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Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration[2]

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Abstract

Background—The association between lutein/zeaxanthin intake and age-related macular degeneration (AMD) risk may differ by smoking status, vitamin C and E intakes, and body fatness.

Objective—The objective was to evaluate the association between lutein/zeaxanthin intake and AMD risk by smoking status, intake of antioxidant vitamins, and body fatness.

Design—We conducted a prospective follow-up study of 71 494 women and 41 564 men aged ≥50 y and had no diagnosis of AMD or cancer. Diet was assessed with a validated semiquantitative food-frequency questionnaire.

Results—During up to 18 y of follow-up, we documented 673 incident cases of early AMD and 442 incident cases of neovascular AMD with a visual loss of 20/30 or worse due primarily to AMD. Lutein/zeaxanthin intake was not associated with the risk of self-reported early AMD. There was a statistically nonsignificant and nonlinear inverse association between lutein/zeaxanthin intake and neovascular AMD risk; the pooled multivariate relative risks for increasing quintiles of intake were 1.00 (referent), 0.80, 0.84, 0.97, and 0.72 (95% CI: 0.53, 0.99) (*P* for trend = 0.14). For early AMD, the association with lutein/zeaxanthin intake did not vary by smoking status, intakes of vitamins C and E, or body mass index. For neovascular AMD, a nonlinear inverse association was found among never smokers.

Conclusions—These data do not support a protective role of lutein/zeaxanthin intake on risk of self-reported early AMD. The suggestion of inverse associations related to the risk of neovascular AMD needs to be examined further.

Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss in the elderly that severely affects quality of life (1,2). Because of increasing longevity, the burden of this disease continues to grow in the United States. It is estimated that AMD affects >1.7 million persons and will affect almost 3 million people in the United States by 2020 (3). Because few treatment options are available for the disease (4), prevention is important.

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Lutein and zeaxanthin are carotenoids with no vitamin A activity. These carotenoids have been a major focus of research efforts related to AMD because they are concentrated in the macula and compose the macular pigment, which functions both as antioxidants and as blue-light filters to protect the macula from light damage (5–7). A high density of macular pigment is associated with a lower risk of AMD (8,9). Dietary or supplemental intake of lutein and zeaxanthin can directly increase macular pigment density in humans and animals (10–16). However, the link between lutein/zeaxanthin intake and AMD has been inconsistent. Although several epidemiologic studies have examined the association between dietary or serum concentrations of lutein/zeaxanthin and AMD risk, some (17–24) but not others (25–32), found an inverse association. We previously examined lutein/zeaxanthin intake as well as other antioxidant vitamins and carotenoids in relation to AMD risk in our large prospective studies of women and men and found no association (33). It is possible, however, that the relation is limited to neovascular AMD (there were few cases in our previous analysis) or that the relation is complex and other factors need to be carefully considered. A recent experimental study suggests that zeaxanthin in combination with ascorbic acid or α-tocopherol may protect the retina against oxidative damage (34,35). Another study found an interaction between lutein and ascorbic acid in reducing oxidative stress (36). Because adipose tissue may trap lutein and zeaxanthin (37), persons who are overweight or obese may have lower concentrations of these carotenoids available to the macula. Furthermore, smoking is a well-established risk factor for AMD (38) and may modify the association between lutein/zeaxanthin and AMD. Therefore, with an additional 4 y of follow-up, we examined lutein/zeaxanthin intake in combination with intakes of antioxidant vitamins (vitamins C and E), body mass index (BMI), and smoking in 2 large prospective studies of men and women. We examined AMD as early versus neovascular types because the etiology of these subtypes may be different.

Subjects and Methods

Study participants

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

Assessment of dietary intake

A semiquantitative food-frequency questionnaire (FFQ) with ≈60 food items was sent to members of the female cohort in 1980. An expanded FFQ with ≈130 food items was administered to women in 1984, 1986, and every 4 y thereafter and to men in 1986 and every 4 y thereafter. Participants were asked how often, on average, they had consumed each type of food during the past year. A serving size was specified for each food in the FFQ. The questionnaire had 9 possible responses, ranging from never or less than once per month to ≥6 times/d. Participants also reported their current use and dose of vitamins C and E supplements and brands and types of multivitamins biennially. Intakes of vitamins and carotenoids from foods were calculated from US Department of Agriculture (USDA) sources (39). To calculate vitamin intake from food plus supplements combined, the contributions from multivitamins and other supplements were added to vitamin intakes from food only. Food composition data for specific types of carotenoids were based on the USDA-National Cancer Institute carotenoid database developed by Chung-Ahuja et al (40) and Mangels et al (41). The carotenoid content of tomato-based food products was updated with values from the USDA (42). Carotenoid values in our nutrient database were updated again in January 2006 using SR16 USDA data,

which are more complete and include carotenoids from foods not previously available. We used the regression-residual method to adjust nutrient intakes for total energy intake (43).

The reproducibility and validity of lutein/zeaxanthin intake have been assessed in these cohorts with the use of plasma concentrations (44). The Pearson correlation coefficient between dietary intake over the previous year by FFQ and plasma concentrations of lutein/zeaxanthin was 0.23 in nonsmoking women and 0.38 in nonsmoking men (44).

Population for analysis

For this analysis, we began follow-up when diet was measured with similar FFQs in the cohorts: in 1986 for men (HPFS) and in 1984 for women (NHS) because foods contributing to lutein/zeaxanthin intake were less complete in 1980 when diet was first measured in women. We 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 (15 753 women and 1595 men). Participants who reported a diagnosis of AMD or cancer (except nonmelanoma skin cancer) at baseline were excluded (4492 women and 2013 men), and these exclusions were updated every 2 y. We also excluded participants who did not respond to any of the follow-up questionnaires asking about a diagnosis of AMD (1986–2002 in the NHS and 1988–2002 in the HPFS; 514 women and 970 men). Finally, we excluded those who did not report having an eye exam during follow-up (4028 women and 4804 men) to minimize any influence of undiagnosed disease. Because AMD is rare in younger populations, we restricted our analysis to participants aged ≥50 y. Participants who were younger than 50 y at baseline were included in the cycle after they reached age 50 y. A total of 66 993 participants (40 276 women and 26 717 men) were included in the analysis at baseline. By 2002, 71 494 women and 41 564 men contributed to the analyses.

Diagnosis of AMD

Cases were defined as incident AMD when their best corrected visual acuity loss was 20/30 or worse [ie, a person 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 (regarding diagnoses received from 1980–1986) and in 1988 for men. If a person reported a diagnosis of AMD, we requested permission to review his or her medical records and contacted the participant's ophthalmologist to either complete a standardized questionnaire or to send us copies of ocular records to confirm the diagnosis. The questionnaire included the date of initial diagnosis, best-corrected visual acuity, signs of AMD (drusen, retinal pigment epithelial hypo- and hyperpigmentation, geographic atrophy, retinal pigment epithelial detachment, subretinal neovascular membrane, or disciform scar), and whether there was visual acuity loss due mainly to AMD. Although photographic evaluation of the eyes for all of the participants would be desirable for case ascertainment, it is not feasible in prospective studies as large as ours, and we need to rely on self-report of AMD diagnosis. Because AMD is a nonfatal disease and often progresses without any symptoms, diagnosis of the disease could be related to a person's health consciousness, which may in turn be associated with dietary intake of interest (eg, lutein/zeaxanthin intake). For this reason, our case definition required a visual loss of 20/30 or worse, ie, disease of sufficient severity to likely warrant medical attention, and only women who had an eye examination during follow-up were included.

We conducted analyses based on subgroups of AMD (early and neovascular) because these subtypes may have different etiologies and risk factors. The early form of AMD was defined as the presence of drusen or retinal pigment epithelial changes. The neovascular form of AMD, usually associated with greater visual impairment, included retinal pigment epithelial detachment, choroidal neovascular membrane, or disciform scar. On the basis of an

international classification system (45), these subtypes correspond to early and neovascular age-related maculopathy (ARM), respectively. 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 case definition of AMD has been 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) (38). Among cases with photographs of sufficient quality to grade, 86% (36 of 42) were classified as having definite AMD, and 93% (39 of 42) were classified as definite or probable AMD by both readers. Regarding the classification of subtypes of AMD, there was 100% (23 of 23) concordance between the retinal specialist and the reporting ophthalmologist for early AMD and 86% (12 of 14) for neovascular AMD.

A total of 4797 women and 2073 men reported a diagnosis of AMD in the cohorts until 2002 follow-up; 2321 women (48%) and 940 men (45%) were confirmed to have AMD by their ophthalmologist. For the remainder of participants reporting AMD, they did not grant permission for their ophthalmologist to be contacted (12% in women and 10% in men), indicated the initial report was in error (19% in women and 23% in men), or did not have the diagnosis confirmed by their ophthalmologist (18% in women and 16% in men). We then excluded women and men who did not have visual loss of 20/30 or worse or whose visual loss was not attributable to AMD; 818 women and 395 men were available for analysis. Because of the limited numbers of cases with geographic atrophy (n = 75 women and n = 23 men), we were not able to conduct an analysis for them and did not combine them with either the early or the neovascular form because these may have different etiologies.

Statistical analysis

Participants were divided into quintiles according to their lutein/zeaxanthin intake. In the primary analysis, intake data were updated according to the cumulative average of intake over the follow-up period examined. For example, in women, 1984 intake was used for the 1984–1986 follow-up and the average of 1984 and 1986 intakes was used for the 1986–1990 follow-up, and so on. Baseline and most recent intake were each examined alone in secondary analyses. Study participants contributed person-time in each 2-y interval from the time the baseline FFQ was returned or from the time the first questionnaire was returned after they reached 50 y of age until a diagnosis of AMD or cancer, death, time of last questionnaire return, or end of the follow-up period (1 June 2002 for women and 1 January 2002 for men), whichever came first.

We employed Cox proportional hazards regression to account for potential effects of other risk factors for AMD (46). To control as finely as possible for confounding by age, calendar time, and any possible 2-factor interactions between these 2 time scales, we stratified the analysis jointly by age (in months) at start of follow-up and calendar year of the current questionnaire cycle. Multivariate models also adjusted for smoking status, BMI, energy intake, alcohol intake (47), fish intake (48), and postmenopausal hormone use in women. Of these covariates, smoking, BMI, and postmenopausal hormone use were updated in every 2-y period. SAS PROC PHREG (49) was used for all analysis, and the Anderson-Gill data structure (50) was used to handle time-varying covariates efficiently, with a new data record created for every questionnaire cycle at which a participant was at risk and covariates set to their values at the time the questionnaire was returned.

We examined the association between lutein/zeaxanthin intake and AMD risk by levels of several factors, including smoking status, vitamin C intake, vitamin E intake, and BMI. For smoking status, because there were few current smokers, current smokers were combined with past smokers. For intakes of vitamins C and E, we used approximate median values as cutoffs for these nutrients (<250 and ≥250 mg/d for vitamin C and <15 and ≥15 mg/d for vitamin E).

For BMI (in kg/m^2), we used a cutoff of 25 to separate overweight or obese (≥25) and nonoverweight (<25) persons.

For all relative risks (RRs), 95% CIs were calculated. Tests for trend across quintiles of intake were conducted by using the median within each quintile as a continuous variable (51). Tests for interaction were conducted by introducing a cross-product term in a multivariate model. All *P* values are 2-sided.

We conducted separate analyses for each cohort and pooled the 2 studies to achieve maximum statistical power. Tests for heterogeneity between the 2 studies were conducted, and meta-analytic methods using a random-effects model were used to pool the RRs from the cohorts (52).

We also used methods of competing risk survival analysis to compare effects of lutein/zeaxanthin on early and neovascular AMD. We used the data augmentation method of Lunn and McNeal (53) to estimate the regression parameters for all failure types simultaneously and to perform likelihood ratio tests of the equality of effects of lutein/zeaxanthin on the different types of AMD. To combine results over the 2 studies, we calculated test statistic z to assess statistical significance where z~N (0, 1) under the null hypothesis that the coefficient estimate for early AMD equals the coefficient estimate for neovascular AMD.

Results

We documented 673 cases of early AMD (463 women and 210 men) and 442 cases of neovascular AMD (280 women and 162 men) with visual acuity loss of 20/30 or worse due primarily to AMD during up to 18 y of follow-up in women and up to 16 y of follow-up in men.

The distribution of potential risk factors for AMD by quintiles of lutein/zeaxanthin intake in 1990 in men and women is shown in Table 1. Participants with higher lutein/zeaxanthin intakes were less likely to smoke, to have a BMI ≥ 25, and to consume alcohol and were more likely to consume fish. Postmenopausal women with a higher lutein/zeaxanthin intake were more likely to use postmenopausal hormones.

We examined lutein/zeaxanthin intake in relation to early and neovascular AMD (Table 2). The associations between lutein/zeaxanthin intake and AMD risk were similar in age-adjusted and multivariate models. Lutein/zeaxanthin intake was not associated with risk of early AMD. There was a statistically not-significant and non-linear inverse association between lutein/zeaxanthin intake and neovascular AMD; the pooled multivariate RRs for increasing quintiles of lutein/zeaxanthin intake were 1.00 (referent), 0.80, 0.84, 0.97, and 0.72 (95% CI: 0.53, 0.99) (*P* for trend = 0.14). There was no statistically significant difference in the effect of lutein/zeaxanthin on the different types of AMD. Although the results were similar in women and men, none of the RRs were statistically significant when examined separately. The results for early AMD were similarly null when baseline intake (intake in 1984) or most recent intake was examined (data not shown). The association between lutein/zeaxanthin intake and neovascular AMD was weaker when only baseline intake was evaluated; the pooled multivariate RR for the top versus the bottom quintiles of lutein/zeaxanthin intake was 0.84 (95% CI: 0.50, 1.42). The association between most recent lutein/zeaxanthin intake and neovascular AMD was similar to the association using cumulative updated lutein/zeaxanthin intake. The pooled multivariate RR for the top versus the bottom quintiles of lutein/zeaxanthin intake was 0.78 (95% CI: 0.57, 1.06).

We examined lutein/zeaxanthin intake in relation to early and neovascular AMD by smoking status, intakes of vitamins C and E, and BMI (Table 3). For early AMD, no association was

found by levels of these factors. For neovascular AMD, there was a nonlinear inverse association among never smokers (pooled multivariate RR for the top versus the bottom quintiles: 0.41; 95% CI: 0.18, 0.97). Because some previous studies found a stronger association between lutein/zeaxanthin intake and AMD among younger participants (19,22), we examined the association by age (<70 versus ≥70 y), but did not find that the associations were stronger among younger age group (data not shown).

Discussion

We found no overall association between lutein/zeaxanthin intake and early AMD risk, and the association did not differ by smoking status, vitamin C and E intakes, and BMI. There was some suggestion of a nonlinear inverse association between lutein/zeaxanthin intake and neovascular AMD risk, which tended to be clearer among nonsmokers.

Although there have been several epidemiologic studies of dietary or serum concentrations of lutein/zeaxanthin and AMD risk, the results have been inconclusive. A significant inverse association was found for dietary and serum lutein/zeaxanthin in a case-control study of neovascular AMD (356 cases) (17,18). Subsequent epidemiologic studies of lutein/zeaxanthin have been mixed. Some (19–24) but not others (25–32), found an inverse association. Most of the studies, even those that found inverse associations, were small, used case-control or cross-sectional designs, where recall and selection biases are of concern, and included few neovascular AMD cases. A cross-sectional study of the participants in the third National Health and Nutrition Examination Survey found that a higher lutein/zeaxanthin intake was related to lower pigmentary abnormalities (n = 51) and late AMD (n = 16) in some age groups (19). A case-control study of neovascular AMD (n = 72) found that lutein/zeaxanthin intake was associated with lower risk (20). A cross-sectional study with 64 early and 14 late AMD cases found an inverse association between plasma zeaxanthin but not lutein and AMD risk (21). Another cross-sectional study with prediagnostic blood samples and 34 early and 7 late AMD found an inverse association with plasma lutein and zeaxanthin (23). Three cohort studies with early AMD cases only or with mostly early AMD cases found no inverse association (27,28, 30). Therefore, the evidence of inverse association is more consistent for neovascular AMD. There is an ongoing randomized clinical trial of supplementation of lutein/zeaxanthin and n−3 fatty acids and AMD (Age-Related Eye Disease Study II), although the results may not be available in the near future. Previously in our 2 cohorts, we examined lutein/zeaxanthin intake as well as other antioxidant vitamins and carotenoids in relation to AMD risk and found no associations (33). However, after adding more cases and, more importantly, after using recently updated nutrient data to our lutein/zeaxanthin score, we observed some inverse association, although it did not have a clear dose-response relation.

Smoking is a major oxidative stress and may lower the bioavailability of lutein/zeaxanthin. Smokers have lower serum lutein and zeaxanthin concentrations than do nonsmokers, independent of dietary lutein/zeaxanthin intake (54,55). Therefore, a high intake of lutein/zeaxanthin may be more important for AMD risk among smokers. However, we found that dietary lutein/zeaxanthin intake was inversely associated with neovascular AMD only among nonsmokers. A modest antioxidant effect of lutein/zeaxanthin may be overwhelmed in the face of the strong oxidative stress due to smoking.

A recent experimental study suggests that zeaxanthin in combination with ascorbic acid or α-tocopherol may protect the retina against oxidative damage (34,35). Another study found an interaction between lutein and ascorbic acid in reducing oxidative stress (36). When we examined lutein/zeaxanthin intake by intakes of vitamins C and E, there were suggestive inverse associations between intakes of lutein/zeaxanthin and neovascular AMD among those with high intakes of these vitamins.

Adipose tissue is a major storage organ for carotenoids, and a higher adipose tissue content may trap lutein/zeaxanthin and make it less available to other organs, including the macula (37). If this is true, we hypothesized that we would find a stronger inverse association among those who are not overweight. In contrast with our hypothesis, however, the association between lutein/zeaxanthin intake and neovascular AMD, if anything, was stronger in those who were overweight or obese.

Our study had several strengths. To our knowledge, this is the largest study of lutein/zeaxanthin intake and AMD, with >400 neovascular AMD cases and one of the few prospective studies of diet and AMD risk. However, we did have limited statistical power in interaction analyses and were not able to evaluate the associations among current smokers and among the obese because of the limited number of cases in these categories. Also, vitamin C intake in our populations was relatively high and we were not able to evaluate the association among those consuming less than Recommended Dietary Allowance of 90 mg for women and 75 mg for men.

We had repeated measures of diet and were able to examine dietary intake incorporating these measures, which can minimize measurement error because of a one-time dietary assessment and thus best reflect long-term dietary intake, which may be most relevant to chronic diseases such as AMD with long duration of development (56). However, the validation correlations for lutein/zeaxanthin calculated from the intake measured by FFQ and serum concentrations were not high compared with other nutrients in our cohort, probably because of variable bioavailabilities, although the values were higher than those from other studies (54). Also, plasma concentrations of lutein/zeaxanthin are more strongly related to macular pigment density (reflecting lutein/zeaxanthin status in the eye) than to dietary intake (57). Thus, more direct assessments of lutein/zeaxanthin status, such as serum concentrations of lutein/zeaxanthin or macular pigment density, may provide a clearer picture of the relation.

We used a more advanced definition of AMD than that of most other epidemiologic studies by restricting cases to those with visual acuity loss of at least 20/30 or worse. This is because we rely on self-report of AMD and because most early AMD cases do not have any symptoms; we might otherwise have misclassified these cases. Using a more advanced definition of AMD, we would have excluded some persons who might have been grouped as “cases” in other studies. As far as being cases in our studies are not related to lutein/zeaxanthin intake, our results would not be biased (58). Persons who are more health conscious may seek medical attention and may have a diagnosis of AMD. However, this may be more of a concern for asymptomatic cases with no visual loss. Furthermore, we restricted participants in our analysis to those who received an eye examination during follow-up. Finally, if the association was biased, it may be more likely true for the less severe form (eg, early AMD cases). However, we found associations for neovascular AMD. Because we did not have a centralized review system for AMD diagnosis and relied on outside review, some diagnoses might have been misclassified, especially in determining the AMD subgroup. This type of misclassification may tend to attenuate the associations with neovascular AMD, if some early cases were included in this group.

It is possible that lutein and zeaxanthin each have a different impact on AMD (23). Even if both carotenoids compose macular pigment, the distribution of the carotenoids in the macula is quite different; zeaxanthin predominates in the central part of the macula and lutein in the periphery (16). A recent study found that zeaxanthin cannot convert to lutein, but, in the retina, lutein can convert to meso-zeaxanthin, which is a form of zeaxanthin that does not exist in the diet (16). Thus, evaluation of either dietary or serum concentrations of lutein and zeaxanthin separately may be necessary to further clarify the role of these carotenoids. Currently, a nutrient

database with separate values for the 2 carotenoids is not available. Studies using plasma concentrations may separate lutein and zeaxanthin values and focus on neovascular forms.

In conclusion, we found no association between lutein/zeaxanthin intake and early AMD risk in 2 large prospective cohorts of women and men. No inverse association was found across the cohorts, subtypes of AMD, and smoking status, intakes of vitamins C and E, and BMI. The suggestion of inverse associations related to risk of neovascular AMD needs to be examined further. Separate evaluation of lutein and zeaxanthin values either from diet or plasma may provide further insight on the roles of these carotenoids in relation to the development of neovascular AMD.

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Table 1

Characteristics of the cohorts according to quintiles of energy-adjusted lutein/zeaxanthin intake in participants aged ≥50 y in 1990[1]

	Quintile of lutein/zeaxanthin intake					
	Women			Men		
Variable	1	3	5	1	3	5
No. of participants	11 369	11 346	11 362	5101	5102	5099
Lutein/zeaxanthin intake (μg/d)	1097 ± 279[2]	2512 ± 195	5852 ± 2797	1209 ± 317	2865 ± 234	6879 ± 315
Age (y)	59 ± 6	59 ± 6	59 ± 6	62 ± 8	62 ± 8	62 ± 7
Current smokers (%)	20	16	15	9	7	6
BMI ≥25 kg/m^2 (%)	50	48	47	58	53	54
Postmenopausal hormone use among postmenopausal women (%)	34	37	38	—	—	—
Alcohol intake (g/d)	4.7 ± 10.2	5.5 ± 9.9	5.2 ± 9.1	11.2 ± 16.9	10.3 ± 14.0	9.6 ± 13.0
Fish intake (servings/wk)	1.7 ± 1.6	2.5 ± 1.9	3.3 ± 2.5	2.1 ± 2.1	2.5 ± 2.2	3.5 ± 2.6

[1] Except for the data on mean age, all data shown are standardized to the age distributions of the cohorts in 1990. For simplicity, only data for lowest, middle, and highest quintiles of lutein/zeaxanthin are shown. Because of the large sample size, all variables showed a significant test for trend ($P < 0.05$).

[2] $\bar{x}$ ± SD (all such values).

Table 2

Relative risks (RRs) and 95% CIs for age-related macular degeneration (AMD) according to quintiles of energy-adjusted lutein/zeaxanthin intake

	Quintile of lutein/zeaxanthin intake (μg/d)					
	1 (1349/1431)[1]	2 (2052/2236)[1]	3 (2653/2953)[1]	4 (3389/3835)[1]	5 (4930/5712)[1]	*P* for trend
Early AMD						
Women (no. of cases)	97	87	96	92	91	
Age-adjusted RR (95% CI)	1.00	0.83 (0.62, 1.11)	0.90 (0.68, 1.20)	0.84 (0.63, 1.12)	0.83 (0.62, 1.10)	0.30
Multivariate[2] RR (95% CI)	1.00	0.84 (0.62, 1.12)	0.93 (0.69, 1.23)	0.87 (0.65, 1.17)	0.89 (0.66, 1.20)	0.62
Men (no. of cases)	31	54	45	31	49	
Age-adjusted RR (95% CI)	1.00	1.61 (1.03, 2.53)	1.33 (0.84, 2.12)	0.92 (0.56, 1.52)	1.48 (0.94, 2.34)	0.53
Multivariate[2] RR (95% CI)	1.00	1.64 (1.04, 2.57)	1.38 (0.86, 2.20)	0.97 (0.58, 1.61)	1.66 (1.04, 2.64)	0.26
Pooled multivariate RR (95% CI)	1.00	1.14 (0.59, 2.21)	1.08 (0.74, 1.57)	0.90 (0.69, 1.15)	1.18 (0.64, 2.17)	0.74
Neovascular AMD						
Women (no. of cases)	60	56	51	65	48	
Age-adjusted RR (95% CI)	1.00	0.85 (0.59, 1.23)	0.77 (0.53, 1.12)	0.94 (0.66, 1.34)	0.69 (0.47, 1.00)	0.11
Multivariate[2] RR (95% CI)	1.00	0.89 (0.62, 1.29)	0.85 (0.58,1.24)	1.05 (0.73, 1.52)	0.79 (0.53, 1.17)	0.42
Men (no. of cases)	41	29	34	34	24	
Age-adjusted RR (95% CI)	1.00	0.63 (0.39, 1.03)	0.75 (0.47, 1.20)	0.77 (0.48, 1.22)	0.52 (0.31, 0.87)	0.04
Multivariate[2] RR (95% CI)	1.00	0.67 (0.41, 1.09)	0.83 (0.51, 1.32)	0.85 (0.53, 1.36)	0.62 (0.37, 1.05)	0.19
Pooled multivariate RR (95% CI)	1.00	0.80 (0.60, 1.08)	0.84 (0.62, 1.13)	0.97 (0.73, 1.30)	0.72 (0.53, 0.99)	0.14

[1] Values are median intakes (μg/d) for women and men, respectively.

[2] Multivariate model was adjusted for age (continuous), smoking [never, past (<25 or ≥25 cigarettes/d), or current (<25 or ≥25 cigarettes/d)], energy intake (continuous), alcohol intake (continuous), fish intake (continuous), and BMI (continuous) and for postmenopausal hormone use (premenopausal, never, current, or past users) for women only.

Table 3

Pooled multivariate relative risks (RRs) and 95% CIs of age-related macular degeneration (AMD) according to quintiles of energy-adjusted lutein/zeaxanthin intake and other factors[1]

	Quintile of intake					
Risk factor	**1**	**2**	**3**	**4**	**5**	***P* for interaction**
Smoking						
Early AMD						
Never (*n* = 262)	1.00	1.11 (0.75, 1.65)	1.10 (0.74, 1.65)	0.95 (0.63, 1.44)	1.07 (0.70, 1.64)	
Past or current (*n* = 397)[2]	1.00	1.14 (0.44, 3.00)	1.08 (0.61, 1.93)	0.88 (0.63, 1.23)	1.27 (0.51, 3.16)	0.66
Neovascular AMD						
Never (*n* = 134)[3]	1.00	0.66 (0.39, 1.11)	0.54 (0.26, 1.13)	0.91 (0.55, 1.52)	0.41 (0.18, 0.97)	
Past or current (*n* = 297)[4]	1.00	0.85 (0.58, 1.22)	0.96 (0.67, 1.39)	1.04 (0.72, 1.49)	0.87 (0.60, 1.28)	0.07
Vitamin C intake						
Early AMD						
<250 mg/d (*n* = 339)	1.00	1.31 (0.42, 4.02)	1.10 (0.57, 2.12)	0.90 (0.64, 1.28)	1.20 (0.42, 3.41)	
≥250 mg/d (*n* = 334)	1.00	0.96 (0.65, 1.43)	1.08 (0.74, 1.58)	0.86 (0.59, 1.27)	1.11 (0.76, 1.60)	0.60
Neovascular AMD						
<250 mg/d (*n* = 232)	1.00	0.88 (0.60, 1.29)	0.83 (0.56, 1.24)	1.05 (0.70, 1.57)	0.81 (0.46, 1.44)	
≥250 mg/d (*n* = 210)	1.00	0.72 (0.45, 1.16)	0.79 (0.50, 1.25)	0.86 (0.55, 1.33)	0.61 (0.38, 0.98)	>0.99
Vitamin E intake						
Early AMD						
<15 mg/d (*n* = 312)	1.00	1.59 (0.56, 4.50)	1.03 (0.68, 1.55)	1.00 (0.68, 1.45)	1.53 (0.63, 3.71)	
≥15 mg/d (*n* = 361)	1.00	0.78 (0.55, 1.11)	0.97 (0.70, 1.35)	0.78 (0.55, 1.11)	0.88 (0.61, 1.27)	0.21
Neovascular AMD						
<15 mg/d (*n* = 234)	1.00	1.10 (0.74, 1.63)	1.07 (0.71, 1.62)	1.22 (0.82, 1.83)	0.74 (0.41, 1.33)	
≥15 mg/d (*n* = 208)	1.00	0.60 (0.38, 0.94)	0.64 (0.41, 1.01)	0.79 (0.52, 1.21)	0.66 (0.42, 1.03)	0.57
BMI						
Early AMD						
<25 kg/m^2 (*n* = 320)	1.00	1.05 (0.42, 2.66)	0.97 (0.68, 1.38)	0.74 (0.51, 1.07)	0.90 (0.45, 1.80)	
≥25 kg/m^2 (*n* = 353)	1.00	1.07 (0.76, 1.51)	1.14 (0.76, 1.70)	1.08 (0.76, 1.55)	1.33 (0.90, 1.98)	0.70
Neovascular AMD						
<25 kg/m^2 (*n* = 192)	1.00	0.88 (0.44, 1.78)	1.22 (0.30, 4.96)	1.05 (0.57, 1.94)	0.95 (0.59, 1.53)	
≥25 kg/m^2 (*n* = 250)	1.00	0.76 (0.34, 1.68)	0.67 (0.27, 1.64)	0.94 (0.46, 1.91)	0.60 (0.39, 0.94)	0.68

[1] Adjusted for the same covariates as in Table 2. Analysis was conducted separately in men and women and then pooled. The *P* value for test for heterogeneity by study (sex) was not significant for any of the *P* values for test of trend.

[2] *n* = 67 (54 female and 13 male) current smokers.

[3] *P* for trend = 0.04.

[4] *n* = 71 (60 female and 11 male) current smokers. *P* for trend = 0.75.