model, the positive association with linolenic acid remained strong [RR for each increase of 0.5% of energy from linolenic acid = 1.61 (95% CI: 1.13, 2.30)].

We also conducted alternative analyses for subgroups of AMD (early and dry and wet) and for advanced AMD, which included cases with wet AMD and early and dry AMD with geographic atrophy. Overall, the results were similar for the subgroups and consistent with those using all AMD cases combined (data not shown).

Finally, we conducted analyses using baseline intake and then the most recent intake as the exposures because we do not know the time period during which diet may affect the development of the disease. The positive association of linolenic acid appeared somewhat stronger when baseline diet was used as the exposure; this was consistent in both cohorts (pooled RR for the first compared with the fifth quintiles: 1.75; 95% CI: 1.34, 2.28). All other findings agreed with results from the cumulative updated analyses; the associations were somewhat weaker when we used the most recent intake.

DISCUSSION

In this large prospective study of women and men, we observed a positive association between intake of total fat and incidence of AMD. We also observed a positive association between linolenic acid intake and AMD and an inverse relation between fish intake and AMD. The association between total fat intake and AMD risk appeared to be due to positive associations with specific fatty acids rather than with fat per se. The RR for total fat was greatly attenuated after adjustment for linolenic acid (r with total fat = 0.5 for both women and men) and for *trans* unsaturated fat (r with total fat = 0.6 for both women and men).

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The results from our study do not completely support the hypothesis that dietary fats are similarly related to both CHD and AMD. Although intake of *trans* unsaturated fat and saturated fat, risk factors for CHD, appeared somewhat positively related to AMD, polyunsaturated fat, an important protective factor for CHD, did not show an appreciable inverse association with AMD. In fact, we observed a positive relation between linolenic acid intake and risk of AMD in both of our cohorts; whereas this polyunsaturated fat was inversely related to CHD risk in the studies (5, 6). Polyunsaturated fat intake may promote oxidative damage by increasing the degree of unsaturation in the macula, a region particularly susceptible to oxidation due to light exposure and high oxygen tension (24). However, linolenic acid is a minor fatty acid in the macula (7). The lack of a specific biologic mechanism for linolenic acid and the fact that we assessed many individual fatty acids, and thus, this could be a chance finding, emphasizes the need for further assessments of these associations.

Our results generally agree with the findings of a preliminary report of the Eye Disease Case-Control Study, which notes an elevated risk of exudative AMD in relation to total fat and vegetable fat intakes (13). In the Beaver Dam Eye Study, intake of saturated fat and cholesterol 10 y before the interview was associated with an elevated risk of early AMD (12). Possible reasons for the disparate results include different case definitions, recall bias, or chance.

Long-chain n−3 fatty acids may have a special role in the function of the retina in addition to their antithrombotic and hypolipidemic effects on the cardiovascular system. Rod outer segments of vertebrate retinas have a high DHA content (7, 25). Although DHA's role in visual development was well documented in animals and humans (8, 26, 27), its role, if any, in retinal function later in life is unknown. However, photoreceptor outer segments are constantly being renewed; therefore, a constant supply of n−3 fatty acids is required and marginal depletion of these fatty acids might impair retinal function and influence the development of degenerative diseases such as AMD. Several studies reported an inverse association of serum DHA concentrations with retinitis pigmentosa, another degenerative disease of the retina (9, 10). The preliminary report from the Eye Disease Case-Control Study notes a nonsignificant inverse association between marine n−3 fatty acids and exudative AMD (multivariate odds ratio: 0.73; 95% CI: 0.5, 1.2) (13). One cross-sectional study found a weak and nonsignificant association of plasma DHA with AMD (odds ratio: 0.82; 95% CI: 0.35, 1.93) (28).

The modest inverse associations between DHA intake and AMD in both men and women suggest a protective role of this fatty acid in the development of the disease. In addition, intake of fish, a major source of DHA, was inversely associated with AMD. However, because the association of AMD with fish intake (particularly tuna) was stronger than that with DHA, we cannot exclude the possibility that some other components in fish may also contribute to the association. Further adjustment for beef, pork, or lamb intake (because fish intake typically replaces red meat intake) had a negligible effect on the RR for fish.

In the present study, the possibility of recall bias was avoided because fat intake was measured before the development of AMD. Misclassification of fat intake was reduced when average intakes during follow-up were used. In addition, we conducted a restricted analysis, in which we excluded participants with cardiovascular disease or diabetes because these conditions may result in changes in dietary habits, and observed essentially the same results.

Because AMD is a nonfatal disease and often progresses without any symptoms, diagnosis of the disease could be related to people's health consciousness, which may in turn be associated with fat intake. For example, persons with a high or low intake of a specific fat may have more frequent eye exams and thus a greater chance of receiving a diagnosis of AMD if they have the disease. For this reason, our case definition required a visual loss of 20/30 or worse, ie, disease of sufficient severity to warrant medical attention. In addition, because the participants in this study were nurses and health professionals, they were likely aware of health issues and thus likely to have similar opportunities for medical contact. The high percentage of participants who had an eye examination during follow-up supports this assumption; these percentages were similar across fat intakes (94–96% in women and 88–90% in men). When we used a stricter case definition—visual loss of 20/50 or worse—or conducted restricted analyses among participants who had an eye examination during follow-up, the results were similar.

Although it is likely that the non-AMD group included some persons with AMD (low sensitivity), as long as the ascertainment of AMD was not related to fat intake and our case definition was highly specific, the RR would be minimally biased (29). We conducted a validation study of our case definition and confirmed this high specificity.

Although we had information on a wide range of potential confounders, we had limited information on several factors, such as sunlight exposure or a family history of AMD. However, it is unlikely that these unmeasured risk factors are strongly correlated with fat intake; thus, they likely did not account for the entire association we observed. Adjustment for other dietary risk factors for AMD such as zinc and vitamin E did not affect the overall associations.

This prospective study raises the possibility that a high intake of linolenic acid may contribute to the occurrence of AMD. Our findings also support the hypothesis that a higher intake of fish may reduce the risk of AMD. These findings need confirmation in additional studies.

We are indebted to the participants in the Nurses' Health Study and the Health Professionals Follow-up Study for their continued cooperation and to Maureen Ireland, Kerry Demers, Laura Sampson, Karen Corsano, Elaine Coughlan-Havas, Sandra Melanson, and Jaylyn Olivo for their unfailing assistance. We also acknowledge Frank E Speizer, Principal Investigator of the Nurses' Health Study, for his input.

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