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Dietary Compound Score and Risk of Age-Related Macular Degeneration in the Age-Related Eye Disease Study

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Abstract

Purpose—Because foods provide many nutrients, which may interact with each other to modify risk for multifactorial diseases such as age-related macular degeneration (AMD), we sought to develop a composite scoring system to summarize the combined effect of multiple dietary nutrients on AMD risk. This has not been done previously.

Design—Cross-sectional study.

Participants—4,003 participants of the Age-Related Eye Disease Study (AREDS) contributed 7,934 eyes.

Methods—Considering dietary intakes of vitamins C and E, zinc, lutein/zeaxanthin, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and low-dietary glycemic index (dGI) from the AREDS baseline information, we assigned each nutrient a percentile rank score then summed them into a Compound score for each participant. Using eye as the unit of analysis, we evaluated the association between the Compound score and risk of prevalent AMD. Validation, fitness, and performance of the model were evaluated using bootstrapping techniques, adjusted quasilielihood under the independence model criterion (QICu), and the c-index, respectively.

Main Outcome Measures—Stereoscopic fundus photographs of the macula were taken and graded at baseline using the AREDS protocol and AMD Classification System.

Results—Our results showed that higher Compound scores were associated with lower risk for early AMD, indicated by drusen, and advanced AMD. Validation analyses indicated that these relationships are robust (the average 50-time bootstrapping per quartile odds ratios [ORs] = 0.727,

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0.827, and 0.753, respectively, for drusen, and 0.616, 0.536, and 0.572, respectively, for advanced AMD). Model selection analyses suggested that the Compound score should be included, but that measures of dietary beta-carotene should not be included.

Conclusion—We found that consuming diets which provide low dGI and higher intakes of the above-mentioned nutrients were associated with the greatest reduction in risk for prevalent drusen and advanced AMD, while dietary beta-carotene did not affect these relationships. These findings warrant further prospective studies.

Introduction

Age-related macular degeneration (AMD) is the major cause of legal blindness for older white adults in Australia, Western Europe, and North America, and studies have provided strong evidence that the disease is caused by the actions and interactions of multiple genetic and environmental factors.¹ With the proportion of aging population increasing rapidly, the disease has brought a significant public health burden and impaired personal quality of life among elderly who develop advanced AMD.² Despite some success in abating progress of advanced diseases, prevention is considered to be far more preferable and of critical importance.³ Furthermore, there are no treatments to prevent substantial loss of vision due to progression of the “dry” advanced stage of this disease, called geographic atrophy.

In 2001, the Age-Related Eye Disease Study (AREDS), a randomized, placebo-controlled trial showed that a high-dose supplement of vitamin C, vitamin E, beta-carotene, and zinc was protective against progression of moderately severe early AMD to advanced AMD.⁵ A prospective observational study from the Rotterdam Study also showed that diets with above-median intakes of all the 4 AREDS trial nutrients were protective against development of early AMD as indicated by large drusen.⁶ In order to search for additional benefit, and determine the value of individual constituents in the AREDS supplement, the NEI launched a new trial, the Age-Related Eye Disease Study 2 (AREDS2), to evaluate the effects of supplementary lutein and zeaxanthin, and/or two omega-3 fatty acids: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).^{7, 8} Because of potential risk for lung cancer in smokers using beta-carotene supplements, the efficacy of a modified AREDS supplement (without beta-carotene) will also be evaluated in the ongoing AREDS2 trial. Importantly, previous studies from both cross-sectional and prospective studies in the Nutrition and Vision Project of the Nurses’ Health Study⁹ and the AREDS^{10, 11} suggested that lowering dietary glycemic index (dGI) may offer an additional way to substantially reduce the risk for AMD.

Foods contain many dietary constituents, many of which might interact with each other to affect the risk for multifactorial diseases such as AMD. Unlike controlled clinical trial studies, in which nutritional supplements can be randomly assigned at baseline, the statistical power of observational studies is often inadequate to evaluate the combined effect of multiple dietary nutrients, especially when the number of the evaluated nutrients is large. For example, the adequate sample size for a study to evaluate diets with above-median intakes of 8 nutrients would be exponentially much larger than that for 4 nutrients, making such studies impractical.

To overcome this barrier and offer an overall reflection of the benefit that a specific dietary pattern may offer, we developed a dietary composite scoring system which aggregates the effects of multiple biologically plausible nutrients. Applying this system in the baseline cross-sectional data from the AREDS, we estimated the combined effect of vitamin C, vitamin E, zinc, lutein and zeaxanthin, DHA, EPA, and low-GI foods from diet on the risk for AMD, and we evaluated if dietary beta-carotene affects this relationship. In addition, as

our scoring system can serve as a summary index of a researcher-defined dietary pattern, it may facilitate future studies on diet-supplement/diet-gene interactions.

Materials and Methods

AREDS Cohort

The AREDS was a long-term multicenter, prospective study dedicated to assess the clinical course, prognosis, risk factors, and prevention strategy of both AMD and cataract.¹² The protocol was approved by a Data and Safety Monitoring Committee and by the Institutional Review Board for each of the 11 participating ophthalmic centers before initiation of the study. Informed consent was obtained from participants prior to enrollment. Detailed recruitment criteria have been described extensively in the AREDS report series. A total of 4,757 participants, aged 55 to 80 y at recruitment, were enrolled from November 1992 to January 1998.

Procedures

Data on possible risk factors for AMD was obtained from a baseline general physical and ophthalmic examination, a detailed questionnaire on basic characteristics and demographic data, and a validated food frequency questionnaire (**FFQ**).

Stereoscopic fundus photographs of the macula were taken and graded at baseline using the AREDS protocol and AMD Classification System.¹³ Eyes were classified into one of five groups according to the size and extent of drusen, presence of geographic atrophy, and neovascular changes of AMD.¹³ The five groups, numbered serially and based on increasing severity of drusen or type of AMD, were defined as follows.

Group 1 (Small Drusen): Eyes had no drusen or non-extensive small drusen ($< 63 \mu\text{m}$).

Group 2 (Intermediate Drusen): Eyes had one or more intermediate drusen ($63 \mu\text{m}$ - $124 \mu\text{m}$), extensive small drusen, or pigment abnormalities associated with AMD.

Group 3 (Large Drusen): Eyes had one or more large drusen ($\geq 125 \mu\text{m}$) or extensive intermediate drusen.

Group 4 (Geographic Atrophy): Eyes had geographic atrophy.

Group 5 (Neovascular): Eyes had choroidal neovascularization or RPE detachment.

Study Subjects

In the present study, we used a similar subject recruitment scheme with our previous study. Of the original 4,757 AREDS participants at baseline, we first excluded 398 persons with diabetes, 108 persons with invalid calorie intake (valid intake ranging from 400 to 3,000 Kcal/d for female and 600 to 3,500 Kcal/d for male), and 248 persons with missing nutritional, non-nutritional and ophthalmologic covariates. The remaining 4,003 persons contributed 7,934 eligible eyes (72 persons contributed only one eligible eye) at baseline, including 2,733 eyes in Group 1, 1,782 eyes in Group 2, 2,672 eyes in Group 3, 159 eyes in Group 4, and 588 eyes in Group 5. We defined Groups 2 and 3 as the drusen group ($n = 4,454$ eyes at baseline), Groups 4 and 5 as the advanced AMD group ($n = 747$ eyes at baseline).

Assessment of Dietary Nutrient Variables

A 90-item modified Block FFQ was administered to AREDS participants at baseline (see **Procedures**). The FFQ collected information about usual dietary intakes over the previous year and classified them into nine possible response categories, ranging from 'never or less than once per month' to 'two or more times per day.' The daily total nutrient intake of an individual was calculated by summing the product of the frequency, serving size, and carbohydrate content per serving from individual food items derived from the nutrition database of the Nutrition Coordinating Center at the University of Minnesota. The FFQ was validated in relation to 24-hour recall using a subset of the AREDS volunteers ($n = 192$). The 24-h recall data was collected twice by telephone interviews at 3- and 6-month post-enrollment. Correlation coefficients between the 24-hour recall and the FFQ are 0.46 for vitamin C, 0.26 for vitamin E, 0.30 for beta-carotene, 0.24 for lutein/zeaxanthin, 0.38 for zinc, 0.35 for EPA, 0.32 for DHA, 0.56 for carbohydrate intake, and 0.51 for calorie (Kuninji N, Gensler G, Milton R, Age-Related Eye Disease Study (AREDS) Research Group. Development and valuation of a food frequency questionnaire in a randomized trial of eye diseases. International Conference on Dietary Assessment Measures. Phoenix, Ariz, 1998.)

Dietary Glycemic Index (dGI)—The glycemic index (**GI**) is a physiological measure of the glycemic quality of carbohydrate-containing foods.¹⁴ It was devised to measure how fast a food raises blood glucose and is defined as the ratio of the area under two-hour blood glucose curves of a test food vs. the same amount (50 g) of available carbohydrate from a reference food (pure glucose or white bread).¹⁴ The GI values for foods in the FFQ were either derived from published values using white bread as the reference food, or imputed from GI values of comparable foods.¹⁵ The **dGI** for each subject was calculated as the weighted average of the GI values for each food item, with the amount of carbohydrate consumed from each food item as the weight ($\sum (GI_i \times W_i)/W$).¹⁶ Indigestible fiber content was subtracted from the carbohydrate content.

All nutritional variables were adjusted for total energy intake using the residuals method.¹⁷

Defining Potential Covariates

The following were considered as potential covariates in our analyses: age, gender, education level (college graduate, and high school or less), race (white and others), body mass index (BMI, computed from weight and height; kg/m^2), smoking status (ever and never), alcohol drinking (g/d), sunlight exposure (hour/d),¹⁸ hypertension history, baseline AMD classification, presence of lens opacity, refractive error (hyperopic and myopic), total calorie intake, and energy-adjusted dietary variables including carbohydrate, protein fat, polyunsaturated fatty acids, arachidonic acid, DHA, EPA, lutein and zeaxanthin, folic acid, niacin, riboflavin, thiamin, vitamin C, vitamin E, beta-carotene, and zinc.

Statistical Methods

Dietary Composite Scoring System—The objective of the present study is to evaluate, in the AREDS cohort, the associations between baseline AMD prevalence and dietary risk factors. These dietary risk factors include **dGI** and those nutrients which were or are being studied in the **AREDS trial (vitamin C, vitamin E, beta-carotene, and zinc)** and **AREDS2 trial (DHA, EPA, and lutein/zeaxanthin)**. To evaluate the effect of a specific dietary pattern of interest, we developed a scoring system based on the percentile ranks of nutrient intakes. First we calculated three composite scores: (a) **DP1 diet**, (b) **DP2 diet**, and (c) **DP3 diet** by specifying the dietary intakes of (a) **vitamin C, vitamin E, and zinc**, (b) **DHA, EPA, and lutein/zeaxanthin (Lz)**, and (c) **dGI**, respectively. Because beta-carotene has been considered to be deleted from the AREDS formula, it was not included in our

composite score analyses. We defined the three dietary patterns to represent diets rich in the AREDS trial nutrients, AREDS2 trial nutrients, and low-GI foods, respectively.

We defined the composite score to be the linear combination of the intake scores from individual nutrients, for example $DP1(P_i) = VitC(P_i) + VitE(P_i) + Zinc(P_i)$. To calculate the composite score of the **DP1** diet for subject P_i (denoted as $DP1(P_i)$), we first ranked and clustered the 4,003 subjects into 100 groups, by the order of energy-adjusted dietary vitamin C intake, from the lowest to the highest intake (i.e., into percentile groups). If the subject fell into the 100th group (highest intake of vitamin C), then we assigned a score of 100 for his/her dietary vitamin C score (denoted as $VitC(P_i) = 100$). We scored his/her dietary vitamin E and zinc intakes (denoted as $VitE(P_i)$ and $Zinc(P_i)$, respectively), similarly. We defined the composite score of the **DP1** diet for **subject P_i** by summing the three scores from the three AREDS trial nutrients, $VitC(P_i)$, $VitE(P_i)$, and $Zinc(P_i)$ (i.e., $DP1(P_i) = VitC(P_i) + VitE(P_i) + Zinc(P_i)$).

Similarly, the **DP2 composite** score was calculated for each participant by summing the three scores from the three AREDS2 trial nutrients (i.e., $DP2(P_i) = DHA(P_i) + EPA(P_i) + Lz(P_i)$).

In order to have a consistent direction of the relationships between the three composite scores and the risk for AMD, we defined the composite score for the **DP3** diet as ‘100 minus dGI(P_i)’ (i.e., $DP3(P_i) = 100 - dGI(P_i)$).

To summarize the effects of the three pre-defined dietary patterns, we defined the score of ‘**Compound diet**’ as $Compound(P_i) = DP1(P_i) + DP2(P_i) + DP3(P_i)$ and related the **Compound score** to the risk for prevalent AMD.

In order to maximize power we used eyes as the unit in the analyses of the associations between dietary risk factors and risk for AMD. We used eyes with AMD lesions (Groups 2 through 5 at baseline; see **Procedures**) as our cases and those in Group 1 at baseline as our controls. We first estimated odds ratios (**ORs**) and 95% confidence intervals (**CIs**) relating individual nutrients to the risk for AMD by logistic regression analysis using the generalized estimating equation (**GEE**) method to estimate the coefficients and to adjust the standard errors of the model terms for the correlated data resulting from repeated measurements (both eyes) on the same individual (Table 1).¹⁹ The associations with the three dietary composite scores (**DP1**, **DP2**, **DP3**), and the **Compound diet score** were then examined (Fig 1).

To test for linear trends across the quartile categories of the dietary composite scores or nutrients, we assigned the median value in each category to everyone within the category and then included this as a continuous variable in the regression models. The P value for trend was derived from the P value for the regression coefficient of the continuous variable for the composite score or nutrient.

Validation of Dietary Compound Score—To validate our scoring system, we assessed the relationship between **Compound score** and the risk for AMD by the bootstrap technique (SAS %boot macro).²⁰ In bootstrapping, sub-samples of the data are repeatedly analyzed. Each sub-sample, of the same size as the original dataset, is treated as a random sample with replacement from the full sample. Thus, bootstrapping offers the possibility of simulating the performance of the model as if it were applied to future samples. As applied here, bootstrapping involves performing the logistic analyses 50 times for which 50 computer-generated samples were derived from the original data set by random selection with replacement, i.e., each of the resamples was obtained by random sampling with replacement from the original dataset and had the same sample size with the original dataset. For each

bootstrap sample, the model was refitted and the average ORs for the 2nd, 3rd, and 4th quartile groups of **Compound score** were calculated. For example, the bootstrapping for advanced AMD analysis (2733 controls + 747 cases) consists of three steps:

1. Select 3,480 (= 2733+747) subjects from the original data (2733 controls + 747 cases) with replacement (i.e., a selected subject was put back to the original sampling pool to ensure every sampling procedure with equal probability).
2. Run the model with this bootstrap sample and compute the ORs of interest.
3. Repeat this process 50 times as if the model is applied to 50 random sampling data sets.

Model selection—We used the quasilielihood under the independence model criterion (**QIC**) statistic to evaluate the goodness-of-fit of a GEE model.²¹ We evaluated four models, including ‘base model,’ ‘base model + beta-carotene,’ ‘base model + **Compound score**,’ and ‘base model + beta-carotene + **Compound score**.’ The base model included all the covariates listed in the section regarding **Defining Potential Covariates**. To adjust for the difference in the number of covariates between models, **QICu** defined as **QIC**+2p, where p is the number of parameters in the model, was used. The model with the smaller **QICu** means better fit or reliability.

The predictive accuracy assessed by the **c-index**, which is the area under the receiver-operating characteristic (**ROC**) curve,^{22, 23} was compared among the 4 models. A higher c-index means a better model performance.

SAS (version 9.1; SAS Institute Inc, Cary, NC) software was used for statistical analyses. The statistical significance level was set at 0.05 and all tests were two-sided.

Results

The distribution of baseline AREDS characteristics has been published elsewhere.¹⁰ Compared with control group (n = 2,733 eyes), cases in the drusen group (intermediate drusen plus large drusen, n = 4,454) were significantly older, less educated, more likely to be white, more likely to be a smoker, more likely to have a hypertension history and lens opacity. In addition to the above characteristics, cases in the advanced AMD group (n = 747) had higher BMI and were more likely to be hyperopic.

In the analyses for each nutrient (Table 1), we found few significant ORs suggesting a protective effect (OR < 1) against either drusen or late AMD in vitamin E, zinc, beta-carotene, EPA, and lutein plus zeaxanthin. However, the ORs of vitamin E for advanced AMD showed a marginally significant trend (P = 0.052).

The **DP1** composite score showed no significant association with drusen (Fig 1a) but a marginally significant relationship with advanced AMD (4th vs. 1st quartile of the score, OR = 0.7, 95% CI, 0.47, 1.02; P for trend = 0.07) (Fig 1b). The analyses for the **DP2** score showed an ambiguous relationship with drusen (2nd vs 1st quartile of the score, OR = 0.83, 95% CI, 0.69, 1.00; P for trend = 0.51) (Fig 1c), but a protective association of the **DP2** score with prevalent advanced AMD (P for trend = 0.03) was observed (Fig 1d). For the **DP3** score (**DP3(Pi)** = **100 – dGI(Pi)**), the lower the dGI the lower the risk for both drusen (P for trend = 0.05) (Fig 1e) and advanced AMD (P for trend = 0.008) (Fig 1f). As expected, the **Compound score** summarized the protective effects of **DP1**, **DP2**, and **DP3** scores against advanced AMD (P for trend = 0.002) (Fig 1h). Mainly due to the effect of **DP3** score, the **Compound score** also showed a protective effect for drusen (Fig 1g). We also separately related **DP1**, **DP2**, **DP3** (the three composite scores), and the **Compound score**

to the risk for intermediate drusen (n= 1,782) and large sized drusen (n= 2,672). While the findings for intermediate sized drusen showed no significant trend, the findings for large sized drusen were similar to those for the drusen group as a whole (intermediate drusen plus large drusen, n= 4,454) (data not shown). However, there was only a marginally significant trend ($P = 0.084$) for the association of the **Compound score** and large drusen.

The average 50-time bootstrap OR estimates for the second, third, and fourth quartile groups of **Compound score** are 0.727, 0.827, and 0.753, respectively, for drusen. They are 0.616, 0.536, and 0.572, respectively, for advanced AMD. Compared with the OR estimates from the original data set (Fig 1g and 1h), these results suggest robust relationships between **Compound score** and risk for drusen and advanced AMD.

The model selection analyses comparing models with vs. without including **Compound score** (QICu = 9174.54 vs. 9187.05 and c-index = 0.64 vs. 0.637 for drusen; QICu = 3171.91 vs. 3188.70 and c-index = 0.752 vs. 0.746 for advanced AMD) suggested that it is informative and appropriate to include Compound scores in the logistic models (Table 2). However, including dietary beta-carotene intake in the model did not improve either reliability (QICu) or performance (c-index) of the model.

Discussion

At present there are no reports of simultaneous analyses of multiple dietary constituents and risk for AMD. Applying our dietary composite scoring system in the AREDS baseline cross-sectional data set, the results suggest that the Compound score summarizing the overall effect of diets rich in the AREDS trial nutrients (vitamin C, vitamin E, and zinc), the AREDS2 trial nutrients (DHA, EPA, and lutein/zeaxanthin), and low-GI foods are independently associated with lower risk for prevalent drusen and advanced AMD, while dietary beta-carotene does not affect the risk for earlier or later AMD. Three aspects in this study deserve further discussion: the AREDS data set, the methods used in the development of the composite scoring system, and the composite scoring system per se.

Using our scoring system in the AREDS baseline data, we objectively selected nutrients to characterize three dietary patterns and then related them, in combination or alone, to the risk for prevalent AMD. The selected nutrients have been shown in either some randomized trials, epidemiological studies, or *in vitro* or *in vivo* animal studies to be protective against AMD.^{3, 24} Compared with extensively screening from a long list of variables, our approach, which is based on established prior knowledge, reduces false positive findings by examining a smaller number of biologically plausible dietary factors. Moreover, instead of arbitrarily giving a weight to each nutrient, we assigned a percentile score according to the rank of the energy-adjusted nutrient variable in our cohort. In choosing cut-off points for exposure categorization, there is always a dilemma between scientific knowledge of healthy levels of intake and the power to discriminate and to relate outcomes to the contribution of the index item.²⁵ Although using percentile rank scoring ensures an approximately equal sample size for each exposure category, it may result in a non-linearity relationship between the actual intake level and the score, especially in the upper or lower ends of the intake distribution with many outliers. However, for a well-fed population, like the AREDS cohort, the healthy levels of intake are less likely to fall within the extreme ends of the population distributions. Therefore, the nonlinearity relationships should be of less concern in our study. By using iso-caloric nutrient variables, we also diminish the effect of variation in factors other than the nutrient per se, such as body size, physical activity, and metabolic efficiency, etc.¹⁷ The confounding effects were further controlled in the regression models in which we included macronutrient, micronutrient and measured non-nutrient confounders. These attributions of this analytical process indicate that the results may be more unbiased

and instructive to the primary interest of the association between the three dietary patterns and risk for AMD.

In the single-nutrient analyses, only dietary vitamin E intake showed a suggestive protective association for prevalent advanced AMD (Table 1), compared with the results suggesting protective association for all the three of the pre-defined dietary patterns on the risk for prevalent advanced AMD (Fig 1). This result suggests the advantage that dietary pattern analysis aggregates small effects from individual nutrients into an overall reflection of the benefit that diet (as opposed to single nutrients) might offer.

Examining the results for single-nutrient analyses (Table 1), we also noted that a U-shape dose-response pattern may be responsible for the effect of several nutrients, such as beta-carotene and lutein/zeaxanthin. The results imply that high doses of these nutrients may elicit opposite responses to that seen at small doses, i.e., as doses increase there are not only quantitative changes in AMD risk but also qualitative changes compared with low-dose levels. This phenomenon, named hormesis, has been well characterized in many *in vitro* and animal studies but less in humans.²⁶ As a hormetic dose-response relationship will have substantial influences on the dietary guideline for the nutrient, this issue deserves more attentions and needs further study.

Since people eat foods, not single nutrients, collinearity between nutrients may also impede our ability to evaluate the effect of a single nutrient. For example, because fish is the major dietary source of DHA and EPA, the high correlation between DHA and EPA intakes (correlation coefficient = 0.95) in our cohort, and probably in most populations, have hampered our ability to estimate the independent effect from each nutrient. However, our composite score analysis does not waive the necessity of single-nutrient analysis. Instead, this study shows that a hierarchical analysis, i.e., from single-nutrient analysis to composite score analysis, appears to give a better appreciation of the underlying relationship. For example, though the **Compound score** ($\text{Compound}(P_i) = \text{DP1}(P_i) + \text{DP2}(P_i) + \text{DP3}(P_i)$) was significantly associated with presence of drusen, our results suggested that this association is mainly driven by dGI ($\text{DP3}(P_i) = 100 - \text{dGI}(P_i)$) (Fig 1). While the scoring system was designed to measure the combined effect from multinutrients, we did not rule out the effect of nutrient-nutrient interaction on prevalent AMD risk.

Several points are noteworthy in the methods used in our composite scoring system development. First, by employing random selection with replacement,²⁰ our bootstrap samples were somewhat different from the original data set. This technique helped to determine how sensitive our findings are to small changes in the data. The results proved to be quite robust, increasing our confidence that the detected relationship is valid. However, bootstrapping should be complemented by validation by a separate study of a different cohort. Second, in our model selection procedure we used the QIC statistic²¹, which is analogous to Akaike's Information Criterion (AIC) statistic²⁷ used for comparing models fit with likelihood-based methods. The QIC was used, because the GEE method is not a likelihood-based method, making the AIC statistic unsuitable in our GEE logistic model selection. Furthermore, unlike the AIC statistic in which the more complex model must differ from the simple model only by the addition of one or more variables, models do not need to be nested to use QIC or QICu to compare them. Third, although c-index can be used to compare model performance, the difference of c-index between models does not imply the importance of a risk factor. For example, in our analyses the model including **Compound score** (c-index = 0.752) was better in predicting the risk for prevalent advanced AMD than the base model (c-index = 0.746) (Table 2). However, the small difference (0.006) of c-index between these two models does not imply that **Compound score** (the combined effect of the nutrients) has little importance on the risk for advanced AMD. Pepe

et al. have showed that even an odds ratio as large as 3.0 (or as small as 0.33) may have little impact on the c-index.²⁸ It was suggested that, for risk prediction, the actual or absolute predicted risk, which is not captured by the c-index, is of primary clinical interest.²⁹

The AREDS data set has several advantages.¹⁰ Using participants from a well-characterized cohort, we were able to use the standardized collection of risk factor information and photographic grading of AMD from individual eyes. This enabled us to use eyes as the unit of analysis and hence increased our power. Recall and selection bias were minimized because exposure information was collected before outcome evaluation, and retinal classifications were performed in an independent center by graders masked to nutrition data. Non-differential misclassification could have only lead to no associations but would be less likely to result in false positive findings. Consistency with prior evidence and biological plausibility reduced the possibility that the present findings were due to chance. Residual confounding is a concern but should be minimized because we included all known dietary and non-dietary confounders in our analysis. However, the cross-sectional and clinic-based nature of the present study limited its strength in defining causality and generalizability. It is possible that important lifestyle confounders differing in the non-AMD group (Group 1) and the other AREDS AMD groups (Groups 2–5) due to how samples were selected were not measured and might have had an impact on our findings. Until the results of this cross-sectional study are confirmed by randomized trials or population-based prospective studies, it would be inappropriate to make dietary recommendation based on the present findings.

In conclusion, in this study we developed and validated the Compound score for relating the combined effect of dietary multinutrients to AMD risk. The findings that diets rich in low-GI foods and vitamins C and E, zinc, DHA, EPA, and Lz are associated with lower risk for advanced AMD and drusen and that dietary beta-carotene did not affect these associations warrant further study.

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References

1. Haddad S, Chen CA, Santangelo SL, Seddon JM. The genetics of age-related macular degeneration: a review of progress to date. *Surv Ophthalmol.* 2006; 51:316–63. [PubMed: 16818082]
2. Tomany SC, Wang JJ, van Leeuwen R, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology.* 2004; 111:1280–7. [PubMed: 15234127]
3. Chiu CJ, Taylor A. Nutritional antioxidants and age-related cataract and maculopathy. *Exp Eye Res.* 2007; 84:229–45. [PubMed: 16879819]
4. Chang TS, Bressler NM, Fine JT, et al. MARINA Study Group. Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration: results of a randomized clinical trial. *Arch Ophthalmol.* 2007; 125:1460–9. [PubMed: 17998507]
5. 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; 119:1417–36. [PubMed: 11594942]
6. van Leeuwen R, Boekhoorn S, Vingerling JR, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA.* 2005; 294:3101–7. [PubMed: 16380590]

7. Age-Related Eye Disease Study Research Group. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS report no. 20. *Arch Ophthalmol*. 2007; 125:671–9. [PubMed: 17502507]
8. Coleman H, Chew E. Nutritional supplementation in age-related macular degeneration. *Curr Opin Ophthalmol*. 2007; 18:220–3. [PubMed: 17435429]
9. Chiu CJ, Hubbard LD, Armstrong J, et al. Dietary glycemic index and carbohydrate in relation to early age-related macular degeneration. *Am J Clin Nutr*. 2006; 83:880–6. [PubMed: 16600942]
10. Chiu CJ, Milton RC, Gensler G, Taylor A. Association between dietary glycemic index and age-related macular degeneration in nondiabetic participants in the Age-Related Eye Disease Study. *Am J Clin Nutr*. 2007; 86:180–8. [PubMed: 17616779]
11. Chiu CJ, Milton RC, Klein R, et al. Dietary carbohydrate and progression of age-related macular degeneration: a prospective study from the Age-Related Eye Disease Study. *Am J Clin Nutr*. 2007; 86:1210–8. [PubMed: 17921404]
12. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. *Control Clin Trials*. 1999; 20:573–600. [PubMed: 10588299]
13. 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*. 2001; 132:668–81. [PubMed: 11704028]
14. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr*. 1981; 34:362–6. [PubMed: 6259925]
15. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr*. 2002; 76:5–56. [PubMed: 12081815]
16. Wolever TM, Nguyen PM, Chiasson JL, et al. Determinants of diet glycemic index calculated retrospectively from diet records of 342 individuals with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr*. 1994; 59:1265–9. [PubMed: 8198048]
17. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986; 124:17–27. [PubMed: 3521261]
18. McCarty CA, Lee SE, Livingston PM, et al. Ocular exposure to UV-B in sunlight: the Melbourne Visual Impairment Project model. *Bull World Health Organ*. 1996; 74:353–60. [PubMed: 8823956]
19. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986; 42:121–30. [PubMed: 3719049]
20. Efron B. Bootstrap methods: another look at the jackknife. *Ann Stat*. 1979; 7:1–26.
21. Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics*. 2001; 57:120–5. [PubMed: 11252586]
22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982; 143:29–36. [PubMed: 7063747]
23. Chiu CJ, Lee WC, Chiang CP, et al. A scoring system for the early detection of oral submucous fibrosis based on a self-administered questionnaire. *J Public Health Dent*. 2002; 62:28–31. [PubMed: 14700086]
24. SanGiovanni JP, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. *Prog Retin Eye Res*. 2005; 24:87–138. [PubMed: 15555528]
25. Waijers PM, Feskens EJ, Ocké MC. A critical review of predefined diet quality scores. *Br J Nutr*. 2007; 97:219–31. [PubMed: 17298689]
26. Hayes DP. Adverse effects of nutritional inadequacy and excess: a hormetic model. *Am J Clin Nutr*. 2008; 88:578S–81S. [PubMed: 18689405]
27. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Control*. 1974; 19:716–23.
28. Pepe MS, Janes H, Longton G, et al. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *Am J Epidemiol*. 2004; 159:882–90. [PubMed: 15105181]

29. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation*. 2007; 115:928–35. [PubMed: 17309939]

Figure 1.

Association between Dietary Composite Score and Risk for Drusen and Advanced AMD. [†] Abbreviation: **AMD**, Age-related Macular Degeneration; **OR**, odds ratio; **CI**, confidence interval.

[†] All analyses used eyes as the unit. The ORs (95% CIs) were calculated from multivariate-adjusted logistic models using the first quartile group of the nutrient intake as the referent and non-extensive small drusen or no drusen (n = 2,733) as controls. The drusen group (n = 4,454) included intermediate drusen and large drusen. The advanced AMD group (n = 747) included neovascularization and geographic atrophy.

Table 1Associations between Dietary Nutrients and Risk of Age-related Macular Degeneration. [†]

	Drusen n = 4,454	Advanced AMD n = 747
Nutrient	Multivariate-adjusted OR (95% CI)	
Vitamin C		
Q2	0.94 (0.79, 1.13)	0.79 (0.60, 1.04)
Q3	0.93 (0.77, 1.14)	0.83 (0.61, 1.13)
Q4	1.02 (0.81, 1.29)	0.98 (0.70, 1.38)
P for Trend	0.91	0.90
Vitamin E		
Q2	0.82 (0.68, 0.99)	0.81 (0.60, 1.09)
Q3	0.91 (0.74, 1.11)	0.76 (0.54, 1.06)
Q4	0.83 (0.65, 1.06)	0.66 (0.45, 0.99)
P for Trend	0.30	0.052
Zinc		
Q2	0.82 (0.68, 0.98)	0.85 (0.64, 1.13)
Q3	0.93 (0.76, 1.14)	0.67 (0.48, 0.93)
Q4	0.92 (0.72, 1.18)	0.83 (0.56, 1.23)
P for Trend	0.86	0.18
Beta-carotene		
Q2	0.92 (0.77, 1.10)	0.84 (0.63, 1.11)
Q3	0.87 (0.72, 1.05)	0.74 (0.55, 1.00)
Q4	0.97 (0.79, 1.19)	0.98 (0.71, 1.35)
P for Trend	0.70	0.66
DHA		
Q2	0.99 (0.83, 1.18)	0.90 (0.69, 1.19)
Q3	0.97 (0.80, 1.17)	0.84 (0.63, 1.13)
Q4	0.94 (0.77, 1.16)	0.82 (0.59, 1.13)
P for Trend	0.57	0.20
EPA		
Q2	0.94 (0.79, 1.12)	0.87 (0.66, 1.14)
Q3	0.96 (0.80, 1.15)	0.70 (0.53, 0.93)
Q4	1.02 (0.84, 1.24)	0.94 (0.70, 1.26)
P for Trend	0.76	0.33
Lutein/Zeaxanthin		
Q2	0.81 (0.68, 0.97)	0.80 (0.61, 1.05)
Q3	0.80 (0.67, 0.97)	0.66 (0.49, 0.90)
Q4	0.94 (0.77, 1.16)	0.97 (0.70, 1.33)
P for Trend	0.69	0.56

Abbreviation: **OR**, odds ratio; **CI**, confidence interval; **AMD**, age-related macular degeneration; **DHA**, docosahexaenoic acid; **EPA**, eicosapentaenoic acid.

[†]All analyses used eyes as the unit. The ORs (95% CIs) were calculated from multivariate-adjusted logistic models using the first quartile group of the nutrient intake as the referent and non-extensive small drusen or no drusen (n = 2,733) as controls. The drusen group (n = 4,454) included intermediate drusen and large drusen. The advanced AMD group (n = 747) included neovascularization and geographic atrophy.

Table 2

Model Reliability and Performance for GEE Logistic Regression Analyses of Risk for Drusen and Advanced AMD.

Model [†]	Drusen n = 4,454		Advanced AMD n = 747	
	QICu [‡]	c-index [*]	QICu [‡]	c-index [*]
base model	9187.05	0.637	3188.70	0.746
base model + Compound score	9174.54	0.640	3171.91	0.752
base model + beta-carotene	9189.07	0.637	3190.70	0.746
base model + Compound score+ beta-carotene	9176.26	0.640	3173.63	0.752

Abbreviation: **GEE**, generalized estimating equation; **AMD**, age-related macular degeneration; **QIC**, quaslikelihood under the independence model criterion.

[†]The base model included all the covariates listed in **Defining Potential Covariates**.

[‡]QICu is defined as QIC+2p, where p is the number of parameters in the model. The model with the smaller QICu means better fit or reliability.

^{*}A higher c-index means a better model performance.