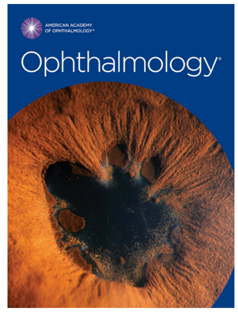

Oral Antioxidant and Lutein/Zeaxanthin Supplements Slow Geographic Atrophy Progression to the Fovea in Age-Related Macular Degeneration

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Conflicts of Interest

All authors declare no support from any other organization for the submitted work. PK has acted as a consultant for Roche, Novartis, Boehringer-Ingelheim, Adecco, Bitfount, and is an equity owner in Big Picture Medical, has received speaker fees from Novartis, Gyroscope, Bayer, Thea, Boehringer-Ingleheim, Apellis, Abbvie, Alimera, Roche, Genentech, Specsavers, Heidelberg Engineering, Topcon, and Santen, has received travel support from Bayer, Topcon, and Roche, and has attended advisory boards for Boehringer-Ingelheim, RetinAI, Novartis, Apellis, Abbvie, and Roche.

Running Head

Oral Supplements and Geographic Atrophy Progression

Abbreviations

AMD: age-related macular degeneration

AREDS: Age-Related Eye Disease Study

BCVA: best-corrected visual acuity

CI: confidence interval

DHA: docosahexaenoic acid

EPA: eicosapentaenoic acid

ETDRS: Early Treatment Diabetic Retinopathy Study

FAF: fundus autofluorescence

FDA: Food and Drug Administration

GA: geographic atrophy

SD: standard deviation

Abstract

Purpose

The only treatments approved to slow geographic atrophy (GA) progression in age-related macular degeneration (AMD) require frequent intraocular injection and suffer from modest efficacy, important risks, and high costs. The purpose of this study was to determine whether oral supplements slow GA progression in AMD.

Design

Post hoc analysis of the Age-Related Eye Diseases Study (AREDS) and AREDS2, multi-center randomized placebo-controlled trials of oral micronutrient supplementation, each with 2x2 factorial design.

Participants

392 eyes (318 participants) with GA in AREDS; 1210 eyes (891 participants) with GA in AREDS2.

Methods

AREDS participants were randomly assigned to oral antioxidants (500 mg vitamin C; 400 IU vitamin E; 15 mg β-carotene); 80 mg zinc; combination; or placebo. AREDS2 participants were randomly assigned to 10 mg lutein/2 mg zeaxanthin; 350 mg docosahexaenoic acid/650 mg eicosapentaenoic acid; combination; or placebo. Consenting AREDS2 participants were also randomly assigned to alternative AREDS formulations: original; no beta-carotene; 25 mg zinc instead of 80 mg; both.

Main outcome measures

(1) Change in GA proximity to central macula over time, and (2) change in square root GA area over time, each measured from color fundus photographs at annual visits and analyzed by mixed-model regression according to randomized assignments.

Results

In AREDS eyes with non-central GA (n=208), proximity-based progression towards the central macula was significantly slower with randomization to antioxidants versus none, at 50.7 µm/year (95% CI 38.0-63.4 µm/year) versus 72.9 µm/year (95% CI 61.3-84.5 µm/year; p=0.012), respectively. In AREDS2 eyes with non-central GA, in participants assigned to AREDS antioxidants without β-carotene (n=325 eyes), proximity-based progression was significantly slower with randomization to lutein/zeaxanthin versus

none, at 80.1 μm/year (95% CI 60.9-99.3 μm/year) versus 114.4 μm/year (95% CI 96.2-132.7 μm/year; p=0.011), respectively. In AREDS eyes with any GA (n=392), area-based progression was not significantly different with randomization to antioxidants versus none (p=0.63). In AREDS2 eyes with any GA, in participants assigned to AREDS antioxidants without β-carotene (n=505 eyes), area-based progression was not significantly different with randomization to lutein/zeaxanthin versus none (p=0.64).

Conclusions

Oral micronutrient supplementation slowed GA progression towards the central macula, likely by augmenting the natural phenomenon of foveal sparing.

Introduction

Age-related macular degeneration (AMD) is the leading cause of legal blindness in countries with relatively high life expectancy.[1,2] Geographic atrophy (GA) is the defining lesion of the atrophic subtype of late AMD.[3] GA is estimated to affect over five million people worldwide and is typically bilateral and relentlessly progressive.[4-6] No treatment is available to prevent its occurrence or restore vision to affected areas. In most cases, GA arises away from the central macula (i.e., non-central GA) and, over the course of years, expands gradually in all directions to involve most of the macula (Figure 1).[5-9] The GA progression rate varies among affected individuals for reasons that are not fully understood.[5-7,11]

The rate of this progression can be measured in several ways, including change over time in GA area[10] and change over time in GA proximity to the center. The GA area-based progression rate is a primary outcome measure in many clinical trials. It is recognized as a clinically important endpoint by the United States Food and Drug Administration (FDA)[10]; on its basis, two drugs to slow GA progression have received FDA approval: pegcetacoplan (a C3 complement inhibitor) and avacincaptad pegol (a C5 complement inhibitor).[12-14] However, limitations of both drugs include administration by repeated intravitreal injection every 1-2 months, relatively modest efficacy, important side effects (including substantially increased risk of new neovascular AMD, committing an eye to potentially life-long anti-VEGF injections), and high cost (more than $2000 per injection).[12-19] Therefore, additional therapeutic approaches to slow GA progression, ideally with oral administration, favorable safety record, and modest cost, remain a high priority.

Incident GA is non-central at onset in approximately two thirds of eyes.[5,20] Interestingly, GA progression into the central macular area is substantially slower than progression in the more peripheral macula, leading to the beneficial phenomenon of foveal sparing.[21-23] The mechanisms underlying this phenomenon are unknown and its strength may vary among individuals.[23,24] When GA involves the macular center-point and has sufficient size, it is usually accompanied by severely decreased visual acuity.[5,25-30] Thus, the time taken for non-central GA to reach the macular center-point is an important metric[21]; hence, for non-central GA, the rate of change of GA proximity to the macular center-point (Figure 1 and Supplementary Figure 2) is a meaningful and complementary outcome measure to area-based progression. In this way, therapeutic approaches that could slow GA progression towards the central macula would be highly valuable and applicable to many individuals.

The Age-Related Eye Diseases Study (AREDS) demonstrated that oral supplementation with high dose antioxidants and zinc decreased the risk of progression to advanced AMD in individuals at high risk.[31] This formulation was modified, following the results of AREDS2; β-carotene was replaced with lutein/zeaxanthin, owing to concerns around increased incidence of lung cancer with β-carotene (in current or previous smokers).[32,33] Since then, for non-advanced AMD, the final AREDS2 formulation, with favorable safety profile and low cost, has been used internationally for many years.[34-36]

However, to date, no evidence has supported the use of the AREDS or AREDS2 supplements to try to slow area-based or proximity-based GA progression.[5,30] From earlier area-based analyses, based on a small subpopulation of 68 AREDS participants, the investigators concluded that their results suggested "no great benefit of AREDS-type supplements on the progression of GA".[30] However, no proximity-based analyses were performed in either AREDS or AREDS2.[5,30] Now, a much larger AREDS subpopulation of eyes with GA, together with a large number from AREDS2, have reading center measurements of both area and proximity available.

Therefore, our main aim in this study was to analyze GA area-based and proximity-based progression rates in the eyes of AREDS and AREDS2 participants, according to the randomized treatment assignments, to evaluate whether oral antioxidant, zinc, lutein/zeaxanthin, or omega-3 fatty acid supplements slow GA progression. The secondary aim was to analyze rates of change in visual acuity in similar ways.

Methods

Study Procedures

The AREDS and AREDS2 designs have been described.[37,38] In the AREDS, 4,757 participants aged 55 to 80 years were recruited between 1992 and 1998 at 11 retinal specialty clinics in the United States. Of these, 3640 participants with signs of early AMD or a more advanced form of AMD were randomized (1:1:1:1 in a 2x2 factorial design, by simple randomization, stratified by retinal specialty clinic) to one of the four study treatments: antioxidants (500 mg of ascorbic acid [vitamin C]; 400 IU of dl-alpha-tocopherol acetate [vitamin E]; and 15 mg of β-carotene), zinc (80 mg as zinc oxide and copper; 2 mg as cupric oxide), antioxidants plus zinc, or placebo. A diagram of the randomization scheme is shown in Figure 3, and a summary of the randomized assignments is provided in Supplementary Table 1.

In the AREDS2, 4,203 participants aged 50-85 years were recruited between 2006 and 2008 at 82 US retinal specialty clinics.[38] Inclusion criteria were the presence of either large drusen in both eyes or late

AMD in one eye and large drusen in the fellow eye. The participants were randomly assigned, in a primary randomization (1:1:1:1 in a 2x2 factorial design, by random blocks, stratified by retinal specialty clinic and by AMD status [large drusen in both eyes or large drusen in one eye and advanced AMD in the fellow eye]), to one of the four study treatments: lutein plus zeaxanthin (10 mg/2 mg), docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) (350 mg/650 mg), lutein/zeaxanthin and DHA/EPA, or placebo. A diagram of the randomization scheme is shown in Figure 3, and a summary of the randomized assignments is provided in Supplementary Table 2. In addition, all participants were offered the original AREDS formulation to take alongside this. Those who agreed to take the AREDS formulation and consented to a second randomization were randomly assigned (1:1:1:1 in a 2x2 factorial design), simultaneously with the primary randomization, to receive one of four alternative AREDS formulations: (i) the original formulation, (ii) the original formulation but with no β-carotene, (iii) the original formulation but with low zinc (25 mg instead of 80 mg), and (iv) the original formulation but with no β-carotene and low zinc. Participants who were current smokers or who had stopped smoking within the year before enrollment were randomly assigned to one of the two arms without β-carotene.

In both studies, at baseline and annual follow-up visits, best-corrected visual acuity (BCVA) was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts, eye examinations were performed, and stereoscopic color fundus photographs were captured and graded centrally at the Wisconsin Reading Center.[39] The participants, investigators, and reading center personnel were masked to the treatment assignments. For both the AREDS and AREDS2, the randomized clinical trial was designed to last five years for each participant.

For both studies, institutional review board approval was obtained at each site and written informed consent was obtained from all participants. The research was conducted under the tenets of the Declaration of Helsinki and, for the AREDS2, complied with the Health Insurance Portability and Accountability Act. The first AREDS participant was enrolled in November 1992 and the last study visit of the last participant for the primary outcome was in April 2001. The trial was registered at ClinicalTrials.gov (https://clinicaltrials.gov/study/NCT00000145) in September 1999, soon after ClinicalTrials.gov was launched. The AREDS2 was registered at ClinicalTrials.gov (https://clinicaltrials.gov/study/NCT00345176) in June 2006. The first participant was enrolled in October 2006 and the last study visit of the last participant for the primary outcome was in October 2012.

Evaluation of Geographic Atrophy on Color Fundus Photographs

For both studies, the definitions of GA and methods to measure GA area and other characteristics on color fundus photographs have been described previously.[5,30,40] The minimum size requirement to define GA was grading circle I-1 (1/8 disc diameter or 217 µm) in the AREDS and grading circle I-2 (1/4 disc diameter or 433 µm) in the AREDS2. For both studies, planimetry tools were used to demarcate the area of GA within the AREDS grid and GA proximity to the central macula (i.e., the foveal center-point) was documented in microns (Supplementary Figure 2).[5,30,39] Grading for GA area measurements and other features was performed independently at the image level, i.e., the reading center graders analyzed each image independently from other images in the full time-series of images for each eye and did not have access to any accompanying clinical information.

In the AREDS, each image was evaluated independently by two reading center graders for GA variables including presence/absence and center-point involvement, with adjudication by an independent senior grader in the case of discrepancy between the first two graders.[41] Following this, GA area and proximity were measured by one grader. In the AREDS2, a similar grading process was followed for images from the baseline study visit.[39] For images from subsequent study visits, each image was graded by a single grader. Longitudinal review was performed at the end of the study to adjudicate any instances of longitudinal discrepancy for GA presence and center-point involvement. Levels of inter-grader agreement for the assessment of GA presence/absence have been analyzed and reported for both the AREDS and AREDS2.[39,41] These were high in both contemporaneous replicate grading exercises and temporal reproducibility exercises. Similarly, levels of inter-grader agreement for GA area have been analyzed for the AREDS2, with low mean difference, narrow limits of agreement, and no systematic bias.[39]

Study Populations

The study population comprised all eyes that had GA measurements available at two or more study visits (without previous or simultaneous neovascular AMD). This included eyes that had GA at baseline (i.e., prevalent GA) and those in which GA developed during follow-up (i.e., incident GA). For the AREDS, the eyes analyzed previously in AREDS Report 26[30] represent a small subset of the current study population. For the AREDS2, the study population has been described previously.[5]

In the proximity-based analyses, the study population comprised only eyes where GA was non-central (i.e., with a proximity variable greater than 0) at the first time-point. In the area-based analyses, the study population comprised all eyes, both those with non-central GA and those with central GA at the first time-point (i.e., irrespective of the proximity variable).

Statistical Methods

The two primary (co-primary) outcome measures were (i) rate of change in GA proximity to the central macula and (ii) rate of change in GA area. Analyses of change over time in GA proximity to the central macula (i.e., rate of GA progression towards the central macula) were performed, using methods similar to those described previously.[42,43] The unit of analysis was the eye. Mixed-model repeated-measures regression was performed with the proximity variable as the outcome measure. The models included the variable of interest (i.e., randomized treatment assignment), years from first time-point with GA (in order to account for the repeated measures, i.e., to obtain the rate of progression towards the central macula), and their interaction term. The models also included terms for age, sex, smoking status, and proximity at first time-point with GA, to account for differences among participants. To account for the correlation between both eyes of the same participant and between different visits of the same eye, an unstructured and a first-order autoregressive covariance structure (UN@AR(1)), respectively, was specified.[44] Longitudinal data were considered for the duration of the 5-year clinical trial, i.e., the time during which participants persisted in the randomized supplement assignments, not during any subsequent epidemiologic follow-up. However, on the rare occasion that proximity reached zero during follow-up, all subsequent time-points were censored.

The primary analyses were performed as main effects analyses (also known as factorial or at-the-margins analyses) of the randomized treatment assignments, since this is the appropriate statistical approach for clinical trials with a 2x2 factorial design.[45,46] In the AREDS, the comparisons comprised: (i) antioxidants versus no antioxidants and, separately, (ii) zinc versus no zinc. Hence, for antioxidants, for example, the comparison was between (i) participants randomized to antioxidants only and participants randomized to antioxidants and zinc, versus (ii) participants randomized to zinc only and participants randomized to placebo. In the AREDS2, the comparisons comprised: (i) lutein/zeaxanthin versus no lutein/zeaxanthin (primary randomization), (ii) lutein/zeaxanthin versus no lutein/zeaxanthin (primary randomization, but in the study population assigned by secondary randomization to no β-carotene, performed since lutein/zeaxanthin and β-carotene are known to compete for intestinal absorption[47]), (iii) DHA/EPA versus no DHA/EPA (primary randomization), (iv) β-carotene versus no β-carotene (secondary randomization), and (v) zinc 80 mg versus 25 mg (secondary randomization). However, in supplementary analyses of both the AREDS and AREDS2 datasets, a 4-level treatment variable was used, with the placebo assignment as reference. In other supplementary analyses of both the AREDS and AREDS2 datasets, the analyses were repeated for the prevalent and the incident GA cohorts, considered separately.

For both the AREDS and AREDS2, analyses of change over time in GA area were performed in the larger analysis subpopulations, comprising eyes with non-central and with central GA at the first time-point, using methods similar to those described previously.[5,42] Again, the unit of analysis was the eye. Mixed-model repeated-measures regression was performed with square root of GA area as the outcome measure. The square root transformation was used, to reduce the dependence of area-based progression rate on baseline lesion size.[5,48-53] The models included the variable of interest (i.e., AREDS randomized treatment assignment), years from first time-point with GA, and their interaction term. The models also included terms for age, sex, smoking status, square root of GA area at first time-point with GA, presence/absence of central involvement at first time-point with GA, and correlation between eyes. In the AREDS analyses, the models also included a term for presence/absence of GA in fellow eye at first time-point with GA; this term was not included in the AREDS2 analyses, as the information was not available for all eyes. In the AREDS2 analyses, the models also included a term for GA configuration at first time-point with GA; this term was not included in the AREDS analyses, as the information was not available for all eyes.

Again, the primary analyses were main effects analyses, while supplementary analyses used the 4-level treatment variable. In other supplementary analyses, the analyses were repeated for the prevalent and the incident GA cohorts, considered separately. In addition, in other supplementary analyses, the area-based analyses were repeated in the study population used in the proximity-based analyses (i.e., only those with non-central GA at the first time-point), in order to provide a direct comparison of the proximity versus area results in the same study population.

In supplementary analyses, for both the AREDS and AREDS2, the rate of change in BCVA over time was analyzed by mixed-model regression, with adjustment for the same variables as those described above, in each of the two study subpopulations.

All analyses were performed with commercially available statistical software (SAS version 9.4; SAS Institute, Cary, NC). Given the post hoc nature of the study, the analyses were considered exploratory, and statistical significance was set at $p=0.05$, based on two-sided testing. Throughout this report, the word significant is used to indicate statistical significance, unless specified otherwise.

Results

Rate of Geographic Atrophy Progression towards Central Macula according to Randomized Treatment Assignment in Age-Related Eye Diseases Study

The study population for these analyses, i.e., eyes with at least two annual study visits with GA, and with non-central GA at the first visit, comprised 208 eyes of 183 participants. Their demographic and clinical characteristics are shown in Table 3. Mean follow-up was 3.0 years (standard deviation [SD] 1.4).

The results of main effects analyses of the GA proximity-based progression rate towards the central macula, according to randomized treatment assignment, are shown in Table 4. GA progression towards the central macula was significantly slower in eyes of participants randomized to antioxidants versus no antioxidants, at 50.7 µm/year (95% CI 38.0-63.4 µm/year) and 72.9 µm/year (95% CI 61.3-84.5 µm/year), respectively (p=0.012). No significant difference was observed for the comparison of zinc versus no zinc.

The results of supplementary analyses with a 4-level treatment variable are shown in Supplementary Table 5. GA progression towards the central macula was slower in eyes of participants randomized to antioxidants alone than of those randomized to placebo, at 39.8 µm/year (95% CI 21.2-58.4 µm/year) and 73.2 µm/year (95% CI 56.4-89.9 µm/year), respectively (p=0.009). For the other two comparisons, no significant difference was observed. The results of supplementary analyses of the prevalent and incident GA cohorts are shown in Supplementary Table 6.

Geographic Atrophy Area-Based Progression Rate according to Randomized Treatment Assignment in Age-Related Eye Diseases Study

The study population for these analyses, i.e., eyes with at least two annual study visits with GA, comprised 392 eyes of 318 participants. Their demographic and clinical characteristics are shown in Table 3. Mean follow-up was 3.1 years (SD 1.5).

The results of main effects analyses of the GA area-based progression rate, according to randomized treatment assignment, are shown in Table 4. No significant difference was observed between eyes of participants randomized to antioxidants versus no antioxidants, or to zinc versus no zinc. The results of supplementary analyses with a 4-level treatment variable are shown in Supplementary Table 7.

The results of supplementary analyses of the prevalent and incident GA cohorts are shown in Supplementary Table 8. In most cases, no significant difference was observed between the randomized treatment assignments. However, for eyes with incident GA, a significant difference was observed for the comparison of antioxidants versus no antioxidants (p=0.048). Area-based progression was slower in eyes of participants randomized to antioxidants versus no antioxidants, at 0.240 mm/year (95% CI 0.206-0.275 mm/year) and 0.286 mm/year (95% CI 0.256-0.315 mm/year), respectively.

The area-based analyses were repeated in the study population used in the proximity-based analyses (i.e., those with non-central GA), to provide a direct comparison of the proximity versus area results in the same study population (Supplementary Table 9). In most cases, no significant difference was observed between the randomized treatment assignments. However, for eyes with incident GA, a significant difference was observed for the comparison of antioxidants versus no antioxidants (p=0.007). Area-based progression was slower in eyes of participants randomized to antioxidants versus no antioxidants, at 0.258 mm/year (95% CI 0.194-0.321 mm/year) and 0.379 mm/year (95% CI 0.319-0.440 mm/year), respectively. Hence, the pattern of results was more similar to that of the area-based analyses in the larger study population than the proximity-based analyses in the same study population.

Rate of Change in Best-Corrected Visual Acuity according to Randomized Treatment Assignment in Age-Related Eye Diseases Study

The results of analyses of rate of change in visual acuity over time, according to randomized treatment assignment, are shown in Supplementary Table 10. In most cases, no significant difference was observed between the randomized treatment assignments. However, in the incident GA cohort of the study population for the proximity analyses (i.e., eyes with early non-central GA), a significant difference was observed for the comparison of antioxidants versus no antioxidants (p=0.007). The rate of visual acuity decline was slower in eyes of participants randomized to antioxidants than no antioxidants, at -2.1 letter score/year (95% CI -3.2 to -1.0) and -4.2 letter score/year (95% CI -5.2 to -3.1), respectively.

Rate of Geographic Atrophy Progression towards Central Macula according to Randomized Treatment Assignment in Age-Related Eye Diseases Study 2

The study population, i.e., eyes with at least two annual study visits with GA, and with non-central GA at the first visit, comprised 793 eyes of 646 participants for the primary randomization (including 574 eyes of 467 participants for the secondary randomization). Their demographic and clinical characteristics are shown in Table 11. Mean follow-up was 3.3 years (SD 1.5).

The results of main effects analyses of the GA proximity-based progression rate are shown in Table 12. GA progression towards the central macula was significantly slower in eyes of participants randomized to lutein/zeaxanthin versus no lutein/zeaxanthin, at 84.5 μm/year (95% CI 72.4-96.6 μm/year) and 105.3 μm/year (95% CI 93.2-117.3 μm/year), respectively (p=0.017). For the other comparisons, no significant difference was observed. Given that lutein/zeaxanthin and β-carotene compete for intestinal absorption[47], the lutein/zeaxanthin analyses were performed separately in the study population randomized to no β-carotene (Table 12). In this study population, again, the proximity-based progression rate was significantly slower in eyes of participants randomized to lutein/zeaxanthin versus no lutein/zeaxanthin, at 80.1 μm/year (95% CI 60.9-99.3 μm/year) and 114.4 μm/year (95% CI 96.2-132.7 μm/year), respectively (p=0.011), i.e., with a larger difference between the estimates.

The results of supplementary analyses with a 4-level treatment variable are shown in Supplementary Table 13. GA progression towards the central macula was slower in eyes of participants randomized to lutein/zeaxanthin alone than of those randomized to placebo (p=0.039) and was slower in eyes of participants randomized to lutein/zeaxanthin and DHA/EPA than of those randomized to placebo (p=0.040). The results of supplementary analyses of the prevalent and incident GA cohorts are shown in Supplementary Table 14.

Geographic Atrophy Area-Based Progression Rate according to Randomized Treatment Assignment in Age-Related Eye Diseases Study 2

The study population, i.e., eyes with at least two annual study visits with GA, comprised 1210 eyes of 891 participants for the primary randomization (including 883 eyes of 646 participants for the secondary randomization). Their demographic and clinical characteristics are shown in Table 11. Mean follow-up was 3.3 years (SD 1.4).

The results of main effects analyses of the GA area-based progression rate, according to randomized treatment assignment, are shown in Table 12. Area-based progression was significantly slower in eyes of participants randomized to β-carotene than no β-carotene, at 0.264 mm/year (95% CI 0.244-0.285 mm/year) and 0.301 mm/year (95% CI 0.283-0.320 mm/year), respectively (p=0.009). For the other comparisons, no significant difference was observed.

The results of supplementary analyses with a 4-level treatment variable are shown in Supplementary Table 15, and those of the prevalent and incident GA cohorts in Supplementary Table 16. The results of supplementary analyses of area-based progression rates in the study population from the proximity analyses (i.e., only eyes with non-central GA) are shown in Supplementary Table 17.

Rate of Change in Best-Corrected Visual Acuity according to Randomized Treatment Assignment in Age-Related Eye Diseases Study 2

The results of analyses of rate of change in visual acuity over time, according to randomized treatment assignment, are shown in Supplementary Tables 18 and 19. In the proximity-based study population, in those randomized to no β-carotene, a borderline significant difference was observed for lutein/zeaxanthin versus no lutein/zeaxanthin (p=0.058), with numerically slower visual acuity decline in eyes of participants randomized to lutein/zeaxanthin. In the area-based study population, a significant difference was observed for β-carotene vs no β-carotene (p=0.010), with slower visual acuity decline in eyes of participants randomized to β-carotene. In addition, in the area-based study population, a significant difference was observed for low vs high zinc (p=0.009), with slower visual acuity decline in eyes of participants randomized to low zinc. In most other cases, no significant difference was observed between the randomized treatment assignments.

Discussion

Main Findings

In this analysis of two large clinical trials of participants with AMD, the AREDS results show that oral antioxidant supplements (comprising vitamin C, vitamin E, and β-carotene) led, in eyes with non-central GA, to slower GA progression towards the central macula. The difference was approximately 36%. Similarly, the AREDS2 results show that oral lutein/zeaxanthin supplements also led, in eyes with non-central GA, to slower GA progression towards the central macula. The difference was approximately 35%. The effect of lutein/zeaxanthin appears to be additive to that of the AREDS antioxidant supplements. This is because, in AREDS2 participants assigned to vitamins C and E but no β-carotene, randomization to oral lutein/zeaxanthin led to slower GA progression towards the central macula. However, randomization to β-carotene did not lead to altered GA progression rate towards the central macula. Hence, the effects of lutein/zeaxanthin and vitamins C and E appear complementary.

In the AREDS, the primary analyses demonstrated no difference in area-based GA progression with either antioxidants or zinc. We repeated the area-based analyses in the smaller study population used in the proximity-based analyses (i.e., with non-central GA). First, this permitted us to make direct comparison of the proximity-based and area-based results in the same study population. The distinct results for the two different outcomes strengthen the idea of genuinely differential efficacy of antioxidants on proximity-based vs area-based GA progression. Second, this exploratory approach highlighted a particular subgroup of interest: eyes with incident non-central GA. In this subgroup, randomization to antioxidants led to slower area-based GA progression, with a large effect size. Overall, in the AREDS population of eyes with non-central GA, the prevalent cohort demonstrated a treatment effect with antioxidants for proximity-based but not area-based GA progression, while the incident cohort demonstrated the opposite.

Likely Unifying Explanation and Implications for Understanding Foveal Sparing in Geographic Atrophy

The likely unifying explanation for differences in proximity-based vs area-based progression, and for eyes with central versus non-central GA, is efficacy in slowing GA progression predominantly in the central and paracentral macula, as opposed to the peripheral macula. In this way, efficacy would be detected in proximity-based analyses (performed only on eyes with non-central GA). However, the central macula represents only a very small proportion of the whole macular area (with the central ETDRS subfield accounting for just 3% of the full macular grid[54]). Hence, in analyses of area-based progression in all eyes, minimal efficacy would be observed. However, area-based efficacy would be detected preferentially in eyes with non-central GA, particularly for incident GA, where GA area is small, such that decreased progression into the central/paracentral macula would also affect the GA area metric.

Similarly, for lutein/zeaxanthin, efficacy in slowing GA progression was demonstrated for the proximity-based but not the area-based analyses. Again, we believe that this contrast is likely explained by efficacy predominantly in the central/paracentral macula. Lutein and zeaxanthin are other major antioxidants of the macula that must be obtained from the diet, as they cannot be synthesized by humans.[55,56] Importantly, these carotenoid are highly abundant in the very central macula (i.e., the central ETDRS subfield), with lower abundance in the paracentral subfields and lowest abundance beyond this point.[55,57] Hence, their known distribution appears consistent with the preferential efficacy of supplementation in slowing proximity-based progression in non-central GA. This agreement provides strong biological plausibility for the pattern of results.

The results of our analyses suggest that vitamin C, vitamin E, and lutein/zeaxanthin may make important contributions to the known phenomenon of foveal sparing from GA in AMD[5,21,22,26,58], and that oral supplementation may augment this natural phenomenon. The phenomenon of foveal sparing comprises the observations that, first, incident GA occurs less commonly in the central macula, despite precursor lesions (i.e., soft drusen) occurring most frequently at that location[5,8,59,60], and, second, that GA progression rates in the macula increase with increasing eccentricity.[22] Indeed, one study has shown that GA progression into the central macula is approximately 4-fold slower than elsewhere.[21] Similar observations have been made in GA that is observed in inherited retinal diseases.[23] However, the mechanisms underlying foveal sparing are not fully understood.[23,58] Deciphering these mechanisms is important, to permit the development of therapeutic approaches that enhance or recapitulate them. Importantly, disease-independent mechanisms are thought to be responsible for foveal sparing in GA.[23] Hence, oral antioxidant and carotenoid supplementation may be beneficial not only in AMD, but also in other diseases leading to GA. A beneficial effect might apply not only to inherited retinal diseases, which affect over two million people worldwide[61], but also to drug toxicities, e.g., hydroxychloroquine or pentosan polysulfate retinopathy, in which GA progression to central involvement often occurs even after drug cessation and for which no treatment is available.[62]

Consistency with Previous Analyses Related to Diet

Our study's findings appear consistent with the results of AREDS2 analyses of diet and GA progression, in which we observed a strong association between healthier diet and slower area-based GA progression.[7,42] Of the food components responsible, one of the strongest was whole fruit. Prominent ingredients in fruit include antioxidant molecules, such as flavonoids and provitamin A carotenoids (e.g., β-carotene).[63,64] Hence, both observational data on diet and randomized data on oral supplementation point to the importance of antioxidants in slowing GA progression. Interestingly, previous studies have shown no efficacy of the AREDS supplement components in decreasing the risk of GA development.[31] The discrepancy between lack of efficacy for decreasing GA incidence but positive efficacy in slowing GA progression towards the central macula suggests important differences in the underlying biological mechanisms active at each disease stage.[7]

Relationship between Structural Outcome Measures and Visual Acuity

We had little expectation that slowing proximity-based GA progression would be accompanied by significantly slower decline in VA over the follow-up times achieved in this study. First, in most eyes in this study, GA progression towards the central macula fell short of actual center-point involvement. Second, even with central involvement, the magnitude of visual acuity decline in GA is typically small initially.[25,27] Usually, acuity does not decline substantially until GA is both center-involving and relatively large, such that central involvement may be considered a necessary (if not sufficient) cause for decreased acuity.[25-27] Hence, GA proximity to the central macula remains critical to visual prognosis in the long run, and slowing proximity-based progression and time to central involvement should ultimately preserve visual acuity and visual function, given sufficient follow-up time. For example, preserving GA in a horseshoe or donut configuration for a longer time, by delaying central encroachment and final involvement, would be highly valuable, because these GA configurations are usually associated with good acuity.[65]

Despite our low expectation regarding visual acuity, in the proximity-based analysis population, we observed a slower decline in visual acuity among eyes of participants randomized to lutein/zeaxanthin in the AREDS2. Although we did not observe a similar result for antioxidants in the AREDS, a significant difference was observed in the incident GA cohort. For most of the GA area-based analyses, significant differences in the rate of change of the structural measure were accompanied by equivalent differences in the rate of decline in visual acuity. For example, in the AREDS2, slower GA area-based progression with β-carotene was accompanied by slower decline in visual acuity. In general, despite observations of statistical significance for some of these comparisons, the magnitudes of the differences are unlikely to have been clinically meaningful during the time-course of these studies themselves. This is in keeping with the expectations and explanations discussed above. However, first, these differences may be seen to support the differences observed for the structural analyses. Second, the magnitudes of the differences might become much larger in subsequent years.

Clinical Implications

Our findings may justify a prospective randomized controlled trial of oral antioxidant and lutein/zeaxanthin supplementation in eyes of individuals with non-central GA. If the results were confirmed, this would suggest a new standard of care for patients with GA. At present, no recommendations are available; for example, the American Academy of Ophthalmology Age-Related Macular Degeneration Preferred Practice Pattern guidelines contain no specific recommendations for patients with bilateral GA.[36] For non-advanced AMD (i.e., prior to GA or neovascular AMD), the formulation of supplements typically recommended comprises vitamin C, vitamin E, lutein/zeaxanthin (instead of β-carotene), and zinc, i.e., the final "AREDS2 formulation", which is marketed widely.[32,36,66] The findings of this study indicate that patients with non-central GA in one or both eyes may benefit most from a formulation that comprises vitamins C and E, and lutein/zeaxanthin, but not β-carotene. β-carotene appears to decrease the proximity-based efficacy of lutein/zeaxanthin (presumably through their known competition for intestinal absorption[47]), does not slow proximity-based progression on its own, and is thought to increase the risk of lung cancer in individuals with a positive smoking history.[32,66]

This formulation could include or exclude zinc, according to patient and physician preference. If included, the rationale would be the possibility of decreased risk of neovascular AMD (which can occur following GA[5]). With the inclusion of zinc, this would constitute the same "AREDS2 formulation" described above. This approach would have the potential advantage of simplicity, since individuals could continue taking the same supplement formulation before and after progression from intermediate AMD to GA.

Our findings have other implications. In clinical trials of novel potential therapies to slow GA progression, oral supplement use should be recorded, as this might be a source of unexplained variation in GA progression rates.[11,67] Performing covariate adjustment for this variable may lead to increased precision and power of these clinical trials.[11,68] Indeed, it is not clear whether any interaction might exist between oral supplements and approaches like local complement inhibition. The results may also provide important insights into our understanding of the pathogenesis of GA progression.[7,69] For example, in that oral antioxidants decrease GA progression towards the central macula, oxidative stress appears to be implicated in the mechanisms of GA progression at that location.

Comparison with Literature

We are not aware of any previous study, other than those described in AREDS Report 26 and AREDS2 Report 16, that have analyzed GA progression according to the study randomizations.[5,30] Neither previous study analyzed proximity-based progression rates. In AREDS Report 26, the investigators analyzed a small study population of 68 participants with GA, with low power to observe or rule out an effect of oral supplements.[30] In addition, the analyses were limited by the absence of square root transformation of GA area.

Strengths and Limitations

The major strength of our study is the randomized controlled trial design of the constituent studies; this included three separate randomizations, each with a 2x2 factorial design, permitting analysis of six different oral supplements or doses. This provided a unique opportunity to assess whether various oral supplements may lead causally to slower GA progression. Other strengths include the use of two complementary outcome measures, large sample size, a mean of 3-year follow-up time while taking study supplements, scheduled standard imaging with central masked reading center grading, repeated observations, and adjustment for multiple variables, to increase the relative power and precision of estimated effects. We observed some replication of findings among the two independent randomized trials: in both the AREDS and AREDS2, significant efficacy for proximity-based but not area-based GA progression was observed for two different sets of oral supplements with antioxidant properties. This agreement lends strength to the idea of genuinely differential efficacy of some therapies at the central versus peripheral macula. Indeed, related ideas have been suggested in trials of complement inhibitors.[14]

Potential limitations include the use of color fundus photography, since GA is believed to be detected earlier, and perhaps with less variability of area measurements, on fundus autofluorescence (FAF) images.[70] However, previous studies have demonstrated high correlation between color fundus photography and FAF images in measuring GA area and progression.[70-72] This includes previous large-scale analyses of the AREDS2 GA dataset itself.[70] In these analyses, the investigators analyzed 8070 instances of FAF-color fundus photograph image pairs from 2202 AREDS2 participants, including approximately 2000 instances with GA. GA area-based progression rates were extremely similar between the two modalities, with no significant difference. In addition, the assessment of central macular involvement was considered superior on color fundus photographs than on FAF images. Hence, this factor is unlikely to have altered the results substantially, particularly since it applies equally to all randomized treatment arms in both AREDS and AREDS2. Second, no data are available to permit a direct comparison of randomization to the current AREDS2 supplement (i.e., containing lutein/zeaxanthin instead of β-carotene) vs placebo. This is because, in the AREDS2, all participants took the vitamin C and E doses used in the AREDS. Another limitation is the post hoc (unplanned) nature of the analysis. In this context, the analyses should be considered exploratory, and it is possible that some findings arose by chance alone. We therefore recommend further research in this area to replicate, refute, or modify our findings or recommendations. Finally, the generalizability of the findings to other populations (according to race or other characteristics) and other countries is unknown.

Conclusions

In conclusion, in eyes with non-central GA, oral antioxidant supplementation (comprising very high daily doses of vitamin C, vitamin E, and β-carotene) led to slower progression of GA towards the central macula. In addition, in eyes with non-central GA, oral lutein/zeaxanthin supplementation led to slower progression of GA towards the central macula, even in individuals already taking oral antioxidant supplements. These findings have important implications for the potential preservation of visual function in the long term. These results also highlight important differences in mechanisms of GA progression in the central versus peripheral macula and have implications for our understanding of the mechanisms of foveal sparing. These findings may justify a prospective randomized controlled trial of oral antioxidant and lutein/zeaxanthin supplementation in eyes of individuals with non-central GA.

Figure Legends

Figure 1. Color fundus photographs showing the progression of non-central geographic atrophy towards the central macula over time. Geographic atrophy proximity (i.e., the shortest distance between the macular center-point and the nearest pixel of geographic atrophy) decreased gradually over time from 685 µm (2007) to 68 µm (2011).

Figure 3. Randomization schemes of the Age-Related Eye Diseases Studies (AREDS).

A. AREDS. Participants were randomized 1:1:1:1, using a 2x2 factorial design, to oral antioxidants (vitamin C, vitamin E, and β-carotene) only, zinc only, both antioxidants and zinc, or placebo.

B. AREDS2. Participants were randomized, 1:1:1:1, using a 2x2 factorial design, to oral lutein/zeaxanthin only, docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) only, both lutein/zeaxanthin and DHA/EPA, or placebo. All participants were also offered the original AREDS formulation (i.e., vitamin C, vitamin E, β-carotene, and zinc) to take alongside the randomly assigned primary treatment. Participants who agreed to take the AREDS formulation and consented to a secondary randomization underwent randomization, 1:1:1:1, using a 2x2 factorial design, to one of four alternative AREDS formulations: original formulation, no β-carotene, low zinc (25 mg instead of 80 mg), and both no β-carotene and low zinc. * Participants who were current smokers or who had stopped smoking within the year before enrollment were randomly assigned to one of the two arms without β-carotene.

Abbreviations: AREDS, Age-Related Eye Disease Study; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

References

1. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. Feb 2014;2(2):e106-16. doi:10.1016/S2214-109X(13)70145-1
2. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*. Feb 2021;9(2):e144-e160. doi:10.1016/S2214-109X(20)30489-7
3. Fleckenstein M, Keenan TDL, Guymer RH, et al. Age-related macular degeneration. *Nat Rev Dis Primers*. May 6 2021;7(1):31. doi:10.1038/s41572-021-00265-2
4. Rudnicka AR, Jarrar Z, Wormald R, Cook DG, Fletcher A, Owen CG. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. *Ophthalmology*. Mar 2012;119(3):571-80. doi:10.1016/j.ophtha.2011.09.027
5. Keenan TD, Agron E, Domalpally A, et al. Progression of Geographic Atrophy in Age-related Macular Degeneration: AREDS2 Report Number 16. *Ophthalmology*. Dec 2018;125(12):1913-1928. doi:10.1016/j.ophtha.2018.05.028
6. Fleckenstein M, Mitchell P, Freund KB, et al. The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. *Ophthalmology*. Mar 2018;125(3):369-390. doi:10.1016/j.ophtha.2017.08.038
7. Keenan TDL. Geographic Atrophy in Age-Related Macular Degeneration: A Tale of Two Stages. *Ophthalmology Science*. 2023;3(3)doi:10.1016/j.xops.2023.100306
8. Sassmannshausen M, Behning C, Weinz J, et al. Characteristics and Spatial Distribution of Structural Features in Age-Related Macular Degeneration: A MACUSTAR Study Report. *Ophthalmol Retina*. Dec 20 2022;doi:10.1016/j.oret.2022.12.007
9. Sadda SR, Guymer R, Holz FG, et al. Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT: Classification of Atrophy Report 3. *Ophthalmology*. Apr 2018;125(4):537-548. doi:10.1016/j.ophtha.2017.09.028
10. Csaky K, Ferris F, 3rd, Chew EY, Nair P, Cheetham JK, Duncan JL. Report From the NEI/FDA Endpoints Workshop on Age-Related Macular Degeneration and Inherited Retinal Diseases. *Invest Ophthalmol Vis Sci*. Jul 1 2017;58(9):3456-3463. doi:10.1167/iovs.17-22339
11. Anegondi N, Gao SS, Steffen V, et al. Deep Learning to Predict Geographic Atrophy Area and Growth Rate from Multimodal Imaging. *Ophthalmol Retina*. Aug 28 2022;doi:10.1016/j.oret.2022.08.018
12. Apellis Pharmaceuticals I. FDA Approves SYFOVRE™ (pegcetacoplan injection) as the First and Only Treatment for Geographic Atrophy (GA), a Leading Cause of Blindness. Accessed 02/28/2023, https://investors.apellis.com/news-releases/news-release-details/fda-approves-syfovretm-pegcetacoplan-injection-first-and-only
13. Iveric Bio. Iveric Bio Receives U.S. FDA Approval for IZERVAY™ (avacincaptad pegol intravitreal solution), a New Treatment for Geographic Atrophy. Accessed 08/11/2023, https://ivericbio.com/iveric-bio-receives-us-fda-approval-for-izervay-avacincaptad-pegol-intravitreal-solution-a-new-treatment-for-geographic-atrophy/
14. Heier JS, Lad EM, Holz FG, et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. *Lancet*. Oct 21 2023;402(10411):1434-1448. doi:10.1016/S0140-6736(23)01520-9

15. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Phase 2 Trial. *Ophthalmology*. Feb 2020;127(2):186-195. doi:10.1016/j.ophtha.2019.07.011
16. Wykoff CC, Rosenfeld PJ, Waheed NK, et al. Characterizing New-Onset Exudation in the Randomized Phase 2 FILLY Trial of Complement Inhibitor Pegcetacoplan for Geographic Atrophy. *Ophthalmology*. Sep 2021;128(9):1325-1336. doi:10.1016/j.ophtha.2021.02.025
17. Keenan TDL. Local Complement Inhibition for Geographic Atrophy in Age-Related Macular Degeneration: Prospects, Challenges, and Unanswered Questions. *Ophthalmol Sci*. Dec 2021;1(4):100057. doi:10.1016/j.xops.2021.100057
18. Jaffe GJ, Westby K, Csaky KG, et al. C5 Inhibitor Avacincaptad Pegol for Geographic Atrophy Due to Age-Related Macular Degeneration: A Randomized Pivotal Phase 2/3 Trial. *Ophthalmology*. Apr 2021;128(4):576-586. doi:10.1016/j.ophtha.2020.08.027
19. Khanani AM, Patel SS, Staurenghi G, et al. Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial. *Lancet*. Sep 8 2023;doi:10.1016/S0140-6736(23)01583-0
20. Colijn JM, Liefers B, Joachim N, et al. Enlargement of Geographic Atrophy From First Diagnosis to End of Life. *JAMA Ophthalmol*. Jul 1 2021;139(7):743-750. doi:10.1001/jamaophthalmol.2021.1407
21. Shen LL, Sun M, Ahluwalia A, et al. Natural history of central sparing in geographic atrophy secondary to non-exudative age-related macular degeneration. *Br J Ophthalmol*. May 2022;106(5):689-695. doi:10.1136/bjophthalmol-2020-317636
22. Shen LL, Sun M, Ahluwalia A, Park MM, Young BK, Del Priore LV. Local Progression Kinetics of Geographic Atrophy Depends Upon the Border Location. *Invest Ophthalmol Vis Sci*. Oct 4 2021;62(13):28. doi:10.1167/iovs.62.13.28
23. Bax NM, Valkenburg D, Lambertus S, et al. Foveal Sparing in Central Retinal Dystrophies. *Invest Ophthalmol Vis Sci*. Aug 1 2019;60(10):3456-3467. doi:10.1167/iovs.18-26533
24. Shen LL, Sun M, Khetpal S, Grossetta Nardini HK, Del Priore LV. Topographic Variation of the Growth Rate of Geographic Atrophy in Nonexudative Age-Related Macular Degeneration: A Systematic Review and Meta-analysis. *Invest Ophthalmol Vis Sci*. Jan 23 2020;61(1):2. doi:10.1167/iovs.61.1.2
25. Shen LL, Sun M, Ahluwalia A, et al. Relationship of Topographic Distribution of Geographic Atrophy to Visual Acuity in Nonexudative Age-Related Macular Degeneration. *Ophthalmol Retina*. Aug 2021;5(8):761-774. doi:10.1016/j.oret.2020.11.003
26. Sayegh RG, Sacu S, Dunavolgyi R, et al. Geographic Atrophy and Foveal-Sparing Changes Related to Visual Acuity in Patients With Dry Age-Related Macular Degeneration Over Time. *Am J Ophthalmol*. Jul 2017;179:118-128. doi:10.1016/j.ajo.2017.03.031
27. Agron E, Vitale S, Weber C, Keenan TDL, Cukras CA, Chew EY. Effect of geographic atrophy proximity to the center point of the fovea on visual acuity. presented at: Association for Research in Vision and Ophthalmology Annual Meeting 2023; June 2023; New Orleans. Session ARVO E-Abstract 1753. https://iovs.arvojournals.org/article.aspx?articleid=2789780
28. Bagheri S, Lains I, Silverman RF, et al. Percentage of Foveal vs Total Macular Geographic Atrophy as a Predictor of Visual Acuity in Age-Related Macular Degeneration. *J Vitreoretin Dis*. Sep 2019;3(5):278-282. doi:10.1177/2474126419859454
29. Schmitz-Valckenberg S, Nadal J, Fimmers R, et al. Modeling Visual Acuity in Geographic Atrophy Secondary to Age-Related Macular Degeneration. *Ophthalmologica*. 2016;235(4):215-24. doi:10.1159/000445217
30. Lindblad AS, Lloyd PC, Clemons TE, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol*. Sep 2009;127(9):1168-74. doi:10.1001/archophthalmol.2009.198

31. Age-Related Eye Disease Study Research G. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. Oct 2001;119(10):1417-36. doi:10.1001/archopht.119.10.1417

32. Age-Related Eye Disease Study 2 Research G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. May 15 2013;309(19):2005-15. doi:10.1001/jama.2013.4997

33. Age-Related Eye Disease Study 2 Research G, Chew EY, Clemons TE, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmol*. Feb 2014;132(2):142-9. doi:10.1001/jamaophthalmol.2013.7376

34. Charkoudian LD, Gower EW, Solomon SD, Schachat AP, Bressler NM, Bressler SB. Vitamin usage patterns in the prevention of advanced age-related macular degeneration. *Ophthalmology*. Jun 2008;115(6):1032-1038 e4. doi:10.1016/j.ophtha.2007.08.003

35. Lee AY, Butt T, Chew E, et al. Cost-effectiveness of age-related macular degeneration study supplements in the UK: combined trial and real-world outcomes data. *Br J Ophthalmol*. Apr 2018;102(4):465-472. doi:10.1136/bjophthalmol-2017-310939

36. Flaxel CJ, Adelman RA, Bailey ST, et al. Age-Related Macular Degeneration Preferred Practice Pattern(R). *Ophthalmology*. Jan 2020;127(1):P1-P65. doi:10.1016/j.ophtha.2019.09.024

37. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. *Control Clin Trials*. Dec 1999;20(6):573-600.

38. AREDS2 Research Group, Chew EY, Clemons T, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology*. Nov 2012;119(11):2282-9. doi:10.1016/j.ophtha.2012.05.027

39. Danis RP, Domalpally A, Chew EY, et al. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2). *Invest Ophthalmol Vis Sci*. Jul 8 2013;54(7):4548-54. doi:10.1167/iovs.13-11804

40. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6. *Am J Ophthalmol*. Nov 2001;132(5):668-81.

41. Age-Related Eye Disease Study Research G. The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6. *Am J Ophthalmol*. Nov 2001;132(5):668-81. doi:10.1016/s0002-9394(01)01218-1

42. Agron E, Mares J, Chew EY, Keenan TDL, Group AR. Adherence to a Mediterranean Diet and Geographic Atrophy Enlargement Rate: Age-Related Eye Disease Study 2 Report 29. *Ophthalmol Retina*. Sep 2022;6(9):762-770. doi:10.1016/j.oret.2022.03.022

43. Agron E, Domalpally A, Cukras CA, et al. Reticular Pseudodrusen Status, ARMS2/HTRA1 Genotype, and Geographic Atrophy Enlargement: Age-Related Eye Disease Study 2 Report 32. *Ophthalmology*. Dec 5 2022;doi:10.1016/j.ophtha.2022.11.026

44. Galecki AT. General class of covariance structures for two or more repeated factors in longitudinal data analysis. *Communications in Statistics - Theory and Methods*. 1994/01/01 1994;23(11):3105-3119. doi:10.1080/03610929408831436

45. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomised controlled trials. *BMC Med Res Methodol*. Nov 24 2003;3:26. doi:10.1186/1471-2288-3-26

46. McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: a systematic review. *JAMA*. May 21 2003;289(19):2545-53. doi:10.1001/jama.289.19.2545

47. Eisenhauer B, Natoli S, Liew G, Flood VM. Lutein and Zeaxanthin-Food Sources, Bioavailability and Dietary Variety in Age-Related Macular Degeneration Protection. *Nutrients*. Feb 9 2017;9(2)doi:10.3390/nu9020120
48. Feuer WJ, Yehoshua Z, Gregori G, et al. Square root transformation of geographic atrophy area measurements to eliminate dependence of growth rates on baseline lesion measurements: a reanalysis of age-related eye disease study report no. 26. *JAMA Ophthalmol*. Jan 2013;131(1):110-1. doi:10.1001/jamaophthalmol.2013.572
49. Yehoshua Z, Rosenfeld PJ, Gregori G, et al. Progression of geographic atrophy in age-related macular degeneration imaged with spectral domain optical coherence tomography. *Ophthalmology*. Apr 2011;118(4):679-86. doi:10.1016/j.ophtha.2010.08.018
50. Pfau M, Lindner M, Goerdt L, et al. Prognostic Value of Shape-Descriptive Factors for the Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. *Retina*. Aug 2019;39(8):1527-1540. doi:10.1097/IAE.0000000000002206
51. Mones J, Biarnes M. The Rate of Progression of Geographic Atrophy Decreases With Increasing Baseline Lesion Size Even After the Square Root Transformation. *Transl Vis Sci Technol*. Nov 2018;7(6):40. doi:10.1167/tvst.7.6.40
52. Behning C, Fleckenstein M, Pfau M, et al. Modeling of atrophy size trajectories: variable transformation, prediction and age-of-onset estimation. *BMC Med Res Methodol*. Aug 17 2021;21(1):170. doi:10.1186/s12874-021-01356-0
53. Liefers B, Colijn JM, Gonzalez-Gonzalo C, et al. A Deep Learning Model for Segmentation of Geographic Atrophy to Study Its Long-Term Natural History. *Ophthalmology*. Aug 2020;127(8):1086-1096. doi:10.1016/j.ophtha.2020.02.009
54. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. May 1991;98(5 Suppl):786-806.
55. Arunkumar R, Bernstein PS. Macular Pigment Carotenoids and Bisretinoid A2E. *Adv Exp Med Biol*. 2023;1415:15-20. doi:10.1007/978-3-031-27681-1_3
56. Li X, Holt RR, Keen CL, et al. Potential roles of dietary zeaxanthin and lutein in macular health and function. *Nutr Rev*. May 10 2023;81(6):670-683. doi:10.1093/nutrit/nuac076
57. Owsley C, Swain TA, McGwin G, Jr., Clark ME, Kar D, Curcio CA. Biologically Guided Optimization of Test Target Location for Rod-mediated Dark Adaptation in Age-related Macular Degeneration: Alabama Study on Early Age-related Macular Degeneration 2 Baseline. *Ophthalmol Sci*. Jun 2023;3(2):100274. doi:10.1016/j.xops.2023.100274
58. Curcio CA, Kar D, Owsley C, Sloan KR, Ach T. Age-Related Macular Degeneration, a Mathematically Tractable Disease. *Invest Ophthalmol Vis Sci*. Mar 5 2024;65(3):4. doi:10.1167/iovs.65.3.4
59. Pollreisz A, Reiter GS, Bogunovic H, et al. Topographic Distribution and Progression of Soft Drusen Volume in Age-Related Macular Degeneration Implicate Neurobiology of Fovea. *Invest Ophthalmol Vis Sci*. Feb 1 2021;62(2):26. doi:10.1167/iovs.62.2.26
60. Sunness JS, Bressler NM, Tian Y, Alexander J, Applegate CA. Measuring geographic atrophy in advanced age-related macular degeneration. *Invest Ophthalmol Vis Sci*. Jul 1999;40(8):1761-9.
61. Sahel JA, Marazova K, Audo I. Clinical characteristics and current therapies for inherited retinal degenerations. *Cold Spring Harb Perspect Med*. Oct 16 2014;5(2):a017111. doi:10.1101/cshperspect.a017111
62. Somisetty S, Santina A, Sarraf D, Mieler WF. The Impact of Systemic Medications on Retinal Function. *Asia Pac J Ophthalmol (Phila)*. Mar-Apr 01 2023;12(2):115-157. doi:10.1097/APO.0000000000000605

63. Oteiza PI, Fraga CG, Galleano M. Linking biomarkers of oxidative stress and disease with flavonoid consumption: From experimental models to humans. *Redox Biol*. Jun 2021;42:101914. doi:10.1016/j.redox.2021.101914

64. Gorusupudi A, Nelson K, Bernstein PS. The Age-Related Eye Disease 2 Study: Micronutrients in the Treatment of Macular Degeneration. *Adv Nutr*. Jan 2017;8(1):40-53. doi:10.3945/an.116.013177

65. Sunness JS, Rubin GS, Zuckerbrod A, Applegate CA. Foveal-Sparing Scotomas in Advanced Dry Age-Related Macular Degeneration. *J Vis Impair Blind*. Oct 1 2008;102(10):600-610.

66. Chew EY, Clemons TE, Agron E, et al. Long-term Outcomes of Adding Lutein/Zeaxanthin and omega-3 Fatty Acids to the AREDS Supplements on Age-Related Macular Degeneration Progression: AREDS2 Report 28. *JAMA Ophthalmol*. Jul 1 2022;140(7):692-698. doi:10.1001/jamaophthalmol.2022.1640

67. Arslan J, Samarasinghe G, Benke KK, et al. Artificial Intelligence Algorithms for Analysis of Geographic Atrophy: A Review and Evaluation. *Transl Vis Sci Technol*. Oct 2020;9(2):57. doi:10.1167/tvst.9.2.57

68. Administration USFaD. Guidance Document. Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products. Draft Guidance for Industry. Accessed 02/28/2023, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adjusting-covariates-randomized-clinical-trials-drugs-and-biological-products

69. Grassmann F, Harsch S, Brandl C, et al. Assessment of Novel Genome-Wide Significant Gene Loci and Lesion Growth in Geographic Atrophy Secondary to Age-Related Macular Degeneration. *JAMA Ophthalmol*. Aug 1 2019;137(8):867-876. doi:10.1001/jamaophthalmol.2019.1318

70. Domalpally A, Danis R, Agron E, et al. Evaluation of Geographic Atrophy from Color Photographs and Fundus Autofluorescence Images: Age-Related Eye Disease Study 2 Report Number 11. *Ophthalmology*. Nov 2016;123(11):2401-2407. doi:10.1016/j.ophtha.2016.06.025

71. Yaspan BL, Williams DF, Holz FG, et al. Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration. *Sci Transl Med*. Jun 21 2017;9(395)doi:10.1126/scitranslmed.aaf1443

72. Khanifar AA, Lederer DE, Ghodasra JH, et al. Comparison of color fundus photographs and fundus autofluorescence images in measuring geographic atrophy area. *Retina*. Oct 2012;32(9):1884-91. doi:10.1097/IAE.0b013e3182509778

Table 3. Demographic and Clinical Characteristics of the Study Populations at the First Time-Point with Geographic Atrophy in the Age-Related Eye Diseases Study.

	Eyes with non-central geographic atrophy at first time-point (for proximity-based analyses)					All eyes with geographic atrophy (for area-based analyses)				
Randomized assignment	All arms	Antioxidants only	Zinc only	Antioxidants and zinc	Placebo	All arms	Antioxidants only	Zinc only	Antioxidants and zinc	Placebo
Participants	183	41	57	47	38	318	65	91	91	71
Age (years), mean (SD)	72.2 (5.2)	71.8 (5.8)	72.0 (5.3)	72.4 (5.1)	72.8 (4.7)	71.5 (5.3)	71.4 (5.7)	71.7 (5.1)	71.3 (5.3)	71.5 (5.1)
Women	115 (62.8%)	21 (51.2%)	40 (70.1%)	31 (65.9%)	23 (60.5%)	176 (55.3%)	30 (46.1%)	55 (60.4%)	56 (61.5%)	35 (49.3%)
Smoking status										
Never	77 (42.1%)	14 (34.1%)	28 (49.1%)	19 (40.4%)	16 (42.1%)	122 (38.4%)	19 (29.2%)	40 (44.0%)	34 (37.4%)	29 (40.8%)
Former	89 (48.6%)	23 (56.0%)	25 (43.8%)	26 (55.3%)	15 (39.4%)	163 (51.3%)	39 (60.0%)	42 (46.2%)	50 (54.9%)	32 (45.1%)
Current	17 (9.3%)	4 (9.7%)	4 (7.0%)	2 (4.2%)	7 (18.4%)	33 (10.4%)	7 (10.8%)	9 (9.9%)	7 (7.7%)	10 (14.1%)
Follow-up (years), mean (SD)*	3.0 (1.4)	3.3 (1.4)	2.8 (1.3)	2.9 (1.4)	3.2 (1.6)	3.1 (1.5)	3.1 (1.4)	2.9 (1.4)	3.2 (1.4)	3.1 (1.6)
Eyes	208	45	67	54	42	392	77	117	109	89
Cohort										
Prevalent†	85 (40.9%)	22 (48.8%)	22 (32.8%)	18 (33.3%)	23 (54.7%)	164 (41.8%)	35 (45.5%)	42 (35.9%)	47 (43.1%)	40 (44.9%)
Incident†	123 (59.1%)	23 (51.1%)	45 (67.1%)	36 (66.6%)	19 (45.2%)	228 (58.2%)	42 (54.5%)	75 (64.1%)	62 (56.9%)	49 (55.1%)
Central/non-central GA										
Non-central	-	-	-	-	-	216 (55.1%)	47 (61.0%)	70 (59.8%)	56 (51.3%)	43 (48.3%)
Central	-	-	-	-	-	176 (44.9%)	30 (38.9%)	47 (40.1%)	53 (48.6%)	46 (51.6%)
Configuration										
Small (single patch <1DA)	74 (35.6%)	15 (33.3%)	33 (49.2%)	15 (27.7%)	11 (26.1%)	133 (33.9%)	27 (35.1%)	49 (41.9%)	32 (29.4%)	25 (28.1%)
Multifocal	43 (20.7%)	8 (17.7%)	12 (17.9%)	18 (33.3%)	5 (11.9%)	54 (13.8%)	9 (11.7%)	17 (14.5%)	21 (19.3%)	7 (7.9%)
Horseshoe or ring	3 (1.4%)	0 (0%)	2 (2.9%)	0 (0%)	1 (2.3%)	7 (1.8%)	1 (1.3%)	3 (2.6%)	2 (1.8%)	1 (1.1%)
Solid	8 (3.8%)	1 (2.2%)	2 (2.9%)	4 (7.4%)	1 (2.3%)	36 (9.2%)	7 (9.1%)	9 (7.7%)	10 (9.2%)	10 (11.2%)
Indeterminate	6 (2.9%)	2 (4.4%)	1 (1.4%)	2 (3.7%)	1 (2.3%)	8 (2.0%)	3 (3.9%)	1 (0.9%)	2 (1.8%)	2 (2.2%)
Not graded‡	74 (35.6%)	19 (42.2%)	17 (25.3%)	15 (27.7%)	23 (54.7%)	154 (39.3%)	30 (39.0%)	38 (32.5%)	42 (38.5%)	44 (49.4%)
BCVA (ETDRS letters), mean (SD)	76.8 (10.5)	77.0 (10.8)	78.2 (8.6)	75.8 (10.5)	75.7 (12.7)	68.4 (17.9)	69.2 (17.3)	69.6 (18.3)	67.2 (18.9)	67.7 (16.6)
BCVA (Snellen equivalent), mean	20/32	20/32	20/25	20/32	20/32	20/40	20/40	20/40	20/40	20/40
GA area (mm^2), mean (SD)	2.8 (3.9)	2.7 (3.2)	2.0 (2.8)	3.4 (4.3)	3.3 (5.1)	3.8 (5.3)	4.1 (7.5)	3.4 (4.0)	3.5 (4.4)	4.3 (5.6)
Proximity to central macula (µm), mean (SD)	486.9 (422.7)	451.7 (498.0)	526.8 (357.1)	454.2 (450.5)	503.0 (403.5)	264.7 (391.8)	270.8 (438.1)	310.1 (375.2)	233.1 (390.2)	238.5 (373.0)

Abbreviations: BCVA=best-corrected visual acuity; DA=disc areas; ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; SD=standard deviation

* follow-up from first time-point with GA

† prevalent GA cohort refers to eyes with GA present at first time-point available, while incident GA cohort refers to eyes with GA observed first during follow-up

‡ for many eyes with GA, no grading for GA configuration was performed, owing to changes in grading protocols

Table 4. Geographic Atrophy Proximity-Based and Area-Based Progression Rates, according to Randomized Assignment to Different Oral Supplements, in the Age-Related Eye Diseases Study.

	Proximity-Based Progression Rate				Area-Based Progression Rate			
Randomized assignment (main effects)	Number of eyes	Estimate* (µm/year)	95% CI (µm/year)	P†	Number of eyes	Estimate‡ (mm/year)	95% CI (mm/year)	P†
No antioxidants	109	72.9	61.3 to 84.5	**0.012**	206	0.255	0.240 to 0.271	0.63
Antioxidants	99	50.7	38.0 to 63.4		186	0.261	0.245 to 0.276	
Difference§		-22.2	-39.4 to -4.9			0.005	-0.017 to 0.027	
No zinc	87	57.9	45.4 to 70.4	0.28	166	0.261	0.245 to 0.278	0.58
Zinc	121	67.4	55.5 to 79.2		226	0.255	0.240 to 0.270	
Difference§		9.5	-7.7 to 26.7			-0.006	-0.028 to 0.016	

Abbreviations: CI=confidence interval

* Mixed-model, repeated-measures regression with geographic atrophy (GA) proximity to central macula as the dependent variable, according to randomized assignment, years from first time-point with GA, and their interaction term, with adjustment for age, sex, smoking, GA proximity at first time-point with GA, and correlation between eyes

† P value for interaction between randomized assignment and years

‡ Mixed-model, repeated-measures regression with square root of GA area as the dependent variable, according to randomized assignment, years from first time-point with GA, and their interaction term, with adjustment for age, sex, smoking, square root of GA area at first time-point with GA, GA central involvement at first time-point with GA, GA presence in fellow eye at first time-point with GA, and correlation between eyes

§ Difference expressed as estimate for not reference minus estimate for reference (e.g., for antioxidants minus no antioxidants)

Table 11. Demographic and Clinical Characteristics of the Study Population at First Time-Point with Geographic Atrophy in the Age-Related Eye Diseases Study 2.

Eyes with non-central geographic atrophy at first time-point (for proximity-based analyses)										
	Primary randomization					Secondary randomization				
Randomized assignment	All arms	Lutein/zeaxanthin only	DHA/EPA only	L/Z and DHA/EPA	Control	All arms	No β-carotene	Low zinc	No β-carotene and low zinc	Original formulation
Participants	646	140	180	170	156	467	153	115	114	85
Age (years), mean (SD)	74.6 (7.0)	74.1 (7.4)	74.5 (6.9)	75.0 (7.1)	74.7 (6.7)	74.2 (7.1)	73.8 (7.2)	74.2 (7.6)	74.6 (6.9)	74.5 (6.3)
Women	380 (58.8%)	88 (62.9%)	100 (55.6%)	110 (64.7%)	82 (52.6%)	263 (56.3%)	91 (59.4%)	67 (58.3%)	62 (54.4%)	43 (50.6%)
Smoking status										
Never	259 (40.1%)	56 (40.0%)	69 (38.3%)	75 (44.1%)	59 (37.8%)	170 (36.4%)	50 (32.7%)	46 (40.0%)	39 (34.2%)	35 (41.2%)
Former	343 (53.1%)	72 (51.4%)	101 (56.1%)	85 (50.0%)	85 (54.5%)	254 (54.4%)	77 (50.3%)	69 (60.0%)	58 (50.9%)	50 (58.8%)
Current	44 (6.8%)	12 (8.6%)	10 (5.6%)	10 (5.9%)	12 (7.7%)	43 (9.2%)	26 (17.0%)	0 (0.0%)	17 (14.9%)	0 (0.0%)
Follow-up (years), mean (SD)*	3.3 (1.5)	3.3 (1.5)	3.3 (1.5)	3.5 (1.4)	3.2 (1.4)	3.4 (1.5)	3.4 (1.4)	3.5 (1.6)	3.3 (1.5)	3.2 (1.4)
Eyes	793	167	219	215	192	574	186	146	139	103
Cohort										
Prevalent†	300 (37.8%)	67 (40.1%)	78 (35.6%)	89 (41.4%)	66 (34.4%)	229 (39.9%)	82 (44.1%)	64 (43.8%)	51 (36.7%)	32 (31.1%)
Incident†	493 (62.2%)	100 (59.9%)	141 (64.4%)	126 (58.6%)	126 (65.6%)	345 (60.1%)	104 (55.9%)	82 (56.2%)	88 (63.3%)	71 (68.9%)
Configuration										
Small (single patch <1DA)	419 (52.8%)	85 (50.9%)	113 (51.6%)	111 (51.6%)	110 (57.3%)	301 (52.4%)	88 (47.3%)	76 (52.1%)	81 (58.3%)	56 (54.4%)
Multifocal	239 (30.1%)	56 (33.5%)	70 (32.0%)	65 (30.2%)	48 (25.0%)	171 (29.8%)	56 (30.1%)	47 (32.2%)	36 (25.9%)	32 (31.1%)
Horseshoe or ring	43 (5.4%)	10 (6.0%)	10 (4.6%)	11 (5.1%)	12 (6.3%)	28 (4.9%)	13 (7.0%)	7 (4.8%)	1 (0.7%)	7 (6.8%)
Solid	68 (8.6%)	13 (7.8%)	17 (7.8%)	21 (9.8%)	17 (8.9%)	56 (9.8%)	25 (13.4%)	9 (6.2%)	14 (10.1%)	8 (7.8%)
Indeterminate	24 (3.0%)	3 (1.8%)	9 (4.1%)	7 (3.3%)	5 (2.6%)	18 (3.1%)	4 (2.2%)	7 (4.8%)	7 (5.0%)	9 (8.7%)
BCVA (ETDRS letters), mean (SD)	74.7 (13.5)	74.0 (14.9)	75.5 (12.6)	74.2 (12.8)	75.1 (13.8)	75.1 (12.7)	74.9 (13.0)	75.1 (13.3)	74.6 (13.0)	76.0 (10.8)
BCVA (Snellen equivalent), mean	20/32	20/32	20/32	20/32	20/32	20/32	20/32	20/32	20/32	20/32
GA area (mm^2), mean (SD)	1.9 (2.9)	2.0 (3.3)	1.8 (2.6)	2.1 (3.1)	1.8 (2.8)	1.9 (3.0)	2.4 (3.9)	2.1 (3.1)	1.3 (1.4)	1.5 (2.2)
Proximity to central macula (µm), mean (SD)	636.0 (489.5)	553.4 (404.0)	659.0 (540.3)	647.8 (484.9)	670.1 (497.1)	631.0 (481.7)	595.9 (446.6)	638.0 (438.1)	662.7 (501.2)	643.1 (570.0)
All eyes with geographic atrophy (for area-based analyses)										
	Primary randomization					Secondary randomization				
Randomized assignment	All arms	Lutein/zeaxanthin only	DHA/EPA only	L/Z and DHA/EPA	Control	All arms	No β-carotene	Low zinc	No β-carotene and low zinc	Original formulation
Participants	891	200	237	225	229	646	203	153	164	126
Age (years), mean (SD)	74.9 (6.9)	74.8 (7.2)	74.9 (6.7)	75.2 (7.0)	74.6 (6.7)	74.7 (7.0)	74.1 (7.1)	74.9 (7.1)	74.7 (7.1)	75.4 (6.3)
Women	512 (57.5%)	121 (60.5%)	133 (56.1%)	138 (61.3%)	120 (52.4%)	356 (55.1%)	121 (59.6%)	88 (57.5%)	89 (54.3%)	58 (46.0%)
Smoking status										
Never	360 (40.4%)	88 (44.0%)	90 (38.0%)	95 (42.2%)	87 (38.0%)	236 (36.5%)	68 (33.5%)	64 (41.8%)	52 (31.7%)	52 (41.3%)
Former	469 (52.6%)	97 (48.5%)	134 (56.5%)	114 (50.7%)	124 (54.1%)	350 (54.2%)	98 (48.3%)	89 (58.2%)	89 (54.3%)	74 (58.7%)

Current	62 (7.0%)	88 (44.0%)	90 (38.0%)	95 (42.2%)	87 (38.0%)	60 (9.3%)	37 (18.2%)	0 (0.0%)	23 (14.0%)	0 (0.0%)
Follow-up (years), mean (SD)*	3.3 (1.4)	3.3 (1.5)	3.2 (1.5)	3.5 (1.4)	3.1 (1.4)	3.3 (1.5)	3.4 (1.4)	3.5 (1.6)	3.1 (1.6)	3.1 (1.4)
Eyes	1210	261	321	320	308	883	282	222	223	156
Cohort										
Prevalent†	453 (37.4%)	101 (38.7%)	108 (33.6%)	133 (41.6%)	111 (36.0%)	345 (39.1%)	122 (43.3%)	95 (42.8%)	81 (36.3%)	47 (30.1%)
Incident†	757 (62.6%)	160 (61.3%)	213 (66.4%)	187 (58.4%)	197 (64.0%)	538 (60.9%)	160 (56.7%)	127 (57.2%)	142 (63.7%)	109 (69.9%)
Central/non-central GA										
Non-central	813 (67.1%)	170 (65.1%)	225 (70.0%)	221 (69.0%)	197 (63.9%)	591 (66.9%)	191 (67.7%)	149 (67.1%)	143 (64.1%)	108 (69.2%)
Central	397 (32.8%)	91 (34.8%)	96 (29.9%)	99 (30.9%)	111 (36.0%)	292 (33.0%)	91 (32.2%)	73 (32.8%)	80 (35.8%)	48 (30.7%)
Configuration										
Small (single patch <1DA)	601 (49.7%)	125 (47.9%)	160 (49.8%)	158 (49.4%)	158 (51.3%)	435 (49.3%)	130 (46.1%)	106 (47.7%)	121 (54.3%)	78 (50.0%)
Multifocal	283 (23.4%)	68 (26.1%)	81 (25.2%)	73 (22.8%)	61 (19.8%)	207 (23.4%)	66 (23.4%)	53 (23.9%)	49 (22.0%)	39 (25.0%)
Horseshoe or ring	59 (4.9%)	14 (5.4%)	13 (4.0%)	14 (4.4%)	18 (5.8%)	39 (4.4%)	19 (6.7%)	11 (5.0%)	1 (0.5%)	8 (5.1%)
Solid	224 (18.5%)	46 (17.6%)	53 (16.5%)	64 (20.0%)	61 (19.8%)	174 (19.7%)	61 (21.6%)	42 (18.9%)	43 (19.3%)	28 (17.9%)
Indeterminate	43 (3.6%)	8 (3.1%)	14 (4.4%)	11 (3.4%)	10 (3.2%)	28 (3.2%)	6 (2.3%)	10 (4.5%)	9 (4.0%)	3 (1.9%)
BCVA (ETDRS letters), mean (SD)	69.1 (18.7)	67.4 (20.5)	69.3 (18.7)	69.7 (17.5)	69.9 (18.1)	69.4 (18.1)	68.9 (20.0)	70.4 (16.5)	67.5 (19.0)	71.6 (15.1)
BCVA (Snellen equivalent), mean	20/40	20/50	20/40	20/40	20/40	20/40	20/40	20/40	20/40	20/40
GA area (mm^2), mean (SD)	2.4 (3.3)	2.5 (3.6)	2.3 (3.2)	2.4 (3.4)	2.3 (3.2)	2.4 (3.4)	2.8 (3.9)	2.5 (3.4)	1.8 (2.1)	2.2 (3.7)
Proximity to central macula (µm), mean (SD)	433.0 (494.6)	367.1 (411.4)	463.3 (535.4)	450.1 (495.3)	437.8 (511.1)	427.0 (488.3)	405.5 (453.8)	432.3 (462.5)	428.0 (503.5)	458.5 (560.0)

Abbreviations: BCVA=best-corrected visual acuity; DA=disc areas; ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; SD=standard deviation

* follow-up from first time-point with GA

† prevalent GA cohort refers to eyes with GA present at first time-point available, while incident GA cohort refers to eyes with GA observed first during follow-up

Table 12. Geographic Atrophy Proximity-Based and Area-Based Progression Rates, according to Randomized Assignment to Different Oral Supplements, in the Age-Related Eye Diseases Study 2.

	Proximity-Based Progression Rate				Area-Based Progression Rate			
Randomized assignment (main effects)	Number of eyes	Estimate* (µm/year)	95% CI (µm/year)	P†	Number of eyes	Estimate‡ (mm/year)	95% CI (mm/year)	P†
Primary randomization								
No lutein/zeaxanthin	411	105.3	93.2 to 117.3	**0.017**	629	0.282	0.266 to 0.299	0.83
Lutein/zeaxanthin	382	84.5	72.4 to 96.6		581	0.280	0.263 to 0.297	
Difference§		-20.8	-37.8 to -3.7			-0.003	-0.026 to 0.021	
No lutein/zeaxanthin¶	174	114.4	96.2 to 132.7	**0.011**	274	0.306	0.283 to 0.330	0.64
Lutein/zeaxanthin¶	151	80.1	60.9 to 99.3		231	0.298	0.272 to 0.324	
Difference§¶		-34.3	-60.8 to -7.8			-0.008	-0.043 to 0.027	
No DHA/EPA	359	97.9	84.9 to 110.9	0.58	569	0.278	0.260 to 0.295	0.60
DHA/EPA	434	93.0	81.7 to 104.3		641	0.284	0.268 to 0.300	
Difference§		-4.9	-22.1 to 12.3			0.006	-0.018 to 0.030	
Secondary randomization								
No β-carotene	325	98.1	84.3 to 111.9	0.24	505	0.301	0.283 to 0.320	**0.009**
β-carotene	249	85.4	69.5 to 101.2		378	0.264	0.244 to 0.285	
Difference§		-12.7	-33.7 to 8.3			-0.037	-0.064 to -0.009	
High zinc (80 mg)	289	93.8	79.1 to 108.5	0.84	438	0.278	0.258 to 0.297	0.32
Low zinc (25 mg)	285	91.7	77.0 to 106.5		445	0.292	0.272 to 0.311	
Difference§		-2.1	-22.9 to 18.7			0.014	-0.014 to 0.041	

Abbreviations: CI=confidence interval; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid

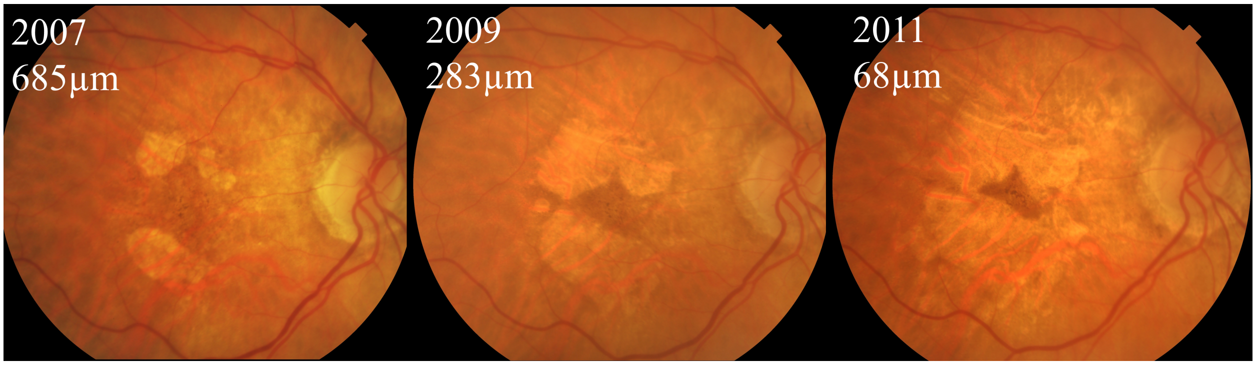
* Mixed-model, repeated-measures regression with geographic atrophy (GA) proximity to central macula as the dependent variable, according to randomized assignment, years from first time-point with GA, and their interaction term, with adjustment for age, sex, smoking, GA proximity at first time-point with GA, and correlation between eyes

† P value for interaction between randomized assignment and years

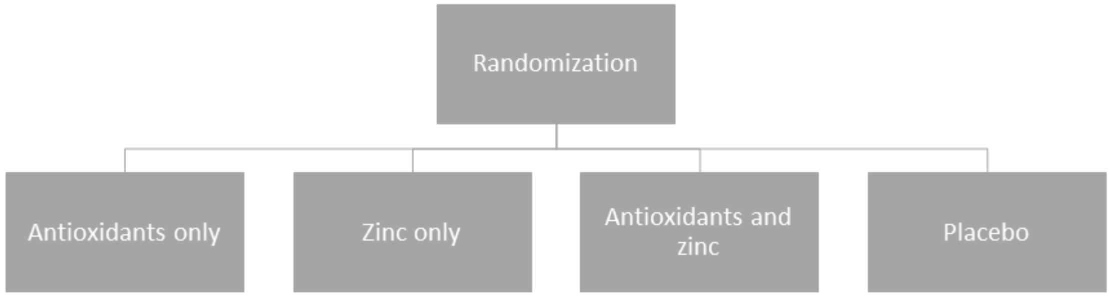
‡ Mixed-model, repeated-measures regression with square root of GA area as the dependent variable, according to randomized assignment, years from first time-point with GA, and their interaction term, with adjustment for age, sex, smoking, square root of GA area at first time-point with GA, GA central involvement at first time-point with GA, GA configuration at first time-point with GA, and correlation between eyes

§ Difference expressed as estimate for not reference minus estimate for reference (e.g., for lutein/zeaxanthin minus no lutein/zeaxanthin)

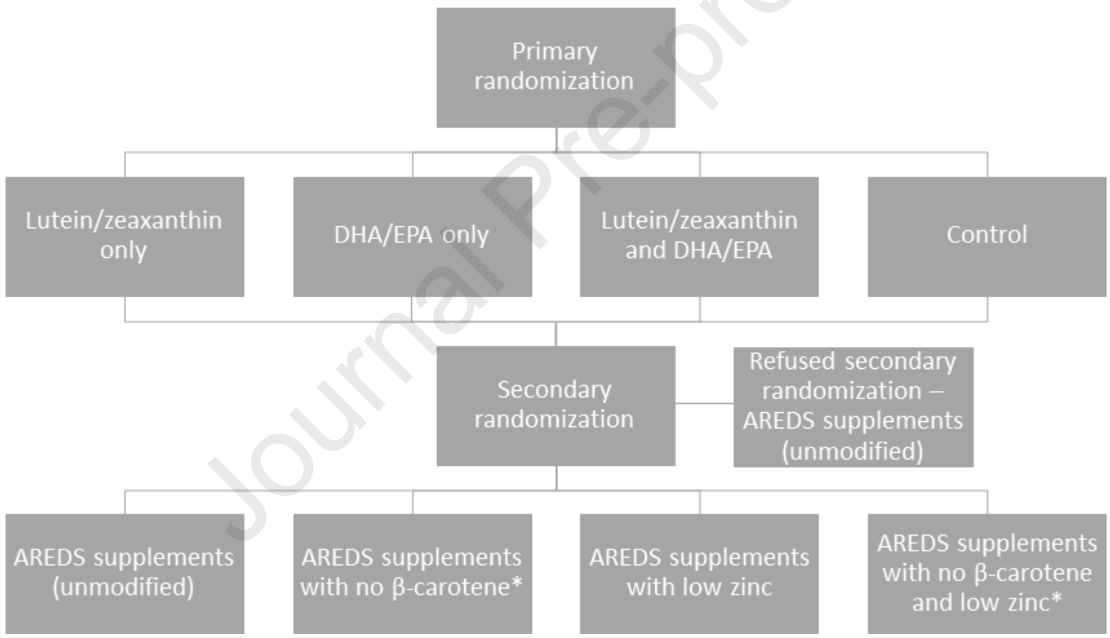
¶ Considering only those participants in the secondary randomization study population who were randomly assigned to no β-carotene (analyzed since lutein/zeaxanthin and β-carotene compete for intestinal absorption)


2007
685µm
2009
283µm
2011
68µm

A. AREDS randomization scheme



B. AREDS2 randomization scheme



Précis

Oral micronutrient supplementation with vitamin C, vitamin E, and lutein/zeaxanthin slows GA progression towards the central macula, likely by augmenting the natural phenomenon of foveal sparing.