

Dietary Intake of Antioxidants and Risk of Age-Related Macular Degeneration

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AGE-RELATED MACULAR DEGENERATION (AMD) is a degenerative disorder of the macula, the central part of the retina. Late-stage AMD results in an inability to read, recognize faces, drive, or move freely. Early AMD is the subclinical stage of the disease and can be diagnosed by funduscopy. The prevalence of late AMD steeply increases with age, affecting 11.5% of white persons older than 80 years.¹ In the absence of effective treatment for AMD, the number of patients severely disabled by late-stage AMD is expected to increase in the next 20 years by more than 50% to 3 million in the United States alone.¹

The pathophysiology of AMD is still poorly understood, and AMD may in fact be a constellation of diseases with different causes. As in other age-related disorders, oxidative stress has been implicated in the etiology of AMD.² The retina seems particularly susceptible to oxidative stress because of its high concentration of oxygen, polyunsaturated fatty acids, and photosensitizers, in combination with an intense exposure to light.³ Epidemiological studies evaluating both dietary intake and serum levels of antioxidant vitamins and AMD have provided conflicting results.⁴⁻⁷ In the randomized, placebo-controlled Age-Related Eye Disease Study (AREDS), supplements containing 5 to 13 times the

Context Age-related macular degeneration (AMD) is the most prevalent cause of irreversible blindness in developed countries. Recently, high-dose supplementation with beta carotene, vitamins C and E, and zinc was shown to slow the progression of AMD.

Objective To investigate whether regular dietary intake of antioxidants is associated with a lower risk of incident AMD.

Design Dietary intake was assessed at baseline in the Rotterdam Study (1990-1993) using a semiquantitative food frequency questionnaire. Incident AMD until final follow-up in 2004 was determined by grading fundus color transparencies in a masked way according to the International Classification and Grading System.

Setting Population-based cohort of all inhabitants aged 55 years or older in a middle-class suburb of Rotterdam, the Netherlands.

Participants Of 5836 persons at risk of AMD at baseline, 4765 had reliable dietary data and 4170 participated in the follow-up.

Main Outcome Measure Incident AMD, defined as soft distinct drusen with pigment alterations, indistinct or reticular drusen, geographic atrophy, or choroidal neovascularization.

Results Incident AMD occurred in 560 participants after a mean follow-up of 8.0 years (range, 0.3-13.9 years). Dietary intake of both vitamin E and zinc was inversely associated with incident AMD. The hazard ratio (HR) per standard deviation increase of intake for vitamin E was 0.92 (95% confidence interval [CI], 0.84-1.00) and for zinc was 0.91 (95% CI, 0.83-0.98). An above-median intake of all 4 nutrients, beta carotene, vitamin C, vitamin E, and zinc, was associated with a 35% reduced risk (HR, 0.65; 95% CI, 0.46-0.92) of AMD. Exclusion of supplement users did not affect the results.

Conclusion In this study, a high dietary intake of beta carotene, vitamins C and E, and zinc was associated with a substantially reduced risk of AMD in elderly persons.

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recommended daily allowance (RDA) of beta carotene, vitamins C and E, and zinc given to participants from retinal clinics with early or monocular late AMD resulted in a 25% reduction in the 5-year progression to late AMD.⁸ We sought to investigate whether antioxidants, as present in normal daily foods, may play a role in the primary prevention of AMD.

METHODS

Study Population

The Rotterdam Study is a population-based, prospective cohort study of the frequency and determinants of com-

mon cardiovascular, locomotor, neurologic, and ophthalmologic diseases.^{9,10} The eligible population comprised all 10 275 inhabitants aged

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55 years or older of a middle-class suburb of Rotterdam, the Netherlands, of whom 7983 (78%) participated. Because the ophthalmologic part of the study became operational after the pilot phase of the study had started, 6780 (66%) took part in the ophthalmic examinations. A baseline home interview and examinations at the study center were performed from 1990 to mid 1993, followed by a first follow-up examination from 1993 to 1994, a second from mid 1997 to the end of 1999, and a third examination from 2000 to the end of 2004. Written informed consent was obtained from all participants. The medical ethics committee of Erasmus University approved the study protocol.

Diagnosis of AMD

The eye examination included 35° fundus photography (Topcon TRV-50VT fundus camera, Topcon Optical Co, Tokyo, Japan) after pharmacologic mydriasis.¹⁰ Transparencies were graded with 12.5× magnification according to the International Classification and Grading System.¹¹ Two experienced graders, masked to dietary intake, graded the follow-up transparencies and afterward compared these with the baseline ones. The grading procedures, definitions, and graders were identical at baseline and follow-up. Consensus sessions and between-grader comparisons were performed regularly. Weighted κ values were 0.72 for soft distinct drusen, 0.80 for hyperpigmentation, and 0.58 for hypopigmentation.

Early-stage AMD was defined as the presence of either large ($\geq 63 \mu\text{m}$), soft, distinct drusen with pigment irregularities or indistinct ($\geq 125 \mu\text{m}$) or reticular drusen with or without pigment irregularities. Drusen are white deposits in the retina that are considered to be the hallmark of early AMD and are important predictors of late AMD.^{10,12} Late-stage AMD, mostly leading to blindness, was defined as geographic atrophy (both central and non-central), choroidal neovascularization, or a combination of both.¹¹

Dietary Assessment

At baseline, participants completed a checklist at home that queried foods and drinks they had consumed at least twice a month during the preceding year as well as dietary habits, use of supplements, and prescribed diets. Next, during their visit to the research center, they underwent a standardized interview with a dietitian based on the checklist, using a 170-item semi-quantitative food frequency questionnaire.^{13,14} A validation study comparing this questionnaire with a 2-week food diary demonstrated reproducible and valid estimates.^{13,14} These dietary data were converted to total energy intake and nutrient intake per day with the computerized Dutch Food Composition Table.¹⁵ For the current study, we selected the carotenoids alpha and beta carotene, beta cryptoxanthin, lutein/zeaxanthin, lycopene, vitamins A (retinol equivalents), C, and E, and iron and zinc as cofactors for antioxidant enzymes. Persons who reported taking supplements containing carotenoids, vitamins A, C, or E, iron, or zinc, as well as multivitamins or multiminerals, were classified as supplement users.

Assessment of Confounders

Information on potential confounders was collected at baseline. Smoking status was categorized as current, former, or never, and number of pack-years was calculated. Serum total cholesterol level was measured in nonfasting blood samples with an automated enzymatic procedure. Blood pressure was defined as the mean of 2 measurements in sitting position at the right brachial artery with a random zero sphygmomanometer. The ankle-arm index was calculated by taking the ratio of systolic blood pressure at the ankle to systolic blood pressure at the arm, using the lowest ratio of both legs. Carotid intima-media thickness and atherosclerotic plaques were assessed ultrasonographically and aortic calcifications on lateral radiographic films of the lumbar spine. A subclinical atherosclerosis composite score (range, 1-4) was constructed by summing points for the population-

based deciles of carotid wall thickness and ankle-arm index, with points added for the presence of carotid plaques and aortic calcifications.¹⁶

Study Sample

The cohort at risk consisted of 5836 persons with no AMD in either eye at baseline; ie, with no drusen or pigment irregularities, hard drusen only, or soft drusen without pigment irregularities. Incidence of AMD was defined as the presence of early- or late-stage AMD in at least 1 eye at 1 of the follow-up examinations. Persons with incident AMD were compared with those with no AMD at baseline and no AMD at any follow-up examinations.

Dietary intake was not assessed in 227 participants with decreased cognitive function (defined as a score < 80 on the Cambridge Examination of Mental Disorders in the Elderly)¹⁷ because their dietary history was deemed unreliable. We also excluded 179 nursing home residents because their food was prepared by nursing home staff and would not reflect past dietary habits. Reliable dietary data were missing in 665 participants because of logical inconsistencies in dietary interviews, missing the baseline dietitian visit when the food-frequency questionnaire was administered, or various other logistical reasons. Baseline characteristics were similar in the 2 groups, although eligible respondents without dietary data were, on average, somewhat older compared with those with data and included fewer women.

Of this baseline cohort, 156 participants died, 419 refused any follow-up examination, and 20 were lost to follow-up before the first follow-up examination. Nonparticipants tended to be older; included more women, nursing home residents, and smokers; and more often had systemic hypertension. They did not differ from participants in their dietary intake of antioxidants; eg, vitamin E ($P = .75$) or zinc ($P = .69$). The study sample thus consisted of 4170 participants who had normal cognition, lived independently, had

reliable dietary assessment and gradable fundus transparencies, and participated in at least 1 follow-up examination.

Data Analysis

We adjusted the dietary intake of antioxidant nutrients for the total energy intake by means of the residual method described by Willett.¹⁸ For each nutrient, linear regression analysis was performed with antioxidant intake as the dependent variable and total energy intake as the independent variable. This regression equation was used to calculate the expected mean antioxidant intake of the study population for the mean total energy intake of the study population. Next, for each individual, the energy-adjusted intake was calculated by adding the expected mean antioxidant intake of the study population to the residual derived from the regression analysis.

We estimated the risk of AMD associated with the dietary intake of antioxidant nutrients at baseline with Cox proportional hazards regression analysis. Intake of each nutrient was entered into the model either as a linear term per standard deviation or as a dummy variable representing 1 of the 3 highest quartiles. Quartiles were analyzed both as a categorical variable and as a continuous variable to test for trend. Quartiles and SDs were based on the distribution within the study sample. We adjusted for age, sex, body mass index, smoking status, pack-years of smoking, systolic blood pressure, serum total cholesterol, composite atherosclerosis score, and alcohol intake in all analyses. We additionally adjusted for intake of polyunsaturated fat in the analysis of the fat-soluble vitamin E because of a reported association between this fat and AMD.¹⁹ Missing values of categorical variables were represented in the model by a missing indicator. For continuous variables, missing values were replaced by the mean or median of the study sample, depending on the distribution. Only the atherosclerosis composite score had more than 1% of the data missing (12.7%). To distinguish

Table 1. Baseline Characteristics of the Study Sample (N = 4170)*

Characteristics	Incident Age-Related Macular Degeneration (n = 560)	No Age-Related Macular Degeneration at Follow-up (n = 3610)	P Value†
Age, y	68.2 (7.1)	66.4 (7.2)	<.001
Women, No. (%)	321 (57.3)	2151 (59.6)	.31
Body mass index‡	26.3 (3.5)	26.35 (3.6)	.66
Smoking status, No. (%)			
Never	183 (32.8)	1207 (33.6)	.86
Former	248 (44.4)	1561 (43.4)	
Current	127 (22.8)	825 (23.0)	
Pack-years of smoking	18.5 (23.8)	16.4 (21.8)	.04
Blood pressure, mm Hg			
Systolic	138.9 (20.3)	137.1 (21.5)	.76
Diastolic	73.4 (10.7)	73.9 (11.0)	.56
Total cholesterol, mmol/L	6.6 (1.2)	6.7 (1.2)	.93
High-density lipoprotein cholesterol, mmol/L	1.38 (0.36)	1.35 (0.36)	.02
Atherosclerosis composite score§	2.7 (1.1)	2.5 (1.1)	.21
Alcohol intake, g/d	10.8 (15.3)	10.6 (15.3)	.20
Antioxidant supplement users, No. (%)	60 (10.7)	499 (13.8)	.09

SI conversions: To convert total and high-density lipoprotein cholesterol to mg/dL, divide by 0.0259.

*Data are expressed as mean (SD) unless otherwise indicated.

†Adjusted for age and sex.

‡Body mass index was calculated as weight in kilograms divided by the square of height in meters.

§Information on the atherosclerosis composite score is presented in the "Methods" section of the text.

between the effect of antioxidants from food and from supplements, all analyses were repeated after exclusion of supplement users at baseline and also after adding supplement users to the highest quartile of dietary intake. Also, analyses were repeated after stratification for smoking status.

One of our aims was to study the regular dietary intake of the combination of nutrients that had been administered at a high dose in AREDS.⁸ To secure large-enough groups with a relatively high or low intake of each of the 4 nutrients, we used the median intake per nutrient, based on the total sample, as the cutoff value. The high-intake group consisted of persons with an above-median intake of each of the 4 nutrients. The low-intake group had a below-median intake of each nutrient, and all persons in between were considered the reference category.

Associations are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). All analyses were performed using SPSS, release 11.0.1 (SPSS Inc, Chicago, Ill).

RESULTS

Mean follow-up of participants was 8.0 years, with a range of 0.3 to 13.9 years (median, 10.6 years). During this period, 560 persons (13.4%) were diagnosed as having incident AMD, the majority of whom had early-stage AMD. Persons with incident early AMD had either large, soft drusen with pigment irregularities (n = 317) or indistinct drusen without (n = 124) or with (n = 77) pigment irregularities. Of the 42 persons with incident late-stage AMD, 14 had the atrophic and 28 the neovascular type. Twelve of them had AMD at the second follow-up examination while 30 did so at the third follow-up. The incidence of AMD in the study sample was similar to the incidence in those with missing data on dietary intake who were not included in the sample (P = .60, adjusted for age and sex). Baseline characteristics of persons with incident AMD as well as the remainder of the cohort are presented in TABLE 1. The mean age was 68.2 years for the incident cases compared with 66.4 years for the remainder (P < .001). Persons with

Table 2. Mean Dietary Intake of Nutrients by Quartile in the Total Study Sample (N = 4170)

	Quartile of Dietary Intake, mg/d							
	1		2		3		4	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Carotenoids								
Alpha carotene	0.5 (0.2)	≤0.7	0.9 (0.01)	>0.7-≤1.0	1.2 (0.1)	>1.0-≤1.4	2.0 (1.2)	>1.4
Beta carotene	2.1 (0.6)	≤2.7	3.2 (0.2)	>2.7-≤3.6	4.0 (0.3)	>3.6-≤4.6	6.2 (0.3)	>4.6
Beta cryptoxanthin	0.05 (0.04)	≤0.1	0.2 (0.04)	>0.1-≤0.3	0.3 (0.04)	>0.3-≤0.4	0.6 (0.2)	>0.4
Lutein/zeaxanthin	1.4 (0.3)	≤1.8	2.0 (0.1)	>1.8-≤2.2	2.5 (0.2)	>2.2-≤2.8	3.6 (1.3)	>2.8
Lycopene	0.1 (0.07)	≤0.3	0.5 (0.1)	>0.3-≤0.7	0.8 (0.1)	>0.7-≤1.1	1.8 (0.8)	>1.1
Vitamins								
Vitamin A (retinol equivalents)	0.5 (0.1)	≤0.6	0.7 (0.03)	>0.6-≤0.8	0.8 (0.04)	>0.8-≤0.9	1.2 (0.5)	>0.9
Vitamin C	63.7 (15.5)	≤84.5	99.4 (8.2)	>84.5-≤113.6	128.4 (9.2)	>113.6-≤146.1	189.3 (46.6)	>146.1
Vitamin E	7.6 (1.9)	≤9.9	11.4 (0.8)	>9.9-≤12.8	14.4 (1.0)	>12.8-≤16.2	20.2 (4.1)	>16.2
Trace elements								
Iron	9.5 (1.0)	≤10.7	11.3 (0.4)	>10.7-≤11.9	12.6 (0.4)	>11.9-≤13.3	14.8 (1.6)	>13.3
Zinc	7.3 (0.9)	≤8.3	9.0 (0.4)	>8.3-≤9.6	10.2 (0.4)	>9.6-≤10.9	12.3 (1.4)	>10.9

Table 3. Risk of Age-Related Macular Degeneration per Standard Deviation (SD) Increase in Dietary Intake of Antioxidant Nutrients

Nutrients	Mean Dietary Intake (SD), mg/d	Adjusted Hazard Ratio per 1-SD Increase (95% Confidence Interval)*
Carotenoids		
Alpha carotene	1.12 (0.84)	0.99 (0.94-1.06)
Beta carotene	3.84 (2.23)	1.00 (0.94-1.06)
Beta cryptoxanthin	0.29 (0.22)	1.01 (0.92-1.10)
Lutein/zeaxanthin	2.37 (1.08)	1.01 (0.93-1.09)
Lycopene	0.80 (0.80)	1.01 (0.97-1.04)
Vitamins		
Vitamin A (retinol equivalents)	0.82 (0.35)	0.95 (0.86-1.05)
Vitamin C	120.20 (52.49)	1.02 (0.94-1.10)
Vitamin E	13.42 (5.19)	0.92 (0.84-1.00)
Trace elements		
Iron	12.04 (2.16)	0.95 (0.86-1.04)
Zinc	9.67 (2.01)	0.91 (0.83-0.98)

*Adjusted for age, sex, body-mass index, smoking status, pack-years of smoking, systolic blood pressure, atherosclerosis composite score, serum total cholesterol, and alcohol intake.

incident AMD reported more pack-years of cigarette smoking ($P=.04$) and had a higher serum high-density lipoprotein cholesterol level ($P=.02$). Other baseline characteristics were not different in the 2 groups.

TABLE 2 shows the mean daily dietary intake of the antioxidant nutrients in the study sample, adjusted for total energy intake. In TABLE 3, the risk of AMD in relation to nutrient intake is presented. A significant inverse association was observed for intake of vitamin E, iron, and zinc. After adjustment, a 1-SD increase in intake was associated with a reduced risk of AMD

of 8% (95% CI, 0%-16%) for vitamin E and 9% (95% CI, 2%-17%) for zinc.

The risk of AMD by quartile of nutrient intake is presented in the FIGURE. The tests for trend for both vitamin E ($P=.04$) and zinc ($P=.06$) intake indicated a dose-response relationship between vitamin E and zinc intake and reduced risk of AMD.

TABLE 4 presents the impact of the combined dietary intake of the 4 antioxidants that were studied in AREDS.⁸ Intake of these nutrients in the present study was considerably lower than the high-dose supplements used in AREDS. An above-median intake of beta caro-

tene, vitamins C and E, and zinc, compared with a below-median intake of at least 1 of these nutrients, was associated with a reduced risk of AMD (HR, 0.65; 95% CI, 0.46-0.92) adjusted for all potential confounders. In persons with a below-median intake of all 4 nutrients, the risk of AMD was increased but not significantly so (HR, 1.20; 95% CI, 0.92-1.56).

Exclusion of the 559 participants who used antioxidant supplements at baseline did not substantially alter the risk estimates (TABLE 5). In addition, adding supplement users to the highest quartile of dietary intake did not change the results (HR, adjusted for the same factors as in Table 5, 0.77; 95% CI, 0.61-0.98). Stratification for smoking status did not substantially change point estimates but widened the confidence intervals (Table 5).

COMMENT

We found that high dietary intake of vitamin E and zinc was associated with a lower risk of incident AMD. An above-median intake of the combination of vitamins C and E, beta carotene, and zinc was associated with a 35% lower risk of incident AMD.

The strengths of our study were the prospective design, the population-based cohort, the detailed and similar grading of AMD at baseline and follow-up, and the long follow-up. Potential

weaknesses were, as in all observational studies, selection bias, information bias, and confounding. Selective nonresponse was unlikely because nonparticipants did not differ from participants in the dietary intake of antioxidants. Bias in the diagnosis of AMD was minimized by the masked grading of photographs by persons unaware of the antioxidant nutrient status. Misclassification potentially could result from the use of only 1 food questionnaire at baseline, but such misclassification would be nondifferential and, therefore, more likely to underestimate the true associations. The questionnaire was not validated for all nutrients included in the current analysis; eg, specific carotenoids and vitamin E. However, for other nutrients, the validity of the questionnaire was shown to be moderate to good. The adjusted Pearson correlation coefficient for vitamin A (including retinol and beta carotene) was 0.48; for vitamin C, 0.64; for iron, 0.42; and for zinc, 0.51.^{13,14} For vegetables, the correlation was 0.39, and for fruit, 0.60. Since alpha and beta carotene and lutein intake are well correlated with total vegetable intake, we presumed equal validity. The same held for the correlation between beta cryptoxanthin and vitamin C. It is possible that other factors can explain the reported associations. Although we adjusted for known confounders, such as smoking and atherosclerosis, unknown factors associated with a healthy diet still may have played a role.

The median nutrient intake used as a cutoff value was at or above the RDA, so the majority of our population presumably consumed a healthy diet. A larger risk reduction was observed for dietary intake above the RDA for all 4 micronutrients than for individual micronutrients. To ensure that diet was the only source of antioxidant intake, we repeated the analysis excluding persons using antioxidant supplements at baseline (13.4%) and also investigated the combined effect of antioxidants from food and from supplements. This resulted in similar risk estimates. The independent association between antioxidant supple-

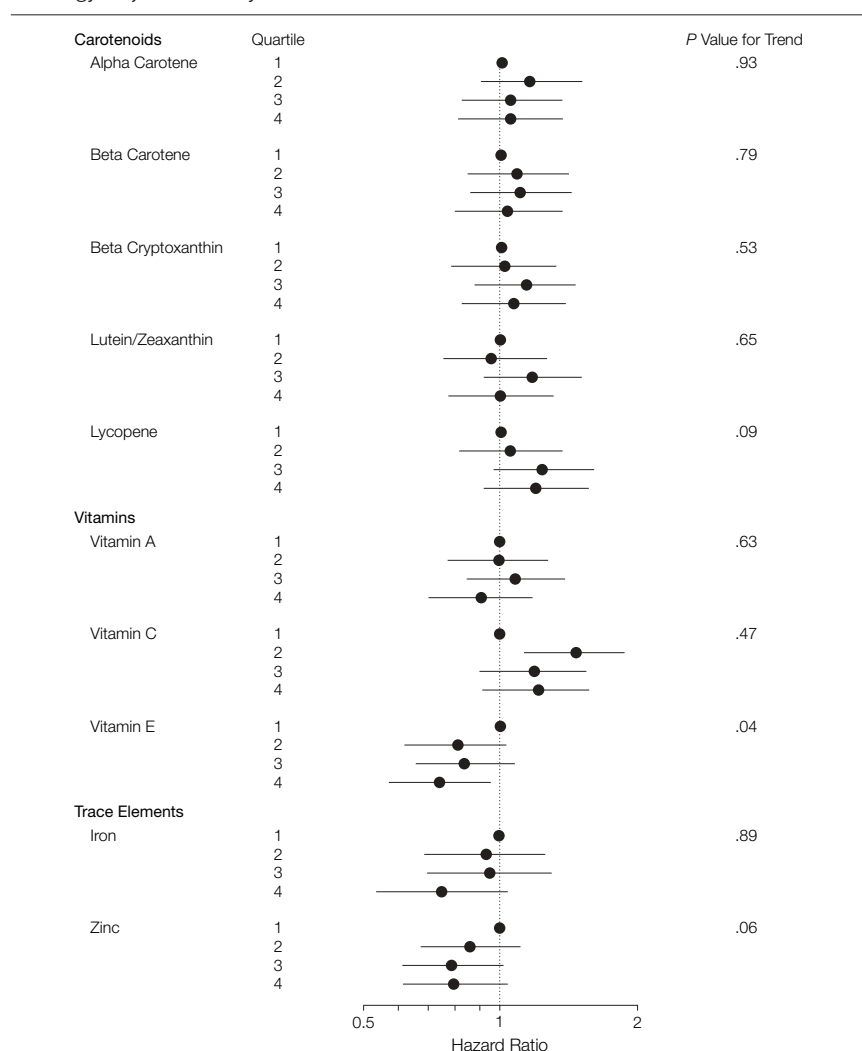
ments and AMD could not be examined because of the relatively small number of antioxidant supplement users in our population and the lack of data on duration and dosage of use.

Recent data suggest that oxidative protein modifications may play a critical role in the formation of drusen.²⁰ This implies that antioxidants may have their strongest effect at the initiation of the disease. We studied a cohort that was free of clinical signs of early-stage AMD at baseline, and our incident cases

were primarily affected by early AMD. Early-stage AMD, however, is a strong predictor of late-stage AMD.^{10,12} Exclusion of the 42 persons with incident late AMD did not change the results. We therefore conclude that dietary antioxidants may delay the development of early AMD and, possibly, of AMD in general.

Different antioxidants may act synergistically³; therefore, we studied the combined effect of nutrients and used the combination previously investi-

Figure. Hazard Ratios for Incident Age-Related Macular Degeneration by Quartile of Energy-Adjusted Dietary Intake of Antioxidant Carotenoids



Error bars indicate 95% confidence intervals. Adjusted for age, sex, body mass index, smoking status, pack-years of smoking, systolic blood pressure, atherosclerosis composite score, serum total cholesterol, and alcohol intake. The lowest quartile was considered the reference group. For each nutrient, the *P* value of the test for trend is given.

gated in AREDS.⁸ We observed a dose-response relationship with a mean intake of beta carotene, vitamins C and E, and zinc as reference. Persons with an above-median intake of these nutrients may be different in other aspects. This residual confounding is inherent to an observational study and can only be dealt with in a randomized trial. However, experimental studies with a randomized change in food consumption are difficult to perform.

Previous studies have shown variable degrees of protection against AMD by different antioxidants. Dietary in-

take of vitamin E was not associated with AMD risk in 1 case-control study in persons with neovascular late AMD⁴ but showed an inverse association with large drusen in a population-based study.⁷ A high intake of lutein and zeaxanthin was associated with a 40% lower risk of late AMD in 1 study⁴ but history of intake of these 2 nutrients was not associated in another study.⁷ A randomized controlled trial of vitamin E supplementation did not show an effect on the incidence of early AMD after 4 years of follow-up.²¹ An inverse association between zinc intake and both

prevalent and incident early AMD was reported in 1 population-based cohort study²² but could not be confirmed in another similar study^{23,24} or in a pooled study in which late AMD and visual acuity data were obtained by self-report.²⁵ In contrast with the aforementioned studies, our results were based on long-term follow-up of a large, population-based cohort with thorough baseline assessment of dietary intake.

Recently, a meta-analysis of 19 clinical trials including AREDS showed that high-dosage (≥ 400 IU/d) vitamin E supplementation may increase all-cause mortality.²⁶ This finding would challenge recommendations for supplement use.⁸ It should be noted that most trials were performed in patients with chronic diseases, in contrast with the general population in our study sample. The mean amount of vitamin E consumed in diet in the highest quartile of our cohort (20.2 mg/d [30 IU/d]) was still considerably lower than high-dose supplementation, and the bioavailability of dietary antioxidants may be different from that in supplements. Dietary replacement also may be less expensive than supplement use.

This study suggests that the risk of AMD can be modified by diet; in particular, by dietary vitamin E and zinc. A higher intake of vitamin E can be achieved by consumption of whole grains, vegetable oil, eggs, and nuts. High concentrations of zinc can be found in meat, poultry, fish, whole grains, and dairy products. Carrots, kale, and spinach are the main suppliers of beta carotene, while vitamin C is found in citrus fruits and juices, green peppers, broccoli, and potatoes. Based on this study, foods high in these nutrients appear to be more important than nutritional supplements. Until more definitive data are available, this information may be useful to persons with signs of early AMD or to those with a strong family history of AMD.²⁷ Although in need of confirmation, our observational data suggest that a high intake of specific antioxidants from a regular diet may delay the development of AMD.

Table 4. Risk of Age-Related Macular Degeneration by Category of Combined Intake of 4 Predefined Antioxidant Nutrients (Vitamins C and E, Beta Carotene, and Zinc)

	Category of Dietary Intake*		
	Low (n = 466)	Middle (n = 3270)	High (n = 434)
Cases of age-related macular degeneration, No. (%)	76 (16.3)	442 (13.5)	42 (9.7)
Hazard ratio (95% confidence interval)			
Unadjusted	1.31 (1.03-1.67)	1.00	0.65 (0.48-0.89)
Age- and sex-adjusted	1.23 (0.97-1.58)	1.00	0.68 (0.49-0.93)
Fully adjusted†	1.20 (0.92-1.56)	1.00	0.65 (0.46-0.92)

*Categories were defined by using the median energy-adjusted daily intake per nutrient as a cutoff value and classifying above-median intake of all nutrients as high intake and below-median intake of all nutrients as low intake. Cutoff values were 114 mg for vitamin C, 13 mg for vitamin E, 3.6 mg for beta carotene, and 9.6 mg for zinc.

†Adjusted for age, sex, body mass index, smoking status, pack-years of smoking, systolic blood pressure, atherosclerosis composite score, serum total cholesterol, and alcohol intake.

Table 5. Risk of Age-Related Macular Degeneration by Category of Combined Intake of 4 Predefined Antioxidant Nutrients (Vitamins C and E, Beta Carotene, and Zinc), Excluding Supplement Users and Stratified by Smoking Status

	Category of Dietary Intake*		
	Low n = 419	Middle n = 2816	High n = 376
Excluding supplement users			
Cases, No. (%)	67 (16.0)	396 (14.1)	37 (9.8)
HR (95% CI)†	1.11 (0.84-1.46)	1.00	0.62 (0.43-0.90)
Smoking status			
Never	n = 128	n = 1096	n = 160
Cases, No. (%)	17 (13.3)	144 (13.3)	16 (10.0)
HR (95% CI)‡	0.85 (0.48-1.50)	1.00	0.74 (0.42-1.31)
Former	n = 182	n = 1434	n = 193
Cases, No. (%)	31 (17.0)	199 (13.9)	18 (9.3)
HR (95% CI)‡	1.26 (0.84-1.99)	1.00	0.58 (0.34-0.98)
Current	n = 154	n = 727	n = 77
Cases, No. (%)	28 (18.2)	97 (13.3)	8 (10.4)
HR (95% CI)‡	1.44 (0.93-2.22)	1.00	0.65 (0.30-1.40)

Abbreviations: CI indicates confidence interval; HR, hazard ratio.

*Categories were defined by using the median energy-adjusted daily intake per nutrient as a cutoff value and classifying above-median intake of all nutrients as high intake and below-median intake of all nutrients as low intake. Cutoff values were 114 mg for vitamin C, 13 mg for vitamin E, 3.6 mg for beta carotene, and 9.6 mg for zinc.

†Adjusted for age, sex, body mass index, smoking status, pack-years of smoking, systolic blood pressure, atherosclerosis composite score, serum total cholesterol, and alcohol intake.

‡Adjusted for all of the above except smoking status and pack-years of smoking.

Author Contributions: Dr de Jong had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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