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Adherence to a Mediterranean Diet and Geographic Atrophy Enlargement Rate:Age-Related Eye Disease Study 2 Report 29

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Abstract

Purpose—To determine whether closer adherence to a Mediterranean diet (and its individual components) was associated with altered speed of GA enlargement.

Design—Post hoc analysis of a cohort within the Age-Related Eye Disease Study 2 (AREDS2) controlled clinical trial.

Participants—1155 eyes (of 850 participants, mean age 74.9 years) with GA at two or more consecutive visits.

Methods—GA area was measured by planimetry from color fundus photographs collected at annual study visits. A modified Alternative Mediterranean Diet Index (aMedi) score was calculated for each participant by food frequency questionnaire. Mixed-model regression analyses of square root GA area were performed according to aMedi.

Main outcome measures: change in square root of GA area over time.

Results—Over mean follow-up of 3.1 years from first appearance of GA, the mean GA enlargement rate was 0.282 mm/year (95% confidence interval 0.270-0.293). GA enlargement was significantly slower in those with higher aMedi, at 0.256 mm/year (0.236-0.276), 0.290 (0.268-0.311), and 0.298 (0.280-0.317; P=0.008), for aMedi tertiles 3, 2, and 1, respectively. Of the nine aMedi components considered separately, significant differences in GA enlargement rate were observed for four: whole fruit (P=0.0004), red meat (P=0.0002), alcohol (P=0.006), and MUFA: SFA (P=0.040), but not for fish (P=0.14). GA enlargement was slower in those

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with higher whole fruit, lower red meat, moderate alcohol, and higher MUFA: SFA intake. In the 768 eyes with non-central GA, aMedi was not associated with slower progression to central involvement: hazard ratios 1.11 (0.83-1.48) and 0.95 (0.71-1.26) for tertiles 2 and 3, respectively.

Conclusions—A Mediterranean-type diet was associated with slower GA enlargement. Diet patterns like this may therefore lead to clinically meaningful delays in vision loss. Several components appeared to contribute most to this association, in a pattern that differed from those most associated with decreased progression to GA. Hence, the Mediterranean diet is associated with protection against both faster progression to GA and faster enlargement of GA, but for partially distinct reasons. These findings may help inform evidence-based dietary recommendations. Understanding the mechanisms responsible may provide insights into the underlying biology and lead to the development of nutritional supplements.

Précis

A Mediterranean diet pattern was associated with significantly slower enlargement of geographic atrophy. The components appearing to contribute most to the association were high whole fruit, low red meat, moderate alcohol, and high MUFA:SFA intake.

Introduction

Geographic atrophy (GA) is the defining lesion of the atrophic subtype of late age-related macular degeneration (AMD). It represents a common, blinding condition and is typically bilateral and relentlessly progressive.[1-4] It is estimated to affect over 5 million people worldwide, with a global prevalence of 0.44%.[3] The condition represents a substantial public health problem because no drug therapies are approved to slow down GA enlargement, though local complement inhibitors have shown promise in this area.[5] Indeed, GA enlargement rate is the primary outcome measure in such trials, and is recognized by the US Food and Drug Administration as a clinically important endpoint.[6,7]

Strong evidence from observational studies has demonstrated an important role for diet in altered risk of progression to late AMD.[8-10] In previous analyses of the Age-Related Eye Disease Study (AREDS) and AREDS2, closer adherence to the alternative Mediterranean diet pattern (aMedi) was very strongly associated with decreased risk of progression to late AMD, particularly GA.[8] Fish intake made a large contribution to this protective association.[8] However, we are not aware of any previous studies exploring whether such dietary patterns may be associated with altered rate of GA enlargement.

Definitions of the Mediterranean diet pattern were originally made to characterize the diets of people living on Crete, since they had low rates of coronary artery disease mortality.[11] Modifications to these definitions have since been made for different populations.[12] Adherence to the Mediterranean diet is associated with multiple health benefits.[13] If adherence to this diet pattern were associated with slower GA enlargement, then dietary modification could represent an important strategy to delay vision loss in affected patients.

The AREDS2 was a multicenter phase III randomized clinical trial (RCT) designed to assess the effects of nutritional supplementation on progression to late AMD.[14] Many participants had GA in one eye at study baseline, while many additional participants developed GA in

one or both eyes during follow-up.[1] Mean rates of GA enlargement in these participants have been described previously, together with clinical and genetic risk factors for altered enlargement rates, but the potential role of diet has not been studied.[1] The aim of this report was to examine in AREDS2 whether closer adherence to the aMedi diet (overall and by component) was associated with slower GA enlargement.

Methods

Study populations and procedures

The AREDS2 study design has been described previously.[14] In brief, 4,203 participants (aged 50-85 years) were recruited between 2006 and 2008 at 82 US retinal specialty clinics. 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. 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 complied with the Health Insurance Portability and Accountability Act.

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. At baseline and annual visits, eye examinations were performed and digital stereoscopic color fundus photographs were captured and graded centrally at the Fundus Photograph Reading Center (University of Wisconsin).[15] The randomized clinical trial lasted five years. Progression to late AMD (including GA/neovascular subtype) was defined by fundus photograph grades, together with history of intravitreal injections for neovascular AMD.[14]

The definitions of GA and methods to measure GA area and other characteristics have been described previously.[1] In brief, GA was defined as a lesion equal to or larger than drusen circle I-2 (diameter 433 um, area 0.146 mm^2, i.e., 1/4 disc diameter and 1/16 disc area) at its widest diameter with at least two of the following features present: circular shape, sharp (well-demarcated) edges, and loss of the RPE (partial or complete depigmentation of the RPE, typically with exposure of underlying choroidal vessels). Planimetry tools were used to demarcate the area of GA within the AREDS grid in square millimeters. In the case of multifocal GA, areas were summed to yield a single value for analysis. If the GA was non-central, GA proximity to the central macula (i.e., the smallest distance between the central macula and the border of the GA closest to the central macula) was documented in microns (using the closest border of the closest lesion, in the case of multifocal GA).[1,15]

Modified Alternative Mediterranean Diet Index score

The assessment of the aMedi in the AREDS2 has been described previously.[8] In brief, a 131-item, semiquantitative Harvard food frequency questionnaire (FFQ) was administered to all participants at randomization.[16,17] Participants were asked how often, on average, they had consumed each food/beverage item during the preceding year. The FFQs were used to determine the number of medium-sized servings of each food item consumed per

week (or gram/day for alcohol). These data were summed for each participant to obtain the intake for each of the nine components that define adherence to the Mediterranean diet: whole fruits, vegetables, whole grains, nuts, legumes, red meat, fish, monounsaturated fatty acid: saturated fatty acid ratio (MUFA: SFA), and alcohol. For each component, sex-specific intake quartiles (1-4) were calculated, with quartile 4 representing highest intake. Alcohol intake was converted into binary format: 4 for intake within the specified intervals (5-15 gram/day (female) or 10-15 gram/day (male)) and 0 for intake above or below the specified intervals.[18] The quartiles for red meat were reversed (i.e., quartile 4 with highest intake scored 1, as least aMedi-adherent, and quartile 1 with lowest intake scored 4). To calculate the aMedi score for each participant, the quartile values for the nine components were summed (range 8-36).

Participant cohorts and statistical methods

The eligibility criteria were: eyes with GA (without prior or simultaneous exudative neovascular AMD) and at least one subsequent study visit (also without exudative neovascular AMD). Participants were excluded if they had no FFQ or missing data for any covariate.

Mixed-model regression was performed for the outcome of square root of GA area, considered longitudinally, using methods described previously.[1] This was done according to aMedi tertiles (with tertile 1 as reference). The analyses used repeated-measures regression with the dietary variable, years from GA first appearance, and their interaction term. To account for the correlation of measures of the same eye between visits, a first-order autoregressive covariance structure (AR[1]) was specified. In secondary analyses, the analyses were repeated while (i) including the AREDS2 treatment arm (i.e., randomization to DHA/EPA, lutein/zeaxanthin, both, or placebo) as a variable in the model, (ii) considering prevalent and incident cases separately (i.e., with GA already present at AREDS2 baseline versus newly arising during follow-up, respectively), and (iii) considering eyes separately according to GA lesion area at baseline (i.e., at AREDS2 baseline for prevalent cases and at first appearance of GA for incident cases).

In all cases, the unit of analysis was the eye and analyses were adjusted for demographic variables (age, sex, education level, and smoking status), total calorie intake, clinical variables known to be associated with altered GA enlargement rate (square root of GA area, central involvement, and configuration, all considered at baseline/first appearance of GA[1]), and correlation between eyes. In sensitivity analyses, three different statistical models were made with different levels of adjustment: in model 1, the results were adjusted only for age, sex, total calorie intake, and correlation between eyes; in model 2, the results were adjusted for the same variables as in model 1, but also the ocular factors described above (square root of GA area, central involvement, and configuration); in model 3, the results were adjusted for the same variables as in model 2, but also lifestyle factors (smoking, educational level, history of diabetes mellitus, and history of hyperlipidemia, each considered at baseline).

Further regression analyses were performed for each of the nine aMedi components: separate models were made for each component (component x), adjusting for the modified total index score that did not include the respective component (modified total index score

= total index score – component x).[8,19] This was done in order to isolate the contribution of each component from that of the overall diet pattern. Again, the unit of analysis was the eye and analyses were adjusted for the same demographic variables (age, sex, education level, and smoking status), total calorie intake, clinical variables, and correlation between eyes.

Separate analyses were performed on the subset of eyes where GA was non-central at baseline/first appearance. First, Cox proportional hazards analyses were performed with progression to central involvement as the binary outcome measure, according to aMedi tertiles, using similar methods to those described above. Second, mixed-model regression was performed for the continuous variable of proximity to the central macula, considered longitudinally, using the same methods as those described above, according to aMedi tertiles (i.e., using repeated-measures regression with the aMedi tertile variable, years from GA first appearance, and their interaction term, with adjustment for age, sex, education level, smoking status, total calorie intake, GA variables (configuration and proximity to central macula, both considered at baseline/first appearance), and correlation between eyes). In all cases, significance was set at p=0.05. All analyses were conducted using SAS version 9.4 (SAS Institute).

Results

The AREDS2 comprised 8406 eyes of 4203 participants with annual color fundus photographs over five years. The number with GA at any time (without prior or simultaneous exudative neovascular AMD) was 1616 eyes of 1168 participants, as described previously.[1] Of these, the number with at least two visits with GA was 1219 eyes of 897 participants, of whom 850 participants (representing 1155 eyes) had dietary data. Their demographic and clinical characteristics are shown in Table 1, and their dietary intake is shown in Supplementary Table 1. The mean follow-up period from first appearance of GA in either eye was 3.1 years (SD 1.5).

Geographic atrophy enlargement according to the Alternative Mediterranean Diet Index score

According to regression analysis, the mean change over time in square root of GA area was 0.282 mm/year (95% confidence interval 0.270-0.293). For the outcome of square root of GA area, a statistically significant interaction was observed between aMedi tertile and years (P = 0.008). GA enlargement was significantly slower in eyes of participants with closer adherence to the aMedi diet and significantly faster in those with lower adherence (Table 2). GA enlargement was 0.298 (95% CI 0.280-0.317), 0.290 (0.268-0.311), and 0.256 (0.236-0.276), for eyes of participants in tertiles 1, 2, and 3, respectively, i.e., consistent with a dose-response association.

In secondary analyses that included the AREDS2 treatment arm (i.e., randomization to DHA/EPA, lutein/zeaxanthin, both, or placebo), no significant interaction was observed between the treatment arm variable and years (p=0.69), and the estimates for GA enlargement remained unchanged at 0.298 (95% CI 0.280-0.317), 0.290 (0.268-0.311), and 0.256 (0.236-0.276), for tertiles 1, 2, and 3, respectively.

In further analyses, a similar pattern of results was observed for eyes with prevalent and incident GA, considered separately (Supplementary Table 2). In eyes considered separately according to baseline GA area, a similar pattern of results was observed for eyes with smaller baseline area, with a large difference between the enlargement rates by aMedi tertile (Supplementary Table 3). In eyes with larger baseline area, no significant difference was observed, though power was low so the confidence intervals for the estimates were wide.

In sensitivity analyses, three different statistical models were made, with different levels of adjustment. The results did not differ substantially between the three models (Supplementary Table 4); in all cases, GA enlargement was significantly slower in eyes of participants with closer adherence to the aMedi diet.

In separate analyses that considered the aMedi score as a continuous variable, rather than in tertiles, again, a statistically significant interaction between aMedi score and years was observed (P = 0.0005). Each positive increment on the aMedi scale (range 9-35) was associated with a significant decrease in GA enlargement rate (estimate −0.007 mm/year, 95% CI −0.013, −0.001; P = 0.019).

Geographic atrophy enlargement according to Intake of individual components of the Alternative Mediterranean Diet

The results for individual aMedi components are shown in Table 3. For the outcome of square root of GA area, statistically significant interactions between intake quartile and years were observed for 4 of the 9 individual components, considered separately: whole fruit (P = 0.0004), red meat (P = 0.0002), alcohol (P = 0.006), and MUFA: SFA (P = 0.040). GA enlargement was slower in eyes of participants with higher whole fruit intake. Conversely, it was faster in eyes of participants with higher red meat intake. GA enlargement was slower in eyes of participants with alcohol intake in the specified interval (as opposed to above or below). Finally, it was slower in eyes of participants with a high MUFA: SFA intake (i.e., relatively higher intake of MUFA than SFA). No statistically significant interaction was observed for fish intake (P = 0.14); GA enlargement was not faster or slower in participants with higher fish intake. Similar results were obtained when the analyses for fish were repeated in the subset of participants not assigned to DHA/EPA (n=549 eyes of 412 participants).

Progression of geographic atrophy to central involvement according to the Alternative Mediterranean Diet Index score

In the subset of eyes where GA was non-central at baseline/first appearance (n=768 eyes of 627 participants), the number that progressed to central involvement, during mean follow-up of 3.2 years (SD 1.5), was 358 eyes (46.6%). In proportional hazards analyses, higher aMedi tertile was not significantly associated with decreased progression to central involvement, as a binary outcome. In comparison to aMedi tertile 1 as reference, the hazard ratio was 1.11 (95% CI 0.83-1.48, p=0.48) for tertile 2 and 0.95 (0.71-1.26, p=0.70) for tertile 3. In the same subset of eyes, higher aMedi tertile was not significantly associated with slower decrease in GA proximity to the central macula, as a continuous variable. The estimates for change in proximity per year were −60 μm (95% CI −122 to 3), −82 μm (−150 to −14),

and −85 μm (−153 to −18), for tertiles 1, 2, and 3, respectively, i.e., with very wide and overlapping confidence intervals.

Discussion

GA enlargement was significantly slower in those with higher adherence to a Mediterranean diet pattern and significantly faster in those with lower adherence. With adherence to this diet pattern considered in tertiles, the difference in enlargement rates between tertiles 1 and 3 was approximately 15%. The idea of a genuine relationship between Mediterranean diet and slower GA enlargement was supported by the observation of a dose-response association. Interestingly, a relatively larger difference was apparent between tertiles two and three. This suggests that the potential benefits of the dietary pattern might be gained particularly by adherence in the highest tertile. Although relatively modest, this difference in enlargement rates could be clinically important over the long time-periods taken for GA to enlarge. In the most common scenario, where GA spares the fovea at onset[1], that degree of slower enlargement could be clinically meaningful in delaying progression to foveal involvement and the profoundly decreased visual acuity that accompanies it. Hence, dietary modification might represent an important strategy to delay disease progression in patients affected by GA. Together with evidence from previous observational studies, the Mediterranean diet pattern has therefore been associated with slower disease progression across a wide spectrum of AMD severity: from AREDS and AREDS2 data, it has been strongly associated with decreased progression to large drusen, to GA, and to neovascular AMD[8]. Now, from AREDS2 data, it has been associated with slower GA enlargement also.

Regarding the potential for delaying progression to foveal involvement, direct evidence to support that idea was not observed in the secondary analyses in this study. Indeed, an interesting distinction was apparent: while the Mediterranean diet pattern was associated with slower GA enlargement overall, no evidence was observed for slower progression to central involvement. Several potential explanations and considerations may be relevant here. First, it is possible that the Mediterranean diet is genuinely associated with slower GA enlargement in the extrafoveal macula but not in the perifoveal macula, perhaps owing to anatomical and vascular differences. Second, the Mediterranean diet may be genuinely associated with both, even though the current study was unable to demonstrate the latter. GA enlargement is known to be substantially slower near the fovea than elsewhere[20,21], such that higher power would be required to demonstrate potential differences by diet. In addition, the AREDS2 design may be less well suited to detect differences in progression to central involvement, given to its wide re-imaging intervals of 12 months and use of color fundus photography alone. Indeed, the confidence intervals for the estimates of change in proximity were very wide, indicating low power. Third, it is possible that the association between the Mediterranean diet and slower GA enlargement overall may arise partly from decreased incidence of additional GA foci (i.e., in addition to slower enlargement contiguously from existing foci). In that case, and if GA progression to central involvement occurs more commonly from contiguous enlargement than from the addition of new foci, then the Mediterranean diet might genuinely be more strongly associated with decreased GA progression in the extrafoveal macula. However, attempting to distinguish between these possibilities is outside the scope of the current study.

These results are important because no approved drug therapies or other interventions are currently available to slow down GA enlargement. Local complement inhibition holds potential promise for slowing GA enlargement, pending additional RCT data and regulatory approval.[5] However, these drugs have relatively modest effect sizes, with enlargement slowed by approximately 17% in the pooled results from two phase III trials of pegcetacoplan and 27% in one phase II/III trial of avacincaptad pegol.[22,23] In addition, they typically require monthly intravitreal injection and carry increased risk of neovascular AMD.[5] By contrast, the Mediterranean diet pattern is associated with decreased risk of progression to neovascular AMD[8] and carries multiple health benefits, both for ocular and systemic health.[13]

Another important implication of these results relates to personalized predictions of GA enlargement rates, which are becoming more important in both clinical trials and routine practice.[5] Existing methods to predict an eye's GA enlargement rate from clinical, imaging, and/or genetic characteristics have imperfect accuracy.[5] The results of the current study likely account for some of the variation in GA enlargement rates between individuals that has remained unexplained by other factors. They suggest that, for highly accurate predictions, dietary behavior may have to be considered alongside clinical, imaging, and genetic characteristics.

Regarding baseline lesion size, the dataset was highly powered to detect differences in enlargement rates for eyes with relatively small lesion size. In stratified analyses, a significant difference by aMedi was observed for these eyes, with a relatively large magnitude of difference between the enlargement rates. However, the dataset had less power to detect differences for eyes with large lesion sizes. In stratified analyses of these eyes, no significant difference by aMedi was observed, nor even any numerical difference. This might argue that the Mediterranean diet is protective against faster GA enlargement only relatively early in the life of GA progression. For example, it is possible that the underlying mechanisms may differ between initial propagation versus subsequent expansion of GA. However, owing to low power for detecting differences in eyes with large lesion size, it is not possible in this study to distinguish between these two possibilities.

The methodology enabled a degree of isolation of the contribution of each aMedi component to the overall results, by analyzing according to each component while simultaneously adjusting for a tailored aMedi score that excluded that component. The approach demonstrated that higher whole fruit intake, lower red meat intake, and higher MUFA: SFA intake appeared to make the largest contributions to the association, with dose-response associations present for each. Moderate alcohol consumption also appeared to contribute to the association. Of interest, higher fish intake did not appear to make a large contribution to the association. The quantity of each component required to reach quartile 4 in this study population is shown in Table 3. For example, for a woman, this was at least 14 medium-sized servings per week for whole fruit, and no more than 1 medium-sized serving per week for red meat.

This pattern of results is different to that observed previously for which individual aMedi components had the strongest associations with decreased progression to GA.[7] In that case,

the component with the strongest association was fish intake, followed by whole fruit intake. These differences highlight an important distinction: although the Mediterranean diet is associated with protection against both faster progression to GA and faster enlargement of established GA, the reasons underlying these associations appear to differ in important ways. Fish intake is most important for the former, while whole fruit intake and limited red meat intake (together with higher MUFA: SFA and moderate alcohol intake) appear most important for the latter.

Indeed, similar ideas have been observed more generally for clinical and genetic risk factors for GA. As described previously[1], some factors are associated with increased risk of both incidence and enlargement (e.g., smoking and *ARMS2/HTRA1* genotype), while other factors are associated with increased incidence only (e.g., *CFH* genotype), and some factors may even be associated in opposite directions (e.g., *C3* genotype). Similarly, AREDS-type supplements cause decreased incidence of GA but have not been found to slow GA enlargement.[1,24] Overall, this suggests that the biological mechanisms underlying progression to GA may be partially distinct from those driving GA enlargement. For this reason, different pharmacological approaches may be required for each stage, though Mediterranean diet adherence may have the advantage of protection at both stages.

Regarding the results for whole fruit intake, the protective association may reflect higher intakes of specific flavonoids or a combination of flavonoids and other antioxidants. The relevant mechanisms for a protective association are uncertain, but current evidence suggests that dietary flavonoids decrease oxidative stress and may interact synergistically with dietary nitrates to enhance vascular responses and endothelial health (at least in the systemic circulation).[25] As one example, oranges are commonly consumed by Americans. Oranges and orange juice contain flavanones and hesperidin, flavonoids that are common in citrus fruits. A protective trend for lower 15-year incidence of late AMD was previously observed among individuals with higher intakes of these citrus flavonoids in the Blue Mountain Eye Study.[26] It is not clear whether these associations were specific to citrus flavonoids, reflected higher flavonoid intake as a broader class, or related to the combination of provitamin A carotenoids in oranges and/or other antioxidants in these fruits. However, the current study did not distinguish between different types of whole fruit, and other fruits may be equally or more relevant.

Regarding the results for MUFA: SFA intake, the association was in the direction that would be expected, since a higher ratio is considered healthier in terms of being more adherent to the Mediterranean diet. However, the variable was originally intended to reflect high intake of plant-based lipids (particularly olive oil) and low intake of saturated lipids, but may not capture this well in North American populations like the AREDS2 participants, in whom olive oil intake was low and the primary sources of MUFA were likely animal rather than plant foods.[7] Hence, the finding of a protective association in this study may also represent higher intake of dairy products (and therefore nutrients, including vitamin D, vitamin B12, calcium, and zinc) and/or lower intake of red meat. For example, several observational studies support the idea of a protective association between vitamin D (intake or serum levels) and AMD.[27,28]

The potential mechanisms responsible for the associations in the current study are not clear. Indeed, the mechanisms underlying GA enlargement themselves are not fully understood. However, the immune system appears to be highly implicated in GA propagation, including the innate immune system (e.g., activated microglia and macrophages secreting pro-inflammatory cytokines and neurotoxic factors), antigen-specific immunity, and immune amplification systems (especially the complement system and the NLRP3 inflammasome).[29,30] The protective mechanisms of the Mediterranean diet relevant here may relate to factors including anti-inflammatory properties, anti-oxidative properties, altered lipid metabolism, protection of vasculature, and neural protection.[31] For example, chronic inflammation is implicated in GA enlargement, and the dietary antioxidants, B vitamins, polyphenols, and polyunsaturated/monounsaturated fatty acids characteristic of typical foods of the Mediterranean diet are known to decrease systemic inflammation.[31] Similarly, the Mediterranean diet improves vascular endothelial function[32,33], which might slow GA enlargement through beneficial effects on the choriocapillaris.[34] In addition, the diet pattern is thought to improve the gut microbiome, which has been linked to AMD progression.[35]

We are not aware of previous studies addressing this question. Very few datasets combine a large number of eyes with GA, GA area measurements, long follow-up time, and detailed dietary information. Related to this, the strengths of this study include the large number of eyes with GA, long follow-up time, prospective and standardized collection of imaging and data at frequent fixed time-points, reading center measurement of GA area in all cases, and detailed dietary information by validated FFQ. Its limitations include its observational nature, such that causality cannot be assessed, together with *post hoc* hypothesis generation, the possibility of residual or unmeasured confounding (e.g., physical activity), and non-differential measurement error by FFQ (though energy adjustment may partially address this[36,37]). In addition, it is possible that the results may have been affected by the AREDS2 randomization, since a quarter of the AREDS2 study population had been assigned to DHA/EPA supplementation, a quarter to lutein/zeaxanthin, and a quarter to both. However, this question may be less relevant since, in previous analyses[1], neither randomization to DHA/EPA nor to lutein/zeaxanthin led to differences in GA enlargement rates. Similarly, in the current analyses, the AREDS2 treatment arm was not significantly associated with altered enlargement rates.

In conclusion, a Mediterranean diet pattern was associated with slower GA enlargement. Higher whole fruit, lower red meat, and higher MUFA: SFA intakes made the largest contributions to this association. Over long time periods, diet patterns like this might lead to clinically meaningful delays in vision loss. In the absence of other highly effective treatment strategies, dietary modification might therefore represent an important approach to delay disease progression in affected patients. Indeed, the Mediterranean diet pattern appears strongly associated with decreased disease progression across a wide spectrum of AMD severity. Understanding the mechanisms responsible may provide important insights into the biology underlying GA enlargement, as well as lead to the development of nutritional supplements to slow progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

aMedi	modified Alternative Mediterranean Diet Index
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FFQ	food frequency questionnaire
GA	geographic atrophy
MUFA	monounsaturated fatty acid
RCT	randomized controlled trial
SD	standard deviation
SFA	saturated fatty acid

References

1. Keenan TD, Agron E, Domalpally A, et al. Progression of Geographic Atrophy in Age-related Macular Degeneration: AREDS2 Report Number 16. Ophthalmology. 2018;125(12):1913–1928. [PubMed: 30060980]
2. Fleckenstein M, Mitchell P, Freund KB, et al. The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. Ophthalmology. 2018;125(3):369–390. [PubMed: 29110945]
3. 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. 2014;2(2):e106–116. [PubMed: 25104651]
4. 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. 2009;127(9):1168–1174. [PubMed: 19752426]
5. Keenan TDL. Local Complement Inhibition for Geographic Atrophy in Age-Related Macular Degeneration: Prospects, Challenges, and Unanswered Questions. Ophthalmology Science. 2021;1(4).

6. 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. 2017;58(9):3456–3463. [PubMed: 28702674]

7. Csaky KG, Richman EA, Ferris FL 3rd. Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium. Invest Ophthalmol Vis Sci. 2008;49(2):479–489. [PubMed: 18234989]

8. Keenan TD, Agron E, Mares J, et al. Adherence to the Mediterranean Diet and Progression to Late Age-Related Macular Degeneration in the Age-Related Eye Disease Studies 1 and 2. Ophthalmology. 2020;127(11):1515–1528. [PubMed: 32348832]

9. Merle BM, Silver RE, Rosner B, Seddon JM. Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: a prospective cohort study. Am J Clin Nutr. 2015;102(5):1196–1206. [PubMed: 26490493]

10. Merle BMJ, Colijn JM, Cougnard-Gregoire A, et al. Mediterranean Diet and Incidence of Advanced Age-Related Macular Degeneration: The EYE-RISK Consortium. Ophthalmology. 2019;126(3):381–390. [PubMed: 30114418]

11. Menotti A, Kromhout D, Blackburn H, Fidanza F, Buzina R, Nissinen A. Food intake patterns and 25-year mortality from coronary heart disease: cross-cultural correlations in the Seven Countries Study. The Seven Countries Study Research Group. Eur J Epidemiol. 1999;15(6):507–515. [PubMed: 10485342]

12. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean Diet; a Literature Review. Nutrients. 2015;7(11):9139–9153. [PubMed: 26556369]

13. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr. 2018;72(1):30–43. [PubMed: 28488692]

14. 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. 2012;119(11):2282–2289. [PubMed: 22840421]

15. 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. 2013;54(7):4548–4554. [PubMed: 23620429]

16. Michaud DS, Giovannucci EL, Ascherio A, et al. Associations of plasma carotenoid concentrations and dietary intake of specific carotenoids in samples of two prospective cohort studies using a new carotenoid database. Cancer Epidemiol Biomarkers Prev. 1998;7(4):283–290. [PubMed: 9568782]

17. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol. 1992;135(10):1114–1126; discussion 1127-1136. [PubMed: 1632423]

18. Lopez-Garcia E, Rodriguez-Artalejo F, Li TY, et al. The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. Am J Clin Nutr. 2014;99(1):172–180. [PubMed: 24172306]

19. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. J Nutr. 2014;144(6):881–889. [PubMed: 24572039]

20. 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. 2021;62(13):28.

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. 2020.

22. 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. 2021;128(4):576–586. [PubMed: 32882310]

23. Apellis. Apellis Announces Top-Line Results from Phase 3 DERBY and OAKS Studies in Geographic Atrophy (GA) and Plans to Submit NDA to FDA in the First Half of

2022. https://investors.apellis.com/news-releases/news-release-details/apellis-announces-top-line-results-phase-3-derby-and-oaks. Accessed 12/13/2021.

24. Age-Related Eye Disease Study Research Group. 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. 2001;119(10):1417–1436. [PubMed: 11594942]
25. Lovegrove JA, Stainer A, Hobbs DA. Role of flavonoids and nitrates in cardiovascular health. Proc Nutr Soc. 2017:1–13.
26. Gopinath B, Liew G, Kifley A, et al. Dietary flavonoids and the prevalence and 15-y incidence of age-related macular degeneration. Am J Clin Nutr. 2018;108(2):381–387. [PubMed: 29982448]
27. Millen AE, Meyers KJ, Liu Z, et al. Association between vitamin D status and age-related macular degeneration by genetic risk. JAMA Ophthalmol. 2015;133(10):1171–1179. [PubMed: 26312598]
28. Agron E, Mares J, Clemons TE, et al. Dietary Nutrient Intake and Progression to Late Age-Related Macular Degeneration in the Age-Related Eye Disease Studies 1 and 2. Ophthalmology. 2021;128(3):425–442. [PubMed: 32858063]
29. Allingham MJ, Loksztejn A, Cousins SW, Mettu PS. Immunological Aspects of Age-Related Macular Degeneration. Adv Exp Med Biol. 2021;1256:143–189. [PubMed: 33848001]
30. Zhang Y, Wong WT. Innate Immunity in Age-Related Macular Degeneration. Adv Exp Med Biol. 2021;1256:121–141. [PubMed: 33848000]
31. Schwingshackl L, Morze J, Hoffmann G. Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. Br J Pharmacol. 2020;177(6):1241–1257. [PubMed: 31243760]
32. Torres-Pena JD, Rangel-Zuniga OA, Alcala-Diaz JF, Lopez-Miranda J, Delgado-Lista J. Mediterranean Diet and Endothelial Function: A Review of its Effects at Different Vascular Bed Levels. Nutrients. 2020;12(8).
33. Shannon OM, Mendes I, Kochi C, et al. Mediterranean Diet Increases Endothelial Function in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Nutr. 2020;150(5):1151–1159. [PubMed: 32027740]
34. Gelfand BD, Ambati J. A Revised Hemodynamic Theory of Age-Related Macular Degeneration. Trends Mol Med. 2016;22(8):656–670. [PubMed: 27423265]
35. Lin P, McClintic SM, Nadeem U, Skondra D. A Review of the Role of the Intestinal Microbiota in Age-Related Macular Degeneration. J Clin Med. 2021;10(10).
36. Kipnis V, Subar AF, Midthune D, et al. Structure of dietary measurement error: results of the OPEN biomarker study. Am J Epidemiol. 2003;158(1):14–21; discussion 22-16. [PubMed: 12835281]
37. Subar AF, Kipnis V, Troiano RP, et al. Using intake biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: the OPEN study. Am J Epidemiol. 2003;158(1):1–13. [PubMed: 12835280]

Table 1.

Participant demographics and characteristics of geographic atrophy at first appearance.

Participants	850
Mean age (years), mean (SD)	74.9 (6.8)
Female	490 (57.6%)
Education level	
High school or less	305 (35.9%)
At least some college	391 (46.0%)
Postgraduate	154 (18.1%)
Smoking status	
Never	346 (40.7%)
Former	451 (53.1%)
Current	53 (6.2%)
Modified Alternative Mediterranean Diet Index tertile	
1	323 (38.0%)
2	235 (27.6%)
3	292 (34.4%)
Follow-up time from first appearance of GA (years), mean (SD)	3.1 (1.5)
Eyes	1155
GA prevalent at study baseline or incident during follow-up	
Prevalent	433 (37.5%)
Incident	722 (62.5%)
BCVA at first appearance of GA (ETDRS letters), mean (SD)	69.1 (18.7)
Central involvement at first appearance of GA	
Central	387 (33.5%)
Non-central	768 (66.5%)
GA area at first appearance of GA (disc areas)	
<0.75	778 (67.4%)
0.75 to <1.5	165 (14.3%)
1.5 to <2.0	53 (4.6%)
2.0 to <4	114 (9.9%)
4	45 (3.9%)
GA configuration at first appearance of GA	
Small (single patch <1 DA)	575 (49.8%)
Multifocal	267 (23.1%)
Horseshoe or ring	54 (4.7%)
Solid	218 (18.9%)
Indeterminate	41 (3.5%)

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

Table 2.

Geographic atrophy enlargement rates, following square root transformation, according to tertiles of the modified Alternative Mediterranean Diet Index score.

aMedi tertile	Estimate* (mm/year)	95% CI (mm/year)	P†
1	0.298	0.280-0.317	0.008
2	0.290	0.268-0.311	
3	0.256	0.236-0.276	

Abbreviations: aMedi=modified Alternative Mediterranean Diet Index; CI=confidence interval

†Mixed-model, repeated-measures regression with the square root of geographic atrophy (GA) area as the dependent variable, according to aMedi tertile, years from GA first appearance/baseline, and their interaction term, with adjustment for age, sex, total calorie intake, GA characteristics at first appearance/baseline (square root of GA area, central involvement, and configuration), smoking, educational level, and correlation between eyes

*P value for interaction between aMedi tertile and years

Table 3.

Geographic atrophy enlargement rates, following square root transformation, according to modified Alternative Mediterranean Diet Index component intake (considering each component separately, in quartiles).

aMedi component	Intake quartile	Servings/week (female)*	Servings/week (male)*	Estimate of GA enlargement (mm/year)†	95% CI (mm/year)	p‡
Whole fruits	1	≤4.0	≤3.0	0.319	0.296-0.342	0.0004
	2	4.5-8.5	3.5-7.0	0.284	0.261-0.307	
	3	9.0-13.5	7.5-12.0	0.277	0.254-0.299	
	4	≥14.0	≥12.5	0.247	0.224-0.271	
Vegetables	1	≤10.5	≤9.0	0.270	0.247-0.293	0.24
	2	11.0-18.0	9.5-15.0	0.285	0.263-0.307	
	3	18.5-27.5	15.5-24.0	0.301	0.277-0.325	
	4	≥28.0	≥24.5	0.272	0.249-0.296	
Whole grains	1	≤2.0	≤1.0	0.290	0.265-0.314	0.69
	2	2.5-5.0	1.5-4.0	0.277	0.254-0.299	
	3	5.5-7.5	4.5-7.0	0.288	0.266-0.311	
	4	≥8.0	≥7.5	0.273	0.249-0.297	
Nuts	1	≤0.5	≤0.5	0.287	0.265-0.309	0.48
	2	1.0-2.0	1.0-2.5	0.279	0.256-0.303	
	3	2.5-5.5	3.0-6.0	0.292	0.269-0.315	
	4	≥6.0	≥6.5	0.267	0.243-0.291	
Legumes	1	<0.5	<0.5	0.286	0.259-0.313	0.89
	2	0.5	0.5	0.276	0.252-0.299	
	3	1.0-1.5	1.0-1.5	0.286	0.266-0.306	
	4	≥2.0	≥2.0	0.278	0.254-0.303	
Red meat§	1	≥5.0	≥7.5	0.312	0.290-0.334	0.0002
	2	3.0-4.5	4.5-7.0	0.301	0.278-0.324	
	3	1.5-2.5	2.5-4.0	0.256	0.231-0.280	
	4	≤1.0	≤2.0	0.254	0.231-0.276	
Fish	1	<0.5	<0.5	0.281	0.252-0.309	0.14
	2	0.5-1.0	0.5-1.0	0.272	0.253-0.290	
	3	1.5-2.0	1.5-2.0	0.304	0.282-0.326	
	4	≥2.5	≥2.5	0.272	0.245-0.299	
MUFA: SFA	1	≤1.05	≤1.08	0.304	0.280-0.327	0.040
	2	1.06-1.21	1.09-1.22	0.290	0.269-0.310	
	3	1.22-1.39	1.23-1.40	0.271	0.246-0.296	
	4	≥1.40	≥1.41	0.258	0.233-0.282	
Alcohol	Outside interval	0-4 or >15 g/day	0-9 or >15 g/day	0.288	0.276-0.301	0.006
	Inside interval	5-15 g/day	10-15 g/day	0.239	0.207-0.272	

Abbreviations: aMedi=modified Alternative Mediterranean Diet Index; CI=confidence interval; GA=geographic atrophy; MUFA: SFA=monounsaturated fatty acid: saturated fatty acid ratio

*Medium-sized servings/week, apart from for MUFA: SFA (considered as a ratio) and alcohol (considered as a binary variable, i.e., intake inside or outside the specified interval)

†Mixed-model, repeated-measures regression with the square root of GA area as the dependent variable, according to component quartile, years from GA first appearance/baseline, and their interaction term, with adjustment for age, sex, total calorie intake, GA characteristics at first appearance/baseline (square root of GA area, central involvement, and configuration), smoking, educational level, and correlation between eyes

‡P value for interaction between component quartile and years

§Red meat quartiles reversed (i.e., 1 for highest intake and 4 for lowest intake)