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Dietary nutrient intake and progression to late age-related macular degeneration in the Age-Related Eye Disease Studies 1 and 2

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Abstract

Purpose—To analyze associations between the dietary intake of multiple nutrients and risk of progression to late age-related macular degeneration (AMD) and its subtypes. Additional objectives were to analyze progression to large drusen and interactions with AMD genotype.

Design—Post hoc analysis of two controlled clinical trial cohorts: Age-Related Eye Disease Study (AREDS; recruitment 1992-8) and AREDS2 (recruitment 2006-8).

Participants—Eyes with no late AMD at baseline in AREDS participants (n=4,504) and AREDS2 participants (n=3,738): total of 14,135 eyes. Mean age was 71.0 years (SD 6.7); 56.5% were female.

Methods—Fundus photographs were collected at annual study visits and graded centrally for late AMD. Dietary intake of multiple nutrients was calculated for each participant from food frequency questionnaires.

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No conflicting relationship exists for any author.

Main outcome measures—Progression to late AMD, geographic atrophy (GA), neovascular AMD, and (separate analyses) large drusen.

Results—Over median follow-up of 10.2 years, of the 14,135 eyes, 32.7% progressed to late AMD. For nine nutrients, intake quintiles 4 or 5 (versus 1) were significantly (P≤0.0005) associated with decreased risk of late AMD: vitamins A, B6, and C, folate, β-carotene, lutein/zeaxanthin, magnesium, copper, and alcohol. For three nutrients, quintiles 4 or 5 were significantly associated with increased risk: saturated fatty acid, monounsaturated fatty acid, and oleic acid. Similar results were observed for GA. Regarding neovascular AMD, nine nutrients were nominally associated with decreased risk (vitamins A and B6, β-carotene, lutein/zeaxanthin, magnesium, copper, docosahexaenoic acid, omega-3 fatty acid, and alcohol) and three with increased risk (saturated fatty acid, monounsaturated fatty acid, and oleic acid). In separate analyses (n=5,399 eyes of 3,164 AREDS participants), 12 nutrients were nominally associated with decreased risk of large drusen.

Conclusions—Higher dietary intake of multiple nutrients, including minerals, vitamins, and carotenoids, is associated with decreased risk of progression to late AMD. These associations are stronger for GA, for which no treatments are available, than for neovascular AMD. The same nutrients tend also to have protective associations against large drusen development. Strong genetic interactions exist for some nutrient-genotype combinations, particularly omega-3 fatty acids and *CFH*. These data may justify further research into underlying mechanisms and randomized trials of supplementation.

Précis

Higher dietary intake of multiple nutrients (including specific vitamins, minerals, carotenoids, and fatty acids) was associated with decreased progression to late age-related macular degeneration, particularly geographic atrophy.

Introduction

Age-related macular degeneration (AMD) is the leading cause of legal blindness in developed countries.[1,2] It arises from a complex interplay between aging, genetics, and environmental factors, including dietary factors.[3-5] Late AMD, the stage with the potential for blindness, occurs in two forms: geographic atrophy (GA) and neovascular AMD. Neovascular AMD requires repeated intravitreal injection of anti-VEGF drugs, while no treatments are clinically available for GA, either to slow down enlargement or restore lost vision. Hence, preventative approaches are attractive for both subtypes of late disease.

Oral supplementation with specific combinations of antioxidants and minerals is known to decrease progression from intermediate to late AMD, particularly neovascular AMD.[6,7] However, it is possible that alternative or additional protection against progression to late AMD may be derived from specific nutrients or other bioactive ingredients in food, which may comprise additional modifiable risk factors for AMD. Some observational studies have observed that higher intakes of particular dietary nutrients are associated with decreased or increased risk of early or late AMD.[5,8,9] However, inconsistencies exist between some of these studies. The most consistent findings have included decreased risk of late AMD

associated with higher dietary intake of omega-3 fatty acids[10] and the carotenoids lutein and zeaxanthin.[11]

Recent analyses of the Age-Related Eye Disease Study (AREDS) and AREDS2 demonstrated that closer adherence to a Mediterranean dietary pattern, and to its fish component, were highly associated with decreased progression to late AMD, particularly GA.[12] Additional analysis of the biologically active nutrients may provide more insights into the molecular basis of disease, with implications for potential preventative strategies.

The AREDS and AREDS2 were multicenter phase III randomized clinical trials (RCT) designed to assess the effects of nutritional supplementation on AMD progression.[13,14] Their primary outcome was progression to late AMD. In both cases, validated food frequency questionnaires (FFQ) were applied at study enrollment, which allowed the estimation of dietary intake levels for multiple nutrients. This permits a broad and unbiased approach to analyzing potential relationships between dietary intake and AMD progression for many nutrients. Owing to the comprehensive nature of this approach, some findings may be novel and others may be consistent with those from previous studies.

The main aim of this study was to use data from the AREDS and AREDS2 to examine potential associations between the dietary intake of multiple nutrients and progression to late AMD, including separate analyses of GA and neovascular AMD. Additional aims included analyzing similar associations for the development of large drusen (using AREDS data) and examining potential interactions between nutrient intake levels and AMD genotype for progression to late AMD.

Methods

Study populations

The study designs for the AREDS and AREDS2 have been described previously.[13,14] In the AREDS, 4,757 participants (55-80 years) were recruited (1992-1998) at 11 US retinal specialty clinics and enrolled into AMD categories (no AMD to unilateral late AMD). In the AREDS2, 4,203 participants (50-85 years) with bilateral large drusen or unilateral late AMD were recruited (2006-2008) at 82 US retinal specialty clinics. Institutional review board approval was obtained at each site and written informed consent was obtained from all participants. The research was conducted under the Declaration of Helsinki and, for AREDS2, complied with the Health Insurance Portability and Accountability Act.

Study procedures

The AREDS participants were randomly assigned to placebo, antioxidants, zinc, or the combination. The RCT component lasted five years. The AREDS2 participants were randomly assigned to receive the supplements that lowered risk of AMD progression in the AREDS, either (i) alone, or with additional (ii) lutein/zeaxanthin, (iii) docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA), or (iv) the combination. Again, the RCT component lasted five years. In both studies, at baseline and annual visits, eye examinations were performed and color fundus photographs were captured and graded centrally at the University of Wisconsin Fundus Photograph Reading Center.[15]

In the AREDS, following close-out at five years, epidemiologic follow-up started immediately in 3,549 of the 4,203 surviving AREDS participants. In the AREDS2, following close-out at five years, 2,923 participants underwent reassessment at 10 years (AREDS2 10-year follow-on study). In the AREDS (for the duration) and the AREDS2 (for the first five years), progression to late AMD (including subtype of late AMD) was defined by fundus photograph grades and/or history of treatment for neovascular AMD, as described previously.[13,14] In brief, progression to late AMD was defined as an eye that did not have late AMD at study baseline but did have late AMD at a follow-up study visit. Late AMD was defined as the presence of GA (central or non-central) on fundus photography, neovascular AMD on fundus photography, or a history of treatment for neovascular AMD. In the AREDS, GA and neovascular AMD were assessed independently. Thus, if an eye progressed to neovascular AMD, it was still assessed for additional progression to GA at subsequent study visits (and vice versa). By contrast, in the AREDS2, this was not the case. In the AREDS2, if an eye progressed to GA, it was still assessed for additional progression to neovascular AMD; however, if an eye progressed to neovascular AMD, it was no longer assessed for additional progression to GA. Similarly, progression to large drusen was defined as an eye that did not have either late AMD or large drusen at study baseline but did have large drusen at a follow-up visit (by reading center grading of fundus photographs). No reversal was possible for any outcome. For example, if an eye progressed to GA during follow-up, subsequent grades of GA presence/absence for the same eye did not contribute to the analyses. In the AREDS2, for eyes with no late AMD at the five-year close-out, progression to late AMD by 10 years was defined (without subtype analysis) as described in the Supplement.

Assessment of the intake of dietary nutrients

In both studies, FFQs were administered to all participants at randomization. The AREDS FFQ, a 90-item, semi-quantitative modified Block FFQ, and its validation, have been described previously.[16] The AREDS2 FFQ, a 131-item, semi-quantitative Harvard FFQ, and its validation, have also been described previously.[17,18] In both FFQs, participants were asked how often, on average, they had consumed each food/beverage item during the preceding year. The FFQs were processed at the University of Minnesota Nutrition Coordinating Center to estimate, for each participant, the daily dietary intake of 38 nutrients in the AREDS and 44 nutrients in the AREDS2. In the AREDS, these estimates excluded any additional intake from oral supplements. The same was true for the majority of nutrients in AREDS2. However, for a minority of nutrients in AREDS2 (α-carotene, β-cryptoxanthin, lutein/zeaxanthin, lycopene, selenium, and those related to fatty acids, including DHA and EPA), the estimates included any additional intake from oral supplements. Each nutrient was divided by total calorie intake to represent nutrient intake density and intake quintiles were calculated (separately for each cohort and for men and women), with quintile 5 representing highest intake. Quintiles were used in order to provide easily interpretable hazard ratios.

Genotype analysis

As part of AREDS and AREDS2, 2,889 (AREDS) and 1,826 (AREDS2) participants consented to genotype analysis. SNPs were analyzed using a custom Illumina HumanCoreExome array.[19] The AMD Genetic Risk Score (GRS), a weighted risk score for

late AMD, was calculated for each participant.[19] Four SNPs at three loci (with highest attributable risk of late AMD) were also selected: *ARMS2* rs10490924, *CFH* rs10922109 and rs1061170, and *C3* rs2230199.

Participant cohorts and statistical methods

The eligibility criteria were: eyes without late AMD at baseline in participants with at least two study visits. In the combined AREDS/AREDS2 cohort, for each of the 33 nutrients where intake was measured in both AREDS and AREDS2, multivariable proportional hazards regression analyses were performed for the outcomes of progression to late AMD, GA, and neovascular AMD, according to intake quintiles (with quintile 1 as the reference). P-trend values were calculated by regression using the energy-adjusted nutrient intake values (as continuous variables). The proportional hazards assumption was tested in all cases. In the one situation where the assumption was not met (for the cohort variable in the combined cohort analysis of neovascular AMD), stratified proportional hazards regression was performed instead.[20] These analyses were repeated for the individual AREDS (38 nutrients) and AREDS2 (44 nutrients) cohorts, considered separately. The Bonferroni level of significance was P=0.0005 for the combined cohort. We considered that P-values higher than that level could be due to chance, given the large number of analyses; however, we did not disregard these associations, as higher P-values for individual nutrients could also reflect how well dietary intake of those nutrients was captured on FFQs and the limitations of nutrient databases, rather than their physiological importance.

The regression analyses were also performed with (i) adjustment for treatment assignment (i.e., the oral supplements or placebo to which the participants were randomized), and (ii) including the interaction term between nutrient intake (treated continuously) and treatment assignment. In AREDS, this included antioxidants as main effect and zinc as main effect and, in AREDS2, this included DHA/EPA as main effect and lutein/zeaxanthin as main effect. For these analyses, follow-up was limited to the duration of the treatment assignment (five years). The regression analyses were also repeated with adjustment for Centrum multivitamin use (in AREDS only, since Centrum use was almost universal in AREDS2).

In the AREDS, similar analyses were performed for the outcome of progression to large drusen. For these analyses, the eligibility criteria were: eyes without large drusen or late AMD at baseline in participants with at least two study visits.

For the nutrients with P≤0.01 for altered progression to late AMD outcomes in quintile 4 or 5 (versus 1), the regression analyses were repeated including the interaction term between nutrient intake (treated continuously) and genotype. For the nutrient-genotype combinations with P-interaction≤0.01, the regression analyses were performed separately for each level of the genetic characteristic.

In all cases, the unit of analysis was the eye and the analyses were adjusted for age, sex, smoking, total calorie intake, body mass index (BMI, for AREDS only), and correlation between eyes. Age, smoking, and BMI were included as risk factors known to be associated with progression to late AMD.[21,22] Sex was included as an important biological variable. Total calorie intake was included to decrease confounding and reduce extraneous variation

from factors like physical activity and metabolic efficiency.[23,24] Age and total calorie intake were treated as continuous variables, while sex, smoking (assessed by self-report), and BMI were treated as categorical variables (as defined in Table 1). Adjustment for correlation between eyes was made in SAS by using the robust sandwich estimate for the covariance matrix in the Wald tests.[25] In analyses of the combined AREDS/AREDS2 cohort, adjustment was also made for the cohort. In order to avoid overadjustment, baseline AMD severity was not included in the models, since it was highly associated with intake for most nutrients; however, additional analyses were conducted where eyes with baseline AMD severity 1-6 versus 7-8 on the AREDS 9-step scale[26] were considered separately.

In order to aid interpretation of the results, correlation analyses were conducted to explore potential correlations between the intake of each nutrient and every other nutrient, using the Pearson correlation coefficient. All analyses were conducted using SAS version 9.4 (SAS Institute Inc.).

Results

Participant cohorts: baseline characteristics

The combined AREDS/AREDS2 cohort contained 14135 eligible eyes of 8130 participants. Their characteristics are shown in Table 1 and their dietary intake in Supplementary Tables 1 and 2. The numbers of eyes that progressed to late AMD, GA, or neovascular AMD by final follow-up (median 10.2 years) were 4624 (32.7%), 2246 (16.1%), and 2100 (14.9%), respectively. Considered separately, the AREDS cohort comprised 8,235 eyes of 4,504 participants and the AREDS2 cohort comprised 6,111 eyes of 3,738 participants. The numbers of eyes that progressed to late AMD were 1744 (21.2%; median follow-up 10.1 years) and 2914 (47.7%; median follow-up 10.4 years), respectively.

For the analyses of progression to large drusen in the AREDS, the cohort contained 5399 eligible eyes of 3164 participants. In this cohort, the number of eyes that progressed to large drusen by final follow-up (median 10.1 years) was 1431 (26.5%).

Proportional hazards regression analyses: progression to late age-related macular degeneration according to the intake of individual dietary nutrients

The results of the proportional hazards regression analyses in the combined AREDS/AREDS2 cohort are shown in Figure 1 and Table 2. The proportional hazards assumptions were met in all cases; the only exception was for the cohort variable in the combined cohort analysis of neovascular AMD so, for these analyses, the results of stratified proportional hazards regression are shown instead. Regarding progression to late AMD, for nine of the 33 nutrients examined, intake quintile 4 and/or 5 (with quintile 1, indicating lowest intake, as reference) was significantly associated with decreased risk at the Bonferroni-adjusted level of P=0.0005: vitamin A, vitamin B6, vitamin C, folate, β-carotene, lutein and zeaxanthin, magnesium, copper, and alcohol. For an additional eight nutrients, association with decreased risk was present at the nominal level (P>0.0005 and <0.05): thiamine, niacin, β-cryptoxanthin, calcium, iron, DHA, EPA, and omega-3 fatty acids (DHA and EPA). Conversely, for three of the nutrients, intake quintile 4 and/or 5 was significantly associated

with increased risk of late AMD at the Bonferroni-adjusted level: total saturated fatty acid, total monounsaturated fatty acid (MUFA), and oleic acid. For an additional two nutrients, association with increased risk was present at the nominal level: cholesterol and linoleic acid.

Regarding progression to GA, for seven nutrients, intake quintile 4 and/or 5 was significantly associated with decreased risk at the Bonferroni-adjusted level: vitamin A, vitamin C, folate, β-carotene, magnesium, copper, and alcohol. For an additional 13 nutrients, association with decreased risk was present at the nominal level: thiamin, riboflavin, niacin, vitamin B6, vitamin B12, β-cryptoxanthin, lycopene, calcium, iron, zinc, DHA, EPA, and omega-3 fatty acids. Conversely, for two of the nutrients, intake quintile 4 and/or 5 was significantly associated with increased risk at the Bonferroni-adjusted level: saturated fatty acid and oleic acid. For an additional two nutrients, association with increased risk was present at the nominal level: MUFA and linoleic acid.

For progression to neovascular AMD, no nutrients had intake quintile 4 and/or 5 significantly associated with altered risk at the Bonferroni-adjusted level. For nine nutrients, association with decreased risk was present at the nominal level: vitamin A, vitamin B6, β-carotene, lutein and zeaxanthin, magnesium, copper, DHA, omega-3 fatty acid, and alcohol. Conversely, for three nutrients, association with increased risk was present at the nominal level: saturated fatty acid, monounsaturated fatty acid, and oleic acid.

The proportional hazards regression analyses were also performed separately on the AREDS cohort alone and the AREDS2 cohort alone. The results are shown in Figures 2 and 3, and in Supplementary Table 3. Of note, in the AREDS2, higher intake of the ‘DHA+DPA+EPA’ variable was significantly associated with decreased risk of GA, with low hazard ratios, but not neovascular AMD. Intake of this variable was not measured in the AREDS (so is not included in the results of the combined cohort). In addition, the results for DHA, EPA, and ‘DHA+EPA’ (considered separately) were each significant in the AREDS (associated with decreased risk of late AMD, GA, and neovascular AMD) but not in the AREDS2. This may relate to the fact that DHA and EPA supplementation was assigned to half of the AREDS2 participants, and/or other reasons discussed in detail below, including the potential importance of docosapentaenoic acid (DPA) and/or very long-chain polyunsaturated fatty acids (VLC-PUFAs).

The analyses of the AREDS cohort alone were repeated separately for eyes with baseline AMD severity 1-6 versus 7-8 on the AREDS 9-step scale (Supplementary Figure 1). In general, for most nutrients with protective associations, the hazards ratios were stronger (further from one) and the P-values more highly significant in the eyes with baseline severity 1-6, while the hazard ratios were generally weaker (closer to one) and the P-values less highly significant in the eyes with baseline severity 7-8. This was particularly true for DHA and EPA for the outcomes of late AMD and neovascular AMD.

Further analyses that included adjustment for treatment assignment demonstrated very similar results to the original analyses, for both the AREDS and AREDS2 cohorts considered separately. In addition, analyses that included the interaction term between

nutrient intake and treatment assignment showed no significant interactions at the Bonferroni-adjusted level. Additional sensitivity analyses that included adjustment for Centrum multivitamin use in the AREDS cohort also demonstrated very similar results to the original analyses.

Proportional hazards regression analyses: progression to large drusen according to the intake of individual dietary nutrients

Proportional hazards regression analyses were performed for progression to large drusen using those eyes in the AREDS cohort without large drusen or late AMD at study baseline. The results are shown in Figure 2 and Table 3. The proportional hazards assumptions were met in all cases. Of the 38 nutrients examined, none had intake quintile 4 and/or 5 significantly associated with either decreased or increased risk at the Bonferroni-adjusted level. For 12 nutrients, association with decreased risk was present at the nominal level: vitamin A, retinol, β-carotene, lutein and zeaxanthin, folate, copper, magnesium, DHA, omega-3 fatty acid, galactose, lactose, and insoluble dietary fiber. Conversely, for three nutrients, association with increased risk was present at the nominal level: saturated fatty acid MUFA, and cholesterol. Further analyses that included adjustment for treatment assignment demonstrated very similar results to the original analyses; additional analyses that included adjustment for Centrum multivitamin use were also very similar.

Genetic interactions with nutrient intake

For the eligible nutrients, analyses of interactions between nutrient intake and genotype were performed for the three late AMD outcomes and for progression to large drusen. The number of nutrient-genotype combinations with P-interaction≤0.01 was nine in the AREDS and two in the AREDS2. For these 11 nutrient-genotype combinations, proportional hazards regression analyses were performed separately for each level of the genotype. The results are shown in Table 4. In the AREDS, regarding late AMD and GA, the combinations with significant results were DHA and/or EPA with *CFH* genotype. By contrast, the relevant combinations for neovascular AMD were DHA and/or EPA with *ARMS2* genotype. For late AMD and GA, higher DHA and/or EPA intake was associated with decreased risk preferentially in participants with low risk genotypes at *CFH*. For example, for late AMD, in those with a protective allel at *CFH*, the hazard ratio associated with highest DHA intake was 0.45 (95% CI 0.30-0.67; p<0.0001). By contrast, in those without protective alleles at *CFH*, no decreased risk was observed with high DHA intake. For neovascular AMD, higher DHA and/or EPA intake appeared associated with decreased risk preferentially in participants with low risk genotypes at *ARMS2*, though the results were less consistent.

Correlations between the dietary intake of different nutrients

Pearson correlation coefficients were calculated for the dietary intake of each nutrient and every other nutrient, in order to aid interpretation of the results. The results are shown in Supplementary Table 4.

Discussion

Main findings and interpretation

A detailed interrogation of multiple nutrients in the AREDS and AREDS2 has strengthened previous evidence for protective associations between the dietary intake of specific nutrients and risk of late AMD. In addition, it has suggested new associations with nutrients that might be studied further in observational cohorts and trials. Few previous studies have performed broad analyses of the relationships between dietary intake and risk of progression to late AMD using prospectively obtained data for a wide range of nutrients. However, multiple reports have investigated particular nutrients. This literature has been reviewed in detail.[5,8] As discussed below, the most consistent findings from previous prospective studies have been for DHA/EPA and lutein/zeaxanthin.

In the current study, multiple dietary nutrients were associated with lower risk for progression to late AMD. This included higher intake of omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs), minerals (e.g., copper, magnesium, and selenium), B vitamins, and antioxidant carotenoids (e.g. vitamin C, β-carotene, and lutein/zeaxanthin), and lower intake of saturated and monounsaturated fats. These findings were generally robust to sensitivity analyses. Most of these associations (except those for MUFA, discussed below) contribute to mounting evidence that a Mediterranean-like diet pattern[27], or the intake of certain individual food components[28], is associated with decreased incidence of late AMD. Indeed, the results are consistent with a recent report (using the same AREDS/AREDS2 cohorts), which showed that adherence to a Mediterranean-like diet pattern, and its individual components, was associated with decreased progression to late AMD.[12]

Fish, fatty acids, and omega-3 long-chain polyunsaturated fatty acids

One of the components of the Mediterranean diet pattern consistently linked to decreased late AMD is fish. A growing body of evidence suggests that these associations may be explained in part by the omega-3 LC-PUFAs found in fish: LC-PUFA intake has been related to lower risk of AMD in many, but not all, previous observational studies.[10,28-40] A meta-analysis in 2008 found that the highest dietary intake quintile of omega-3 LC-PUFAs had an odds ratio of 0.62 for late AMD.[10] In subsequent reports, a cohort study in Australia found no association, though power was low.[40] A cohort study of health professional in the USA found no significant association between dietary DHA/EPA and visually significant late AMD[34]; however, the results of the current study (in which the associations were much stronger for GA) may be relevant, in that 96% of the events captured in the Health Professionals Study were neovascular AMD. Indeed, another cohort study of health professionals in the USA observed significant association between DHA, EPA, and omega-3 LC-PUFA intake and decreased risk of visually significant AMD.[33]

The results of clinical trials of specific omega-3 LC-PUFAs have also been conflicting (as reviewed previously[41]). The AREDS2 comprised an RCT to evaluate the effect of adding 350mg DHA and 650mg EPA to the original AREDS formulation.[42] No significant risk reduction was observed. The negative results of this trial need to be contrasted with the positive results suggested by observational studies, and one previous smaller trial.[43] One

explanation could be differences in the dietary intake of omega-6 fatty acids (e.g. arachidonic and linoleic acids). High omega-6 fatty acid intake inhibits the anti-inflammatory effects of omega-3 LC-PUFAs, since they compete for the same enzymes in the cyclooxygenase and lipoxygenase pathways. The products of these pathways also differ: the omega-3 LC-PUFAs produce anti-inflammatory and anti-angiogenic metabolites, whereas the omega-6 fatty acids produce pro-inflammatory[44] and pro-angiogenic[45] metabolites. In addition, blood and retinal levels of omega-3 and omega-6 fatty acids, and their relation to disease, may also depend on genetic polymorphisms (e.g. in the elongase genes of the *ELOVL* family and the desaturase genes *FADS1* and *FADS2*[46]).

It is also possible that nutrients other than DHA and EPA, but closely related to them, may be responsible. These might include DPA, VLC-PUFAs, or other unknown nutrients often consumed alongside DHA and EPA (presumably in fish) but not present in high concentrations in the AREDS2 DHA/EPA formulation. Fish is a major source of DPA. DPA can be a precursor for EPA, DHA, and other anti-inflammatory lipids.[47] Moreover, dietary fish oils, including DPA[47], DHA, and EPA, can be precursors for VLC-PUFAs[38], which also have anti-inflammatory properties. VLC-PUFAs must be obtained from the diet (as they cannot be synthesized *de novo* in humans) and were not present in the AREDS2 DHA/EPA formulation. Interestingly, retinal membranes have a very high content of omega-3 VLC-PUFAs, and lower levels have been reported in the retinal tissue of eyes with AMD.[38]

B vitamins

The protective associations observed between DHA/EPA intake and late AMD in the current study might also reflect, in part, the effects of other nutrients present in fish. For example, fish contains large quantities of B vitamins.[48] This idea is supported by significant correlations (Pearson rho 0.3-0.4; $P<0.001$) between the intake of DHA and of several B vitamins (e.g. niacin, folate, and vitamins B6 and B12) in the combined AREDS/AREDS2 cohort. However, the protective associations between B vitamins and late AMD persisted after adjusting for DHA intake. Interestingly, a previous RCT containing three of these (folic acid and vitamins B6 and B12) observed a 34% reduction in incident late AMD.[49] Several prospective observational studies also suggest that some of these B vitamins may have protective associations, but the evidence is conflicting.[32,50-53]

A mechanism by which adequate intake of folic acid and vitamins B6 and B12 might protect against AMD could be through prevention of elevated serum homocysteine. Homocysteine accumulates when B vitamin cofactors are missing for enzymes that catalyze intracellular reactions in amino acid and nucleotide metabolism. High serum homocysteine is an independent risk factor for neurodegenerative and cardiovascular diseases and has been associated with AMD.[54,55] However, the association appears complex and in one meta-analysis was limited to neovascular AMD.[55] This complexity might be explained by the variable status of the three B vitamin cofactors, other B vitamins, or common variants in methylenetetrahydrofolate reductase, a key enzyme in the conversion of homocysteine to methionine.[51,56]

A protective association between folate intake and progression to GA, but not neovascular AMD, was previously reported in a subset of the AREDS cohort.[53] The results of the current

analyses were consistent between AREDS and AREDS2. Indeed, the results of the current analyses extend the evidence to include lower risk for the development of large drusen. However, in these cohorts, the associations of folate cannot be disentangled from those with other B vitamins and minerals (e.g. iron, magnesium, and zinc), given high levels of correlation between their intakes (Pearson rho > 0.6). This may reflect the fact that fortified breakfast cereals and green vegetables usually contain high levels of both folate and these B vitamins and minerals.

Minerals

The intake of minerals present in fish might also explain, in part, the protective associations observed between omega-3 PUFA intake and late AMD. Several minerals, also associated with decreased late AMD (copper, iron, magnesium, and selenium), had intake levels correlated with DHA and EPA intake (Pearson rho 0.3-0.4; P<0.001). Following adjustment for DHA or EPA intake, the associations between these minerals and decreased late AMD persisted in most cases.

Antioxidants

Fruits and vegetables contain abundant antioxidant nutrients associated with decreased late AMD in the combined cohort. This includes vitamin C, pro-vitamin A carotenoids (α-carotene, β-carotene, and β-cryptoxanthin) and lutein/zeaxanthin. A large body of evidence in other prospective studies is consistent with lower risk for AMD among those with higher intake of these.[5,9] Higher lycopene intake was also associated with decreased GA in the current study. Lycopene has not been observed in the retina and the association might reflect the intake of other phytochemicals found in lycopene-rich foods. For example, tomatoes are rich in lycopene but also an important source of nitrates. Indeed, previous studies have observed decreased incidence of AMD and glaucoma in individuals with higher intake of nitrates.[57,58]

Carotenoids: lutein/zeaxanthin

Multiple studies have observed that higher dietary intake of lutein/zeaxanthin is associated with decreased prevalence or incidence of late AMD[11,59-63], consistent with the results from the current study. A meta-analysis in 2012 found that high lutein/zeaxanthin intake had an odds ratio of 0.74 for late AMD.[11] In a subsequent cohort study of US health professionals, high dietary and supplement-based lutein/zeaxanthin intake was associated with decreased risk of visually significant late AMD (representing over 96% neovascular AMD).[59] A similar pattern of results was observed for other carotenoids including β-cryptoxanthin, α-carotene, and β-carotene. These findings are broadly consistent with the results of the current study, though their results would likely have differed if they had been able to identify incident GA cases. Finally, high quality evidence for the effects of lutein/zeaxanthin comes from the AREDS2 RCT.[42] Adding lutein and zeaxanthin (10 mg and 2 mg, respectively) to the original AREDS formulation caused a borderline significantly decreased risk of progression to advanced AMD.

Monounsaturated fatty acid

MUFA intake was related to higher risk for progression to late AMD in the combined cohort and AREDS alone. Associations between MUFA intake and AMD in previous observational studies have been inconsistent. US cohorts have generally demonstrated positive associations between MUFA intake and AMD[64-66], while southern European cohorts have generally demonstrated negative associations.[40,67,68] These inconsistencies may reflect whether MUFA sources are from animal or plant foods and from high or low nutrient-dense foods. In the US and northern European countries, the primary sources of MUFA are meat, dairy, and sugary foods, which are high in saturated fats and low in nutrient density.[69,70] Two other studies reported positive associations between MUFA intake and AMD[71,72]; however, these associations were reversed following adjustment for other dietary fats that were substantial sources of energy (i.e. PUFAs and saturated fatty acids). In the present study, MUFA intake was highly correlated with saturated fat intake (Pearson's rho > 0.7–0.8), suggesting that it may have come principally from meat and dairy food. Clinical trials indicate that replacing saturated fatty acid and carbohydrates with MUFA intake from plant and animal sources has beneficial effects on cardiovascular disease risk factors that have been related to AMD.[73]

Age-related macular degeneration stages and subtypes

Subtype analysis of late AMD outcomes revealed overlapping but partially distinct results for GA and neovascular AMD. In general, more nutrients holding significant associations with decreased risk were observed for GA than for neovascular AMD. Of the nine nutrients significantly associated with decreased risk of late AMD, the majority were associated with decreased risk both of GA (either at the Bonferroni or the nominal level) and of neovascular AMD (at the nominal level). Conversely, of the nine nutrients nominally associated with decreased risk of neovascular AMD, the majority were also associated with decreased risk of GA. Overall, these findings suggest some pathophysiological pathways that are common to both GA and neovascular AMD and other pathways that are partially distinct. Interestingly, the results contrast sharply with those for the AREDS and AREDS2 supplements. In the current study, the associations were generally strongest for protection against GA, whereas the AREDS/AREDS2 supplements preferentially decrease the risk of neovascular AMD.[6,7] Hence, diet and oral supplementation might potentially play complementary rather than competitive roles in decreased the risk of late AMD.

The pattern of results observed in the AREDS and AREDS2 cohorts, considered separately, was relatively similar. This was despite the substantial differences between the two cohorts, including decade of study, participant age, genetic risk profile, dietary habits, FFQ used, as well as the very high level of baseline disease severity in AREDS2. However, the levels of significance observed were generally higher in AREDS than AREDS2. For example, of the nutrients with significant associations at the Bonferroni level in the combined cohort, many had associations at the Bonferroni level in the AREDS and at the nominal level in the AREDS2; almost all had at least nominal associations in both cohorts, in the same direction. The likely reasons for the differences and the generally higher level of significance observed in AREDS than AREDS2 may include: (i) the substantially higher proportion of participants with relatively advance AMD at study baseline in AREDS2, (ii) the higher median GRS in AREDS2 participants[21], (iii) differences in food items listed on the FFQs and the underlying

databases, and (iii) the fact that AREDS2 participants appear to have been better nourished at baseline than those in AREDS (e.g., substantially higher intakes of DHA, EPA, and ALA omega-3 fatty acids).

In general, the results did not differ substantially according to treatment assignment group in either AREDS or AREDS, and no significant interactions were observed between nutrient intake and the treatment assignment. Hence, the protective associations between the intake of these nutrients and progression to late AMD appear to be largely independent of any of the oral supplements administered in either study, comprising antioxidants, zinc, lutein/zeaxanthin, and DHA/EPA. Similarly, the results were not affected by multivitamin intake in AREDS participants and persisted despite almost universal multivitamin intake in AREDS2 participants.

Regarding progression to large drusen, no nutrients demonstrated associations between higher intake and altered risk that were significant at the Bonferroni level. This presumably relates partly to the relatively low number of progression events, as expected for this earlier stage of a chronic age-related disease that takes decades to manifest. However, multiple nutrients had associations with decreased risk that were nominally significant. For some of these nutrients, this evidence was supported by nominal association for multiple quintiles (e.g., for folate, insoluble fiber, and lutein/zeaxanthin) or nominal associations with low hazard ratios in analyses as continuous variables (e.g., for copper and magnesium). The genuine existence of decreased risk of drusen progression through specific dietary nutrients would be an important finding since, aside from smoking cessation, no interventions are available to decrease progression to this highly prevalent disease stage. Of interest, recent analyses of the same dataset revealed an association between a Mediterranean dietary pattern and decreased risk of large drusen formation.[12]

It is interesting to examine to what extent the associations with progression to late AMD were similar or different to those with progression to large drusen. Overall, the pattern was similar. Of the 12 nutrients and molecules nominally associated with decreased risk of large drusen, all except one (lactose) were also associated (at least nominally) with decreased risk of late AMD. Conversely, of the nine nutrients significantly associated (at the Bonferroni level) with decreased risk of late AMD in the combined cohort, all except two (alcohol and vitamin C) were also nominally associated with decreased risk of large drusen. In addition, the lipid nutrients associated with increased risk of late AMD were similar to those associated with increased risk of large drusen. Further studies will be required to examine more clearly the potential for nutrients selectively associated with decreased or increased progression risk in a stage-specific manner.

Interactions with genotype

Importantly, the genetic analyses revealed strong interactions between omega-3 LC-PUFA intake and *CFH* genotype in AREDS. The association between higher intake and decreased late AMD and GA was found only in those with low risk genotypes at *CFH*. Equivalent results were recently observed in analyses of the AREDS at the level of food components: similarly, a very strong interaction was observed between fish intake and *CFH* genotype.[12]

Regarding underlying mechanisms, oxidized lipids such as malondialdehyde (MDA) accumulate in the retina in AMD, through oxidative stress, where they tend to provoke chronic local complement activation and inflammation.[74,75] CFH binds these oxidized lipids and is thought to block the proinflammatory effects. However, the AMD-associated CFH variant (402H) binds very poorly to MDA.[74] Hence, it is possible that CFH-directed AMD may arise through either a high risk *CFH* genotype (causing poor CFH binding to oxidized lipids like MDA) and/or low omega-3 LC-PUFA or VLC-PUFA levels in the retina (perhaps leading to stronger complement activation). By contrast, the combination of a low risk *CFH* genotype and high omega-3 LC-PUFA or VLC-PUFA levels in the retina might be strongly protective against local complement activation, which would explain the very low risk of late AMD and GA observed in these individuals.

Clinical implications

The dietary nutrient intake levels observed to have protective associations against progression to late AMD can be examined in Supplementary Table 2, where they are displayed by quintile levels. On comparison with the Institute of Medicine Recommended Dietary Allowances (RDAs)[76,77], different patterns emerged. For some vitamins and minerals (e.g. magnesium), individuals with dietary intakes meeting the RDAs would achieve the intake levels that had protective associations in this study (e.g. quintile 4). However, for other vitamins and minerals (e.g. vitamins B6 and C), the RDA levels fell modestly short of the intake levels with protective associations, i.e. individuals with dietary intakes at the RDA levels would not achieve the intake levels that had protective associations in this study. For other nutrients (e.g. lutein/zeaxanthin), no RDA is available. Further information on the food sources of these nutrients is available from the National Institutes of Health Office of Dietary Supplements.[78] Given that this was a post hoc study of nutrient intake from dietary sources, we strongly recommend that individuals should not use the results to take nutritional supplements that have not undergone explicit testing of safety and efficacy by RCT. In addition, we strongly recommend that individuals should not consume nutritional supplements at levels higher than the Institute of Medicine Tolerable Upper Intake Levels.[76,77]

Strengths and limitations

The combined use of two datasets, both with large size and long follow-up, is an important strength in this study. The datasets benefit from standardized collection of information and reading center grading. Limitations include *post hoc* hypothesis generation, the possibility of residual or unmeasured confounding (e.g. physical activity), and differences in variables between the cohorts (e.g. BMI). In addition, diet assessment by FFQ is known to contain non-differential measurement error, though energy adjustment may partially address this error.[79,80] Because of inherent differences in the FFQs used in AREDS and AREDS2, the assignment of food items to the nutrients analyzed had some differences between AREDS and AREDS2. Since genetic data were not available in many participants, the main analyses were not adjusted for the GRS. The study may have limited generalizability to populations where diets and genotypes differ. Owing to the high degree of multiple testing, the results were presented according to Bonferroni levels of significance. However, the results with

nominal significance may also be relevant, so were indicated separately. Of course, replication in prospective studies is important.

Conclusions

For multiple nutrients, higher dietary intake is associated with decreased risk of progression to late AMD. This includes nutrients in diverse classes, such as minerals, vitamins, and carotenoids. These associations apply to both subtypes of late AMD, but are particularly strong for GA, for which no treatments are currently available. Since AREDS/AREDS2 supplements are protective against neovascular AMD preferentially, diet and oral supplementation may play complementary roles. For several nutrients (especially unsaturated and monounsaturated fats), higher intake is associated with increased risk of late AMD. The nutrients with protective associations against late AMD also tend, with a weaker level of evidence, to have protective associations against the development of large drusen. If genuine, this is important, since very few interventions are available to slow progression to this highly prevalent disease stage. For progression to late AMD and GA, strong genetic interactions exist for some nutrient-genotype combinations, particularly between omega-3 LC-PUFA intake and *CFH* genotype. This may provide important insights into the underlying biological pathways. Further research may shed light on the underlying mechanisms. In addition, these data may justify the organization of an RCT in which particular nutrients are tested in oral supplements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
BMI	body mass index
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid

FFQ	food frequency questionnaire
GA	geographic atrophy
GRS	genetic risk score
LC-PUFA	long-chain polyunsaturated fatty acids
MUFA	monounsaturated fatty acid
RCT	randomized controlled trial
RDA	recommended daily allowance
SD	standard deviation
VLC-PUFA	very long-chain polyunsaturated fatty acids

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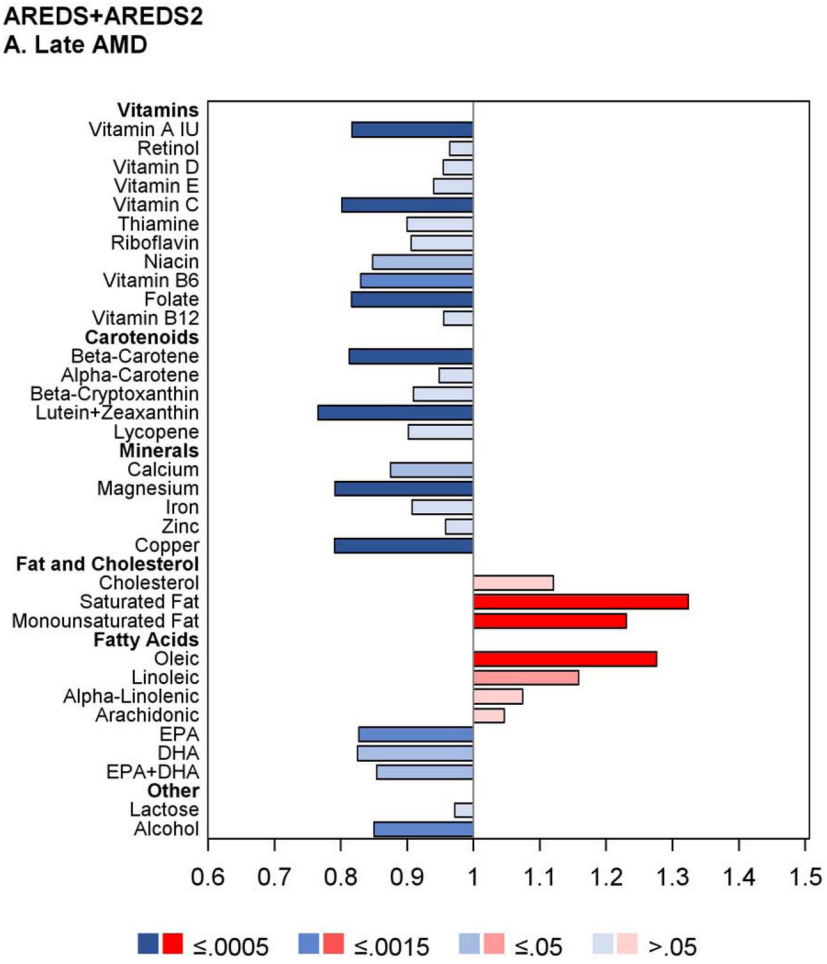
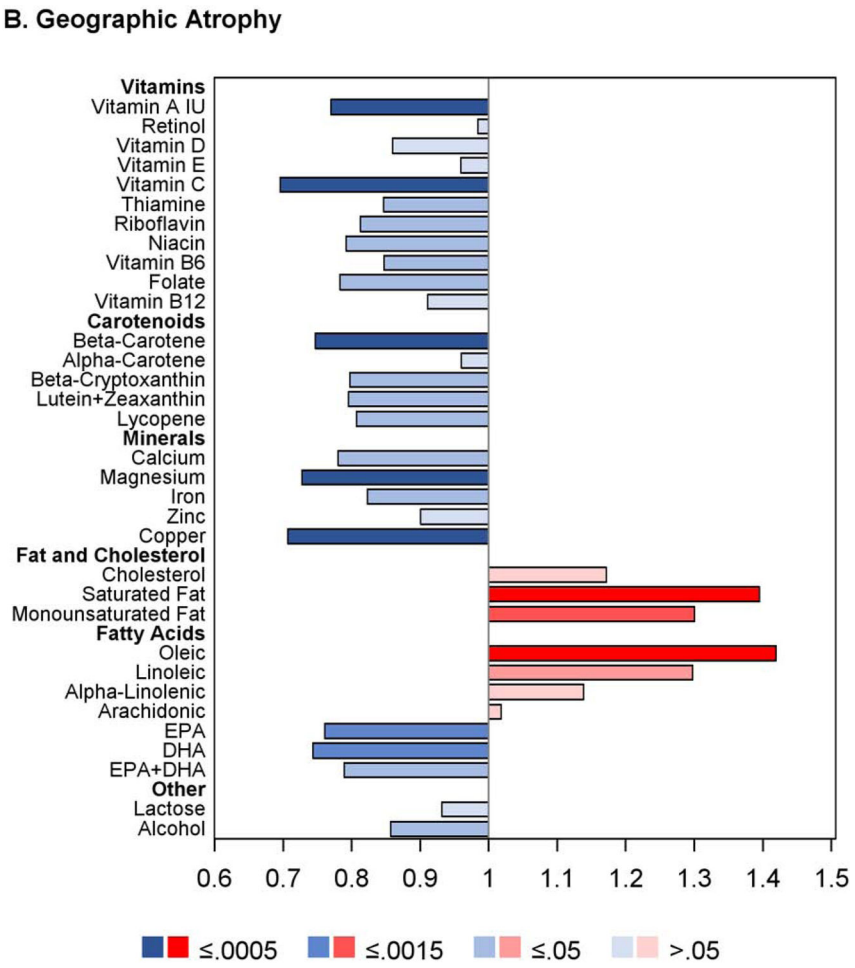




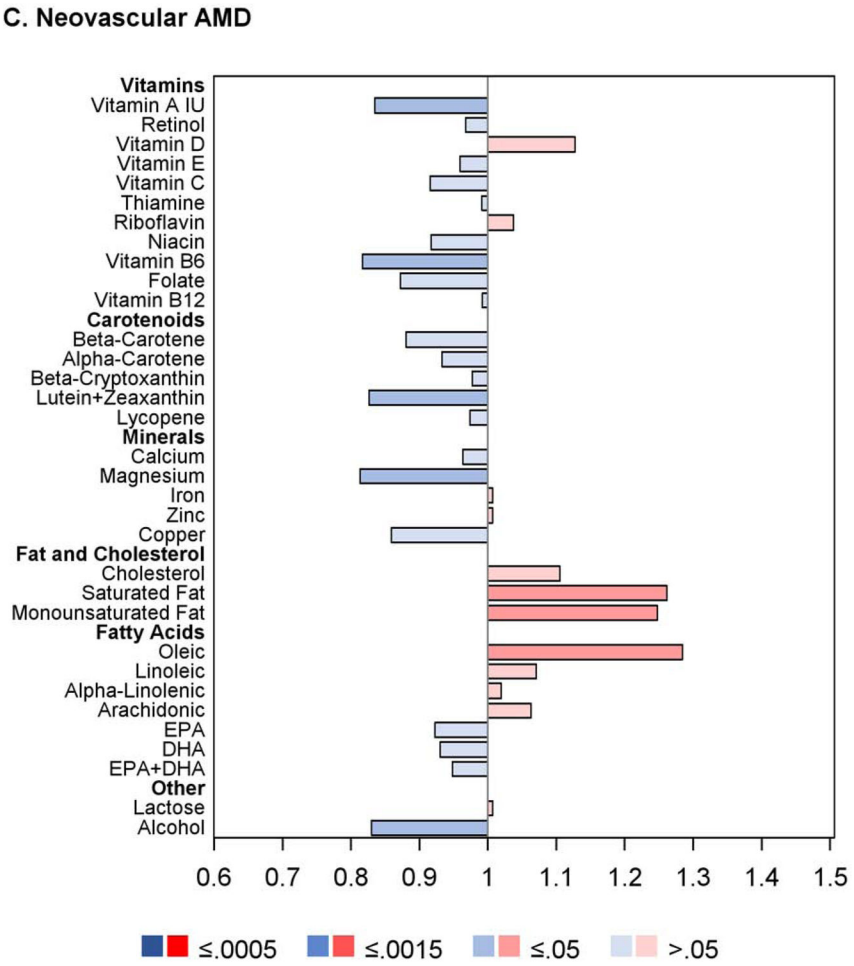
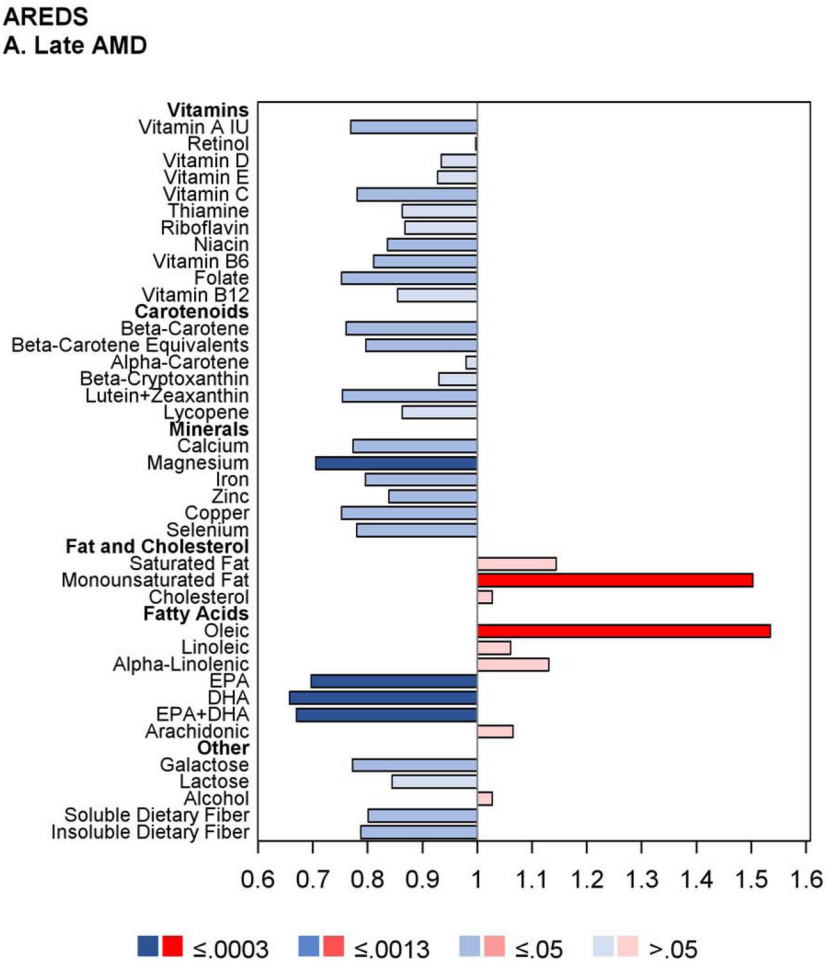
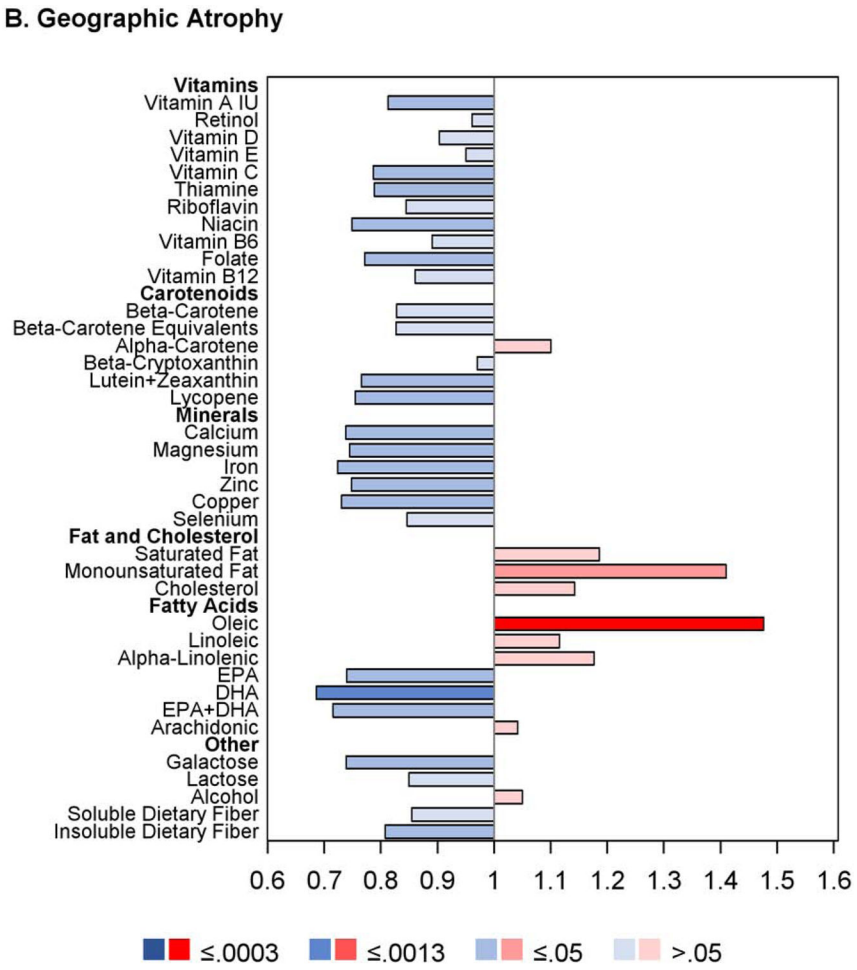
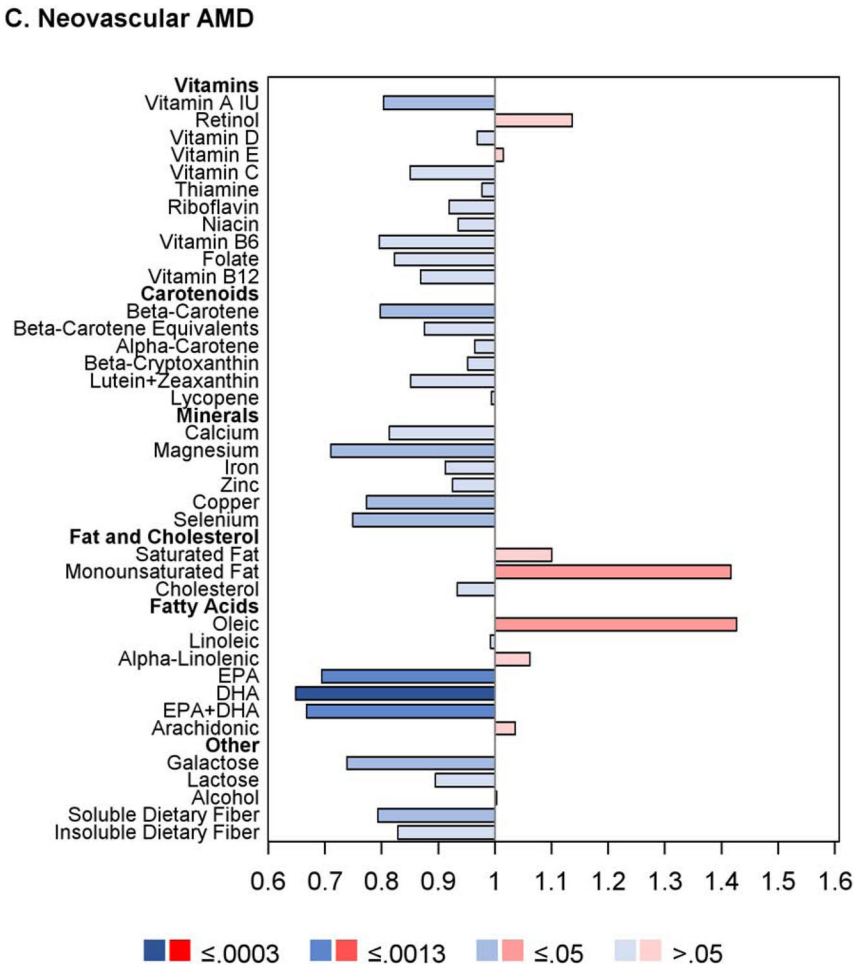


Figure 1.

Butterfly plots showing proportional hazards regression modeling of progression to late age-related macular degeneration outcomes in the combined AREDS/AREDS2 cohort. For each nutrient, the hazard ratio of dietary intake quintile 5 (with quintile 1 as reference) is shown on the x axis, with protective associations in blue and harmful associations in red; smaller P values are denoted by darker colors.







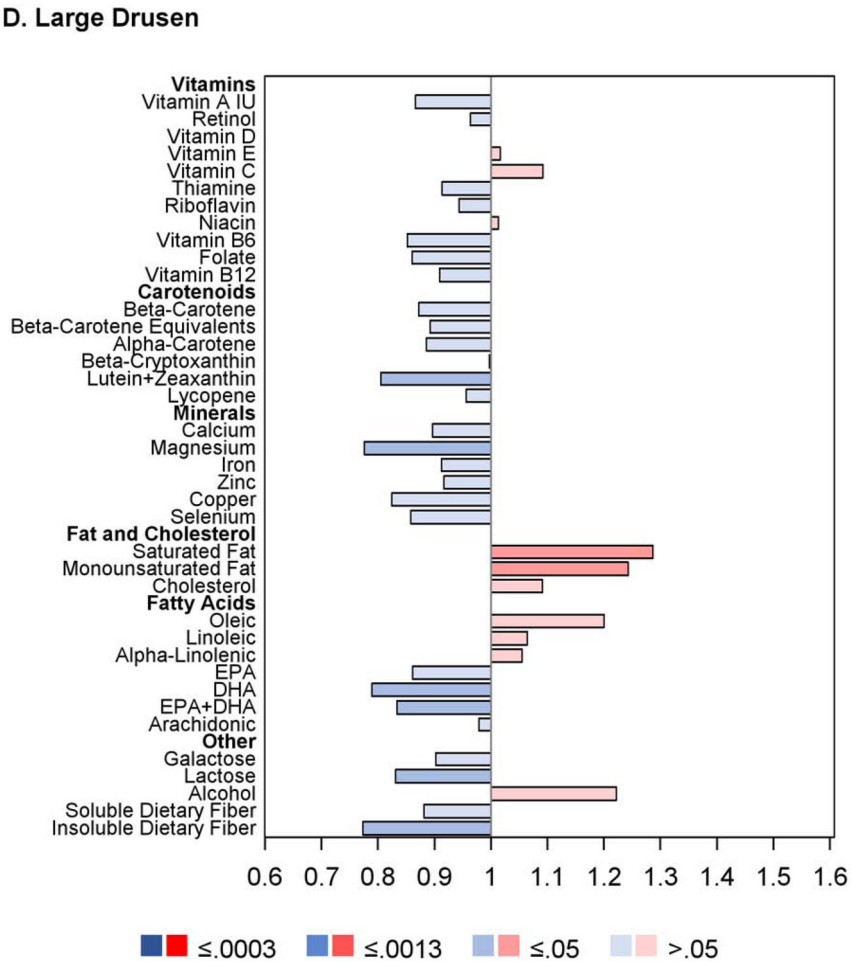
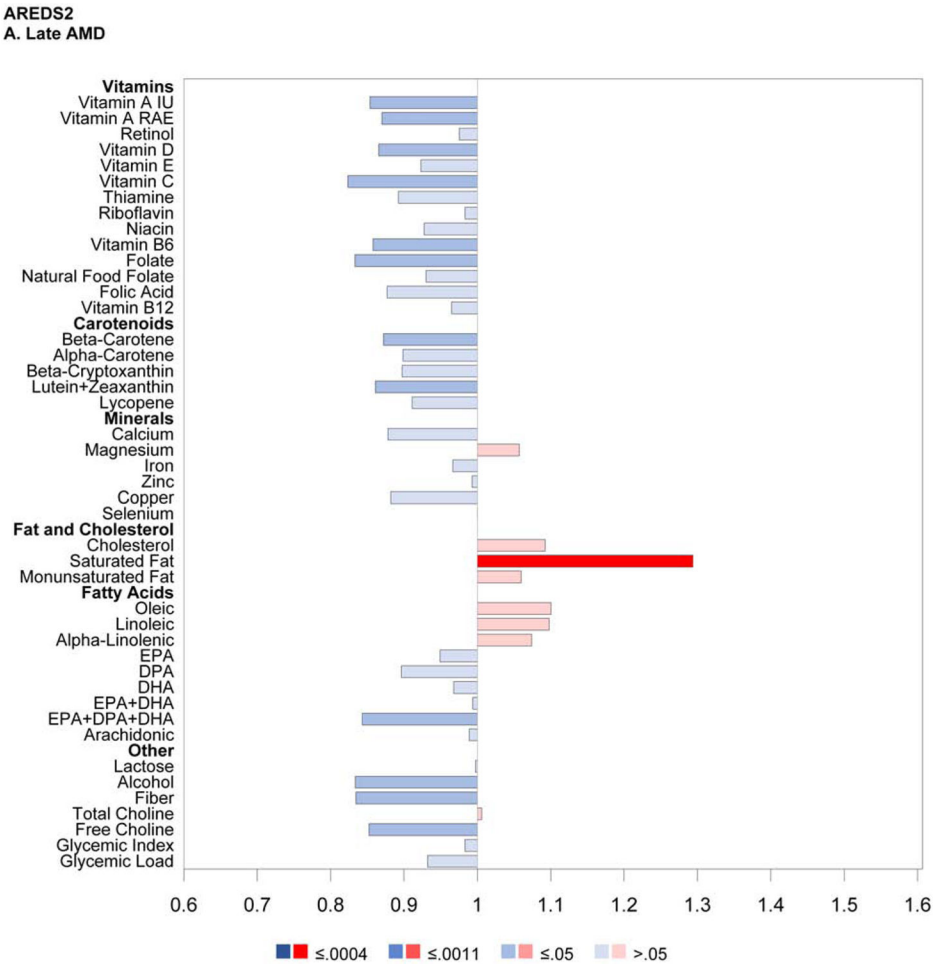
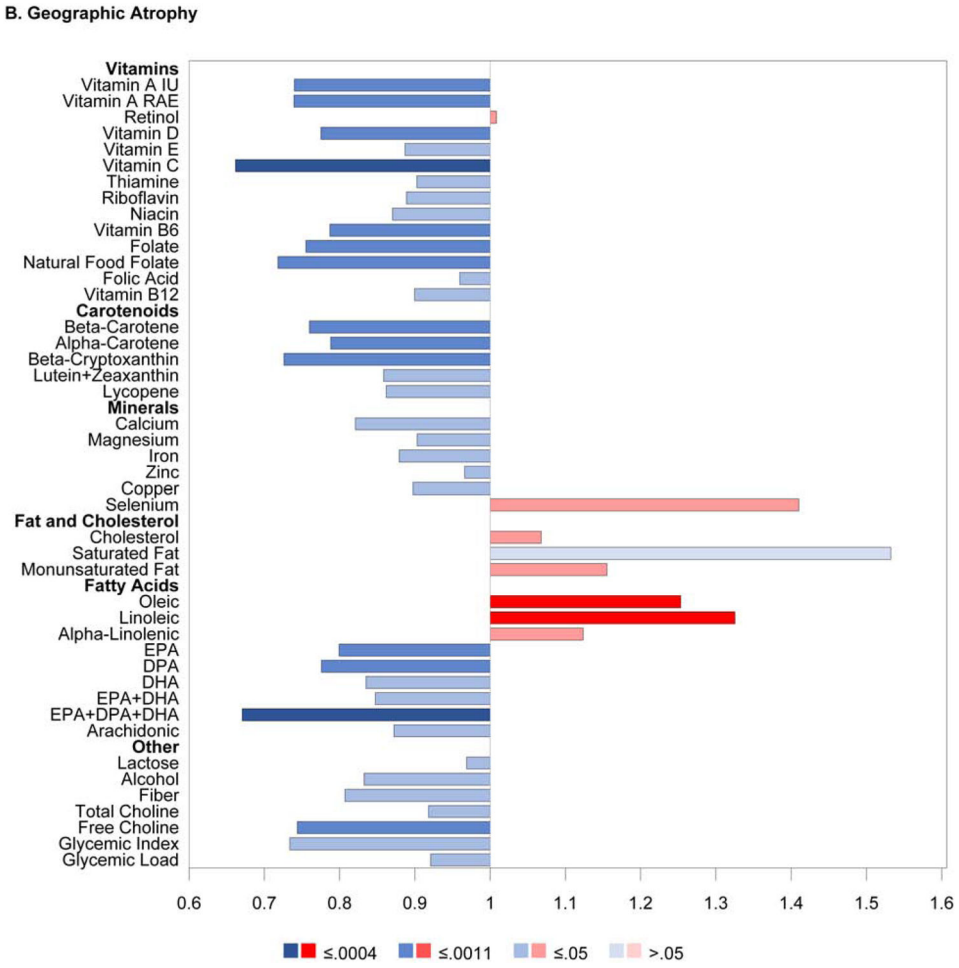


Figure 2.

Butterfly plots showing proportional hazards regression modeling of progression to late age-related macular degeneration outcomes and progression to large drusen in the AREDS cohort. For each nutrient, the hazard ratio of dietary intake quintile 5 (with quintile 1 as reference) is shown on the x axis, with protective associations in blue and harmful associations in red; smaller P values are denoted by darker colors.





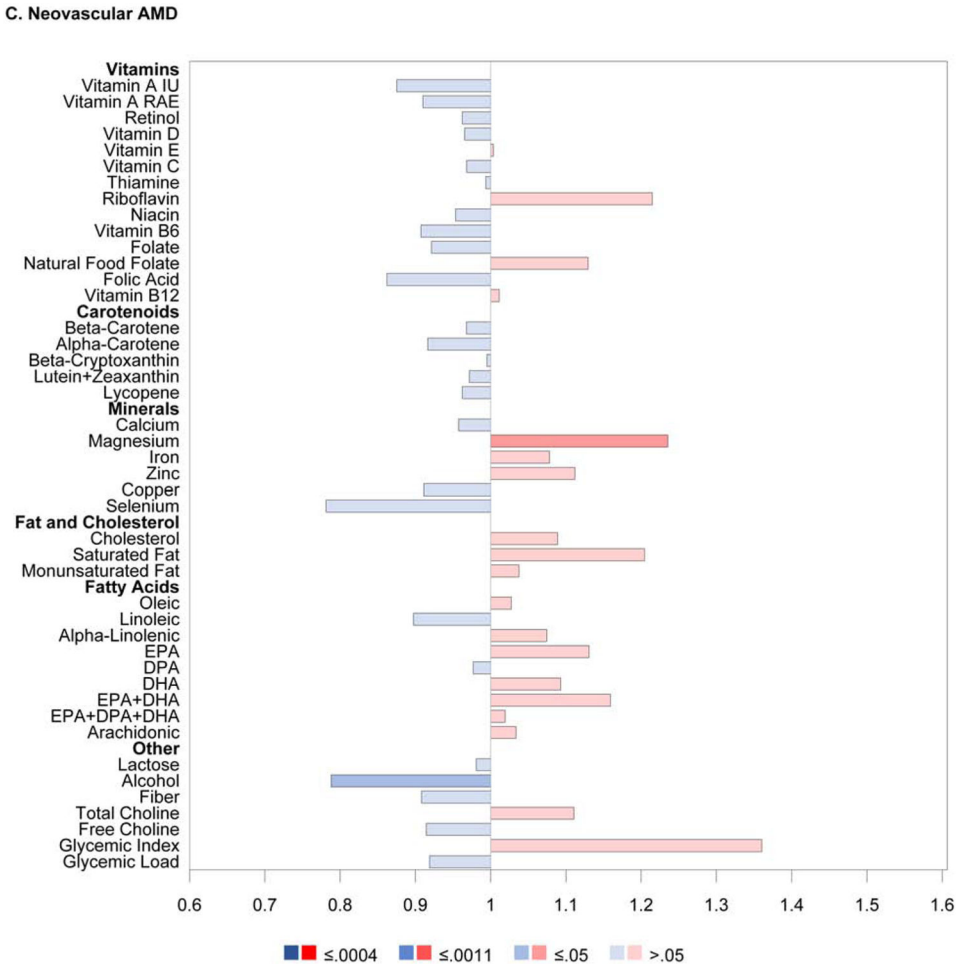


Figure 3.

Butterfly plots showing proportional hazards regression modeling of progression to late age-related macular degeneration outcomes in the AREDS2 cohort. For each nutrient, the hazard ratio of dietary intake quintile 5 (with quintile 1 as reference) is shown on the x axis, with protective associations in blue and harmful associations in red; smaller P values are denoted by darker colors.

Table 1.

Participant demographics at baseline

	Combined cohort	AREDS cohort	AREDS2 cohort
Participants	8,130 *	4,504	3,738
Mean age (years)	71.0 (SD 6.7)	69.3 (SD 5.1)	72.9 (SD 7.7)
Female: n (%)	4,593 (56.5)	2,526 (56.1)	2,129 (57.0)
Smoking status: n (%)			
Never	3,588 (44.1)	2,021 (44.9)	1,626 (43.5)
Former	3,963 (48.7)	2,142 (47.6)	1,870 (50.0)
Current	579 (7.1)	341 (7.6)	242 (6.5)
Body mass index: n (%)			
≤25	-	1,469 (32.6)	-
>25 and ≤30	-	1,889 (41.9)	-
>30	-	1,146 (25.4)	-
AMD severity category 3-4 (AREDS) or ≥7 in worse eye (AREDS2): n (%)			
No	-	2,101 (46.6)	887 (23.7)
Yes	-	2,403 (53.4)	2,851 (76.3)
Mean follow-up time (years)	8.8 (SD 3.0) Median 10.2	9.1 (SD 2.8) Median 10.1	8.6 (SD 3.2) Median 10.4
Participants with genetic data	4,476	2,854	1,718
Genetic risk score group: n (%)			
Low risk groupt †	1,183 (26.4)	979 (34.3)	226 (13.2)
Quartiles 1-2	1,659 (37.1)	1,086 (38.1)	610 (35.5)
Quartiles 3-4	1,634 (36.5)	789 (27.6)	882 (51.3)
ARMS2 risk alleles (rs10490924): n (%)			
0 (GG)	2,071 (46.3)	1,453 (50.9)	665 (38.7)
1 (GT)	1,808 (40.4)	1,106 (38.8)	737 (42.9)
2 (TT)	597 (13.3)	295 (10.3)	316 (18.4)
CFH protective alleles (rs10922109): n (%)			
0 (CC)	2,398 (53.6)	1,300 (45.6)	1,145 (66.6)
1 (CA)	1,637 (36.6)	1,187 (41.6)	486 (28.3)
2 (AA)	441 (9.9)	367 (12.9)	87 (5.1)
CFH risk alleles (rs1061170): n (%)			
0 (TT)	1,140 (25.5)	866 (30.3)	299 (17.4)
1 (TC)	1,998 (44.6)	1,305 (45.7)	734 (42.7)
2 (CC)	1,338 (29.9)	683 (23.9)	685 (39.9)
C3 risk alleles (rs2230199): n (%)			
0 (CC)	2,542 (56.8)	1,672 (58.6)	923 (53.7)
1 (CG)	1,656 (37.0)	1,036 (36.3)	658 (38.3)

	Combined cohort	AREDS cohort	AREDS2 cohort
2 (GG)	278 (6.2)	146 (5.1)	137 (8.0)

Abbreviations: AMD=age-related macular degeneration; AREDS=Age-Related Eye Disease Study; *ARMS2=age-related maculopathy susceptibility 2* gene; *CFH=complement factor H* gene; GA=geographic atrophy; SD=standard deviation

*In the combined cohort, the 112 participants who were in both cohorts were counted only once (using their data from AREDS2)

†Low risk genetic risk score group: participants whose genetic risk score was less than or equal to the mean genetic risk score of a control population without late age-related macular degeneration

Table 2.

Results of the proportional hazards regression modeling of progression to late age-related macular degeneration outcomes, according to quintiles of nutrient intake in the combined AREDS/AREDS2 cohort: hazard ratios and P values.

Nutrient	Late AMD		Geographic Atrophy		Neovascular AMD	
	Q4 vs Q1	Q5 vs Q1	Q4 vs Q1	Q5 vs Q1	Q4 vs Q1	Q5 vs Q1
Vitamin A (IU)	0.80 (0.72, 0.89)	0.82 (0.74, 0.91)	0.76 (0.65, 0.87)	0.77 (0.66, 0.89)	0.85 (0.73, 0.98)	0.83 (0.72, 0.96)
	<.0001	0.0001	0.0002	0.0005	0.022	0.013
Retinol	0.97 (0.86, 1.08)	0.96 (0.86, 1.08)	0.97 (0.83, 1.14)	0.98 (0.84, 1.16)	0.98 (0.84, 1.14)	0.97 (0.83, 1.13)
	0.53	0.54	0.70	0.85	0.82	0.68
Vitamin D	0.94 (0.84, 1.05)	0.95 (0.86, 1.06)	0.91 (0.78, 1.06)	0.86 (0.74, 1.00)	1.07 (0.92, 1.25)	1.13 (0.97, 1.31)
	0.25	0.40	0.21	0.053	0.36	0.12
Vitamin E	0.97 (0.87, 1.10)	0.94 (0.83, 1.06)	1.02 (0.85, 1.21)	0.96 (0.80, 1.14)	1.03 (0.88, 1.21)	0.96 (0.81, 1.14)
	0.67	0.33	0.86	0.64	0.72	0.63
Vitamin C	0.79 (0.71, 0.87)	0.80 (0.72, 0.89)	0.71 (0.62, 0.83)	0.70 (0.60, 0.81)	0.87 (0.75, 1.00)	0.92 (0.79, 1.06)
	<.0001	<.0001	<.0001	<.0001	0.056	0.25
Thiamine	0.88 (0.79, 0.97)	0.90 (0.81, 1.00)	0.87 (0.75, 1.01)	0.85 (0.73, 0.99)	1.00 (0.86, 1.16)	0.99 (0.85, 1.16)
	0.015	0.057	0.068	0.033	0.99	0.91
Riboflavin	0.91 (0.82, 1.01)	0.91 (0.81, 1.01)	0.81 (0.70, 0.94)	0.81 (0.70, 0.95)	1.07 (0.92, 1.25)	1.04 (0.89, 1.21)
	0.088	0.078	0.005	0.008	0.36	0.64
Niacin	0.87 (0.78, 0.97)	0.85 (0.76, 0.95)	0.86 (0.74, 1.00)	0.79 (0.68, 0.93)	0.89 (0.77, 1.04)	0.92 (0.79, 1.07)
	0.012	0.005	0.044	0.004	0.14	0.27
Vitamin B6	0.82 (0.73, 0.92)	0.83 (0.74, 0.93)	0.79 (0.68, 0.92)	0.85 (0.73, 0.99)	0.85 (0.73, 0.98)	0.82 (0.70, 0.95)
	0.0004	0.001	0.003	0.035	0.030	0.010
Folate	0.82 (0.74, 0.92)	0.82 (0.73, 0.91)	0.71 (0.61, 0.82)	0.78 (0.67, 0.91)	0.92 (0.80, 1.07)	0.87 (0.75, 1.02)
	0.0004	0.0002	<.0001	0.002	0.29	0.077
Vitamin B12	0.93 (0.83, 1.04)	0.96 (0.85, 1.07)	0.82 (0.70, 0.96)	0.91 (0.78, 1.07)	0.98 (0.84, 1.14)	0.99 (0.85, 1.15)
	0.19	0.43	0.011	0.24	0.77	0.92
Beta-carotene	0.78 (0.70, 0.87)	0.81 (0.73, 0.90)	0.74 (0.63, 0.85)	0.75 (0.64, 0.87)	0.83 (0.72, 0.97)	0.88 (0.76, 1.02)
	<.0001	0.0001	<.0001	0.0001	0.016	0.088
Alpha-carotene	0.92 (0.83, 1.03)	0.95 (0.85, 1.05)	0.90 (0.77, 1.05)	0.96 (0.83, 1.11)	1.01 (0.87, 1.17)	0.93 (0.81, 1.08)
	0.14	0.31	0.18	0.59	0.92	0.36
Beta-cryptoxanthin	0.87 (0.78, 0.97)	0.91 (0.82, 1.01)	0.82 (0.70, 0.95)	0.80 (0.68, 0.93)	0.94 (0.81, 1.09)	0.98 (0.84, 1.14)
	0.011	0.080	0.009	0.004	0.39	0.77
Lutein and zeaxanthin	0.74 (0.67, 0.83)	0.77 (0.69, 0.85)	0.77 (0.66, 0.90)	0.80 (0.68, 0.93)	0.78 (0.68, 0.91)	0.83 (0.71, 0.96)
	<.0001	<.0001	0.0007	0.004	0.0015	0.013
Lycopene	0.96 (0.86, 1.07)	0.90 (0.81, 1.01)	0.82 (0.71, 0.95)	0.81 (0.70, 0.94)	1.03 (0.89, 1.19)	0.97 (0.84, 1.13)
	0.50	0.064	0.010	0.005	0.68	0.73
Calcium	0.99 (0.89, 1.10)	0.87 (0.78, 0.98)	0.90 (0.77, 1.04)	0.78 (0.67, 0.91)	1.10 (0.95, 1.27)	0.96 (0.82, 1.13)
	0.83	0.020	0.15	0.002	0.22	0.65

Nutrient	Late AMD		Geographic Atrophy		Neovascular AMD	
	Q4 vs Q1	Q5 vs Q1	Q4 vs Q1	Q5 vs Q1	Q4 vs Q1	Q5 vs Q1
Magnesium	0.86 (0.77, 0.95)	0.79 (0.71, 0.88)	0.83 (0.71, 0.96)	0.73 (0.62, 0.85)	0.88 (0.76, 1.02)	0.81 (0.70, 0.95)
	0.005	<.0001	0.013	<.0001	0.084	0.007
Iron	0.85 (0.77, 0.95)	0.91 (0.81, 1.01)	0.80 (0.69, 0.93)	0.82 (0.71, 0.96)	0.97 (0.83, 1.12)	1.01 (0.87, 1.17)
	0.004	0.081	0.004	0.011	0.66	0.92
Zinc	0.95 (0.85, 1.05)	0.96 (0.86, 1.07)	0.86 (0.74, 0.99)	0.90 (0.77, 1.05)	1.05 (0.91, 1.22)	1.01 (0.87, 1.17)
	0.31	0.45	0.042	0.17	0.47	0.93
Copper	0.83 (0.74, 0.93)	0.79 (0.70, 0.89)	0.77 (0.66, 0.90)	0.71 (0.60, 0.83)	0.84 (0.72, 0.98)	0.86 (0.73, 1.01)
	0.0015	0.0001	0.0009	<.0001	0.027	0.061
Cholesterol	1.12 (1.00, 1.26)	1.12 (1.00, 1.26)	1.14 (0.98, 1.34)	1.17 (1.00, 1.37)	1.05 (0.90, 1.23)	1.11 (0.95, 1.29)
	0.046	0.053	0.10	0.051	0.51	0.21
Saturated fat	1.12 (1.01, 1.24)	1.32 (1.19, 1.48)	1.17 (1.00, 1.36)	1.39 (1.20, 1.63)	1.06 (0.91, 1.23)	1.26 (1.09, 1.46)
	0.038	<.0001	0.049	<.0001	0.44	0.002
Monounsaturated fat	1.15 (1.03, 1.29)	1.23 (1.10, 1.38)	1.23 (1.05, 1.43)	1.30 (1.11, 1.52)	1.16 (0.99, 1.35)	1.25 (1.07, 1.46)
	0.012	0.0002	0.009	0.0009	0.061	0.005
Oleic acid	1.13 (1.01, 1.26)	1.28 (1.14, 1.43)	1.17 (1.00, 1.37)	1.42 (1.22, 1.66)	1.15 (0.98, 1.34)	1.28 (1.10, 1.50)
	0.029	<.0001	0.057	<.0001	0.086	0.002
Linoleic acid	1.03 (0.92, 1.15)	1.16 (1.03, 1.30)	1.11 (0.95, 1.30)	1.30 (1.10, 1.52)	0.97 (0.83, 1.12)	1.07 (0.92, 1.25)
	0.58	0.014	0.19	0.002	0.65	0.39
Alpha-linolenic acid	1.07 (0.96, 1.19)	1.07 (0.96, 1.20)	1.06 (0.91, 1.23)	1.14 (0.98, 1.32)	1.09 (0.94, 1.26)	1.02 (0.88, 1.18)
	0.20	0.20	0.45	0.089	0.26	0.80
Arachidonic acid	1.01 (0.90, 1.14)	1.05 (0.93, 1.18)	1.01 (0.86, 1.19)	1.02 (0.86, 1.20)	0.95 (0.81, 1.12)	1.06 (0.90, 1.25)
	0.89	0.46	0.90	0.84	0.56	0.46
EPA	0.85 (0.76, 0.96)	0.83 (0.74, 0.93)	0.80 (0.69, 0.93)	0.76 (0.65, 0.89)	0.91 (0.78, 1.06)	0.92 (0.79, 1.07)
	0.006	0.0009	0.004	0.0008	0.23	0.30
DHA	0.84 (0.75, 0.95)	0.83 (0.73, 0.93)	0.78 (0.67, 0.92)	0.74 (0.63, 0.88)	0.85 (0.73, 1.00)	0.93 (0.79, 1.09)
	0.004	0.002	0.002	0.0006	0.044	0.38
EPA and DHA	0.86 (0.76, 0.96)	0.85 (0.76, 0.96)	0.81 (0.70, 0.95)	0.79 (0.67, 0.93)	0.85 (0.72, 0.99)	0.95 (0.81, 1.11)
	0.008	0.009	0.010	0.005	0.038	0.51
Lactose	1.02 (0.91, 1.14)	0.97 (0.87, 1.09)	0.98 (0.84, 1.15)	0.93 (0.79, 1.09)	1.11 (0.96, 1.29)	1.01 (0.86, 1.18)
	0.73	0.61	0.85	0.39	0.16	0.93
Alcohol	0.79 (0.72, 0.88)	0.85 (0.77, 0.93)	0.74 (0.65, 0.85)	0.86 (0.75, 0.98)	0.84 (0.73, 0.96)	0.83 (0.73, 0.95)
	<.0001	0.0008	<.0001	0.023	0.009	0.006

Abbreviations: AMD=age-related macular degeneration; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; IU=international units; Q=quintile

Footnotes:

- results are shown in comparison to quintile 1 (reference), following adjustment for age, sex, smoking status, total calorie intake, body mass index (for AREDS participants only), and correlation between eyes

- AREDS2 data: the results for late AMD are based on events over the full study period (i.e., including the AREDS2 10-year follow-on study), while the results for geographic atrophy and neovascular AMD are based on events up until the AREDS2 close-out (median 5 years). This is because, in the AREDS2 10-year follow-on study, late AMD subtype information was not captured from all data sources

Table 3.

Results of the proportional hazards regression modeling of progression to large drusen, according to quintiles of nutrient intake in the AREDS cohort: hazard ratios and P values.

Nutrient	Q4 vs Q1	Q5 vs Q1
Vitamin A (IU)	0.82 (0.68, 0.99)	0.87 (0.72, 1.04)
	0.043	0.13
Retinol	1.02 (0.85, 1.23)	0.96 (0.80, 1.16)
	0.82	0.70
Beta-carotene equivalents	0.82 (0.68, 0.99)	0.89 (0.74, 1.07)
	0.041	0.23
Alpha-carotene	0.97 (0.81, 1.18)	0.89 (0.73, 1.07)
	0.79	0.20
Beta-carotene	0.82 (0.68, 0.99)	0.87 (0.73, 1.05)
	0.041	0.15
Beta-cryptoxanthin	1.01 (0.84, 1.22)	1.00 (0.82, 1.21)
	0.92	0.98
Lycopene	0.91 (0.76, 1.10)	0.96 (0.80, 1.15)
	0.34	0.62
Lutein and zeaxanthin	0.90 (0.75, 1.09)	0.81 (0.66, 0.98)
	0.28	0.028
Thiamine	0.84 (0.70, 1.01)	0.91 (0.76, 1.10)
	0.064	0.34
Riboflavin	0.85 (0.71, 1.02)	0.94 (0.79, 1.13)
	0.086	0.53
Niacin	0.94 (0.78, 1.14)	1.01 (0.84, 1.23)
	0.53	0.89
Vitamin B6	0.84 (0.70, 1.01)	0.85 (0.71, 1.03)
	0.067	0.094
Vitamin B12	0.90 (0.75, 1.08)	0.91 (0.76, 1.09)
	0.27	0.31
Folate	0.79 (0.65, 0.95)	0.86 (0.71, 1.04)
	0.011	0.12
Vitamin C	0.99 (0.82, 1.20)	1.09 (0.90, 1.33)
	0.92	0.38
Vitamin D	0.98 (0.81, 1.18)	1.00 (0.83, 1.21)
	0.30	1.00
Vitamin E	0.97 (0.81, 1.16)	1.02 (0.84, 1.22)
	0.72	0.86
Zinc	0.87 (0.73, 1.04)	0.92 (0.76, 1.10)
	0.14	0.36

Nutrient	Q4 vs Q1	Q5 vs Q1
Selenium	0.88 (0.73, 1.05)	0.86 (0.71, 1.03)
	0.15	0.10
Copper	0.81 (0.67, 0.98)	0.82 (0.68, 1.00)
	0.028	0.053
Iron	0.89 (0.74, 1.07)	0.91 (0.76, 1.10)
	0.20	0.34
Magnesium	0.85 (0.70, 1.02)	0.78 (0.64, 0.94)
	0.088	0.011
Calcium	1.01 (0.83, 1.21)	0.90 (0.74, 1.08)
	0.95	0.25
Saturated fat	1.28 (1.06, 1.55)	1.29 (1.06, 1.56)
	0.011	0.010
Monounsaturated fat	1.20 (1.00, 1.45)	1.24 (1.02, 1.51)
	0.049	0.028
Oleic acid	1.17 (0.98, 1.41)	1.20 (0.99, 1.46)
	0.090	0.064
Linoleic acid	0.90 (0.75, 1.09)	1.06 (0.89, 1.28)
	0.28	0.50
Alpha-linolenic acid	0.93 (0.77, 1.11)	1.05 (0.88, 1.26)
	0.42	0.56
EPA	0.87 (0.73, 1.05)	0.86 (0.72, 1.03)
	0.14	0.11
DHA	0.86 (0.72, 1.03)	0.79 (0.66, 0.95)
	0.10	0.011
EPA and DHA	0.86 (0.71, 1.03)	0.83 (0.70, 1.00)
	0.099	0.050
Arachidonic acid	1.05 (0.88, 1.26)	0.98 (0.81, 1.18)
	0.56	0.83
Cholesterol	1.23 (1.03, 1.47)	1.09 (0.91, 1.31)
	0.023	0.35
Galactose	0.83 (0.69, 1.00)	0.90 (0.75, 1.08)
	0.046	0.27
Lactose	0.98 (0.82, 1.17)	0.83 (0.69, 1.00)
	0.81	0.049
Alcohol	1.03 (0.83, 1.29)	1.22 (0.98, 1.52)
	0.79	0.073
Insoluble dietary fiber	0.78 (0.65, 0.95)	0.77 (0.64, 0.94)
	0.011	0.009
Soluble dietary fiber	0.97 (0.80, 1.16)	0.88 (0.73, 1.07)

Nutrient	Q4 vs Q1	Q5 vs Q1
	0.72	0.20

Abbreviations: DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; IU=international units; Q=quintile

Footnotes:

- results are shown in comparison to quintile 1 (reference), following adjustment for age, sex, smoking status, total calorie intake, body mass index, and correlation between eyes

Table 4.

Results of proportional hazards regression of the progression to late age-related macular degeneration outcomes, according to interactions between nutrient intake and participant genotype, separately in the AREDS and AREDS2 cohorts: hazard ratios and P values.

Nutrient	SNP	0		1		2	
		Q4 vs Q1	Q5 vs Q1	Q4 vs Q1	Q5 vs Q1	Q4 vs Q1	Q5 vs Q1
AREDS							
Late AMD							
DHA	*CFH* rs10922109	1.22 (0.95, 1.58)	0.93 (0.71, 1.24)	0.81 (0.57, 1.15)	0.45 (0.30, 0.67)	0.86 (0.21, 3.60)	0.77 (0.20, 3.04)
	(0=CC; 1=CA; 2=AA)	0.12	0.63	0.24	<.0001	0.84 *	0.71 *
EPA	*CFH* rs10922109	1.01 (0.77, 1.31)	0.94 (0.71, 1.24)	0.68 (0.46, 1.01)	0.53 (0.35, 0.79)	0.70 (0.24, 2.00)	0.19 (0.04, 0.91)
	(0=CC; 1=CA; 2=AA)	0.96	0.67	0.056	0.002	0.50 *	0.037 *
EPA+DHA	*CFH* rs10922109	1.16 (0.90, 1.49)	0.90 (0.68, 1.19)	0.70 (0.48, 1.02)	0.49 (0.33, 0.73)	0.78 (0.25, 2.47)	0.49 (0.14, 1.66)
	(0=CC; 1=CA; 2=AA)	0.26	0.46	0.062	0.0005	0.67 *	0.25 *
Geographic atrophy							
DHA	*CFH* rs1061170	0.39 (0.20, 0.75)	0.50 (0.26, 0.93)	0.94 (0.65, 1.36)	0.65 (0.44, 0.95)	1.46 (0.97, 2.19)	0.99 (0.64, 1.53)
	(0=TT; 1=TC; 2=CC)	0.005	0.030	0.75	0.028	0.068	0.96
DHA	*CFH* rs10922109	1.34 (0.98, 1.83)	0.95 (0.68, 1.32)	0.59 (0.38, 0.91)	0.49 (0.31, 0.77)	0.90 (0.21, 3.77)	0.63 (0.14, 2.79)
	(0=CC; 1=CA; 2=AA)	0.069	0.75	0.016	0.002	0.88 *	0.55 *
EPA+DHA	*CFH* rs1061170	0.35 (0.18, 0.68)	0.51 (0.28, 0.93)	0.93 (0.64, 1.34)	0.70 (0.47, 1.02)	1.14 (0.76, 1.69)	0.96 (0.63, 1.47)
	(0=TT; 1=TC; 2=CC)	0.002	0.027	0.68	0.065	0.52	0.85
Neovascular AMD							
DHA	*ARMS2* rs10490924	0.96 (0.61, 1.51)	0.41 (0.23, 0.72)	1.35 (0.94, 1.94)	0.89 (0.60, 1.33)	1.07 (0.63, 1.84)	1.20 (0.68, 2.11)
	(0=GG; 1=GT; 2=TT)	0.86	0.002	0.11	0.58	0.79	0.54
EPA	*ARMS2* rs10490924	0.92 (0.58, 1.48)	0.46 (0.26, 0.81)	0.97 (0.67, 1.42)	0.90 (0.61, 1.32)	0.93 (0.54, 1.61)	1.33 (0.77, 2.30)
	(0=GG; 1=GT; 2=TT)	0.74	0.008	0.88	0.58	0.81	0.31
EPA+DHA	*ARMS2* rs10490924	0.91 (0.57, 1.47)	0.46 (0.26, 0.81)	1.11 (0.77, 1.60)	0.84 (0.57, 1.23)	1.14 (0.66, 1.96)	1.15 (0.67, 2.00)
	(0=GG; 1=GT; 2=TT)	0.71	0.007	0.56	0.36	0.64	0.61
AREDS2							
Late AMD							

Nutrient	SNP	0		1		2	
		Q4 vs Q1	Q5 vs Q1	Q4 vs Q1	Q5 vs Q1	Q4 vs Q1	Q5 vs Q1
Alcohol	*C3* rs2230199	0.93 (0.73, 1.19)	1.08 (0.86, 1.35)	0.88 (0.67, 1.16)	0.66 (0.50, 0.88)	0.47 (0.23, 0.94)	0.51 (0.29, 0.91)
	(0=CC; 1=CG; 2=GG)	0.57	0.53	0.36	0.005	0.034	0.023
Geographic atrophy							
Copper	GRS group	0.31 (0.09, 1.07)	1.00 (0.41, 2.44)	0.59 (0.34, 1.05)	1.18 (0.73, 1.92)	0.76 (0.50, 1.14)	0.91 (0.61, 1.36)
		0.065	1.00	0.07	0.50	0.18	0.65

Abbreviations: AMD=age-related macular degeneration; *ARMS2=age-related maculopathy susceptibility 2* gene; *CFH=complement factor H* gene; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; GRS=genetic risk score; Q=quintile

Footnotes:

- results are shown in comparison to quintile 1 (reference), following adjustment for age, sex, smoking status, total calorie intake, body mass index (for AREDS participants only), and correlation between eyes

* very low events numbers, owing to very low likelihood of progression to late AMD in participants with two protective alleles (irrespective of nutrient intake), hence no statistical significance despite hazard ratios below one