AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Mediterranean Diet Score and Its Association with Age-Related Macular Degeneration

The European Eye Study

Ruth E. Hogg, PhD,[1] Jayne V. Woodside, PhD,[1] Alanna McGrath, BSc,[1] Ian S. Young, MD,[1] Jesus L. Vioque, MD, PhD,[2] Usha Chakravarthy, MD, PhD,[1] Paulus T. de Jong, MD,[3] Mati Rahu, PhD,[4] Johan Seland, MD,[5] Gisele Soubrane, MD,[6] Laura Tomazzoli, MD,[7] Fotis Topouzis, MD,[8] Astrid E. Fletcher, PhD[9]

Purpose: To examine associations between adherence to a Mediterranean diet and prevalence of age-related macular degeneration (AMD) in countries ranging from Southern to Northern Europe.

Design: Cross-sectional, population-based epidemiologic study.

Participants: Of 5060 randomly sampled people aged 65 years or older from 7 study centers across Europe (Norway, Estonia, United Kingdom, France, Italy, Greece, and Spain), full dietary data were available in 4753. The mean age of participants was 73.2 years (standard deviation, 5.6), and 55% were women.

Methods: Participants underwent an eye examination and digital retinal color photography. The images were graded at a single center. Dietary intake during the previous 12 months was assessed by using a semiquantitative food-frequency questionnaire (FFQ). A previously published Mediterranean Diet Score (MDS) was used to classify participants according to their responses on the FFQ. Multivariable logistic regression was used to investigate the association of the MDS score and AMD, taking account of potential confounders and the multicenter study design.

Main Outcome Measures: Images were graded according to the International Classification System for age-related maculopathy and stratified using the Rotterdam staging system into 5 exclusive stages (AMD 0–4) and a separate category of large drusen (≥125 μm). Age-related macular degeneration 4 included neovascular AMD (nvAMD) and geographic atrophy (GA).

Results: Increasing MDS was associated with reduced odds of nvAMD in unadjusted and confounder-adjusted analysis. Compared with the lowest MDS adherence (≤4 score), those in the highest category MDS adherence (>6 score) showed lower odds of nvAMD (odds ratio, 0.53; 0.27–1.04; P trend = 0.01). The association with MDS did not differ by Y204H risk allele (P = 0.89). For all early AMD (grade 1–3), there was no relationship with MDS (P trend = 0.9). There was a weak trend (P = 0.1) between MDS and large drusen; those in the highest category of MDS had 20% reduced odds compared with those in the lowest (P = 0.05).

Conclusions: This study adds to the limited evidence of the protective effect of adherence to a Mediterranean dietary pattern in those with late AMD, although it does not support previous reports of a relationship with genetic susceptibility. Interventions to encourage the adoption of the Mediterranean diet should be developed, and methods by which such behavior change can be achieved and maintained investigated. *Ophthalmology 2017;124:82-89 © 2016 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is the predominant cause of blindness in high-income countries.[1] It is of growing importance in other settings, in association with increasing longevity.[2] Age-related macular degeneration is considered to be a complex multifactorial disorder, involving an interplay among genetic, environmental, and lifestyle factors, such as smoking,[3] obesity,[4] cardiovascular disease,[5] macular pigment,[6] sunlight exposure,[7] diet,[8] high body mass index,[9] and physical activity.[10]

It has been known for some time that dietary factors can modulate AMD risk.[11,12] Epidemiologic studies have demonstrated that diets high in antioxidant nutrients (vitamins C and E, carotenoids such as lutein and zeaxanthin and fruit, and vegetables rich in these nutrients) or zinc are associated with a decreased occurrence of AMD. Studies also have shown that a high dietary intake of trans fats is a risk factor for late AMD,[13] whereas a higher intake of fish or omega-3 fatty acids is protective against AMD.[13] However, the evidence from clinical trials is less consistent. Although high-dose multivitamin supplementation slowed the progression of AMD,[14] a trial that added lutein and zeaxanthin supplements with or without omega-3 fatty acids to the Age-Related Eye Disease Study (AREDS) supplements showed no substantial added beneficial effect of the AREDS supplements on AMD progression (AREDS2).[15] However, in the prespecified analyses of those subjects with the lowest dietary intake of lutein, there was a beneficial effect of lutein for retarding the progression to late

http://dx.doi.org/10.1016/j.ophtha.2016.09.019
ISSN 0161-6420/16

AMD, especially the neovascular form.[16] Most studies to date have focused on individual food groups or nutrients, yet it is known that diet is a multifactorial lifestyle behavior, with particular foods frequently consumed together, depending on the cultural, geographic, and economic context of the individual. Therefore, researchers are increasingly attempting to analyze relationships between dietary patterns or overall diet and disease, rather than specific foods or nutrients.[17–19] To date, these analyses have been undertaken in populations living in defined geographic locations, such as Melbourne, Australia,[17] and in US Carotenoids in Age-Related Eye Disease Study (CAREDS) participants[20] or US AREDS participants.[18,19] Consequently, there is a greater likelihood that the dietary patterns of the individuals in these studies were similar. This was particularly evident in the application of a Mediterranean Diet Score (MDS) to CAREDS participants[20] in that high scores were uncommon in this sample (0.04%). Because dietary patterns vary by culture, and availability of local food is subject to strong regional influences, a lack of heterogeneity of populations in the prior studies may have reduced the power to detect associations with AMD outcomes. By contrast, the European Eye (EUREYE) Study enrolled participants from 7 countries across Europe with widely differing cultures and dietary patterns, thus providing an interesting context in which to investigate links between diet and AMD. Of note, the dietary questionnaire was modified to reflect locally available foods. For these reasons, we aimed to examine the association between adherence to a Mediterranean diet and prevalence of AMD in countries ranging from Southern to Northern Europe.

Methods

Study Population

We recruited participants between 2001 and 2002 from 7 European countries (Bergen, Norway; Tallinn, Estonia; Belfast, UK; Paris, France; Verona, Italy; Thessaloniki, Greece; and Alicante, Spain) using random sampling of the population older than 65 years of age. Written informed consent was obtained from all study participants. Ethical approval was obtained for each country from the relevant ethics committee, and the study adhered to the Declaration of Helsinki on research into human volunteers.

The study design and methodology have been published.[7,21–26] Participants attended the examination center, where they were first interviewed by trained fieldworkers, underwent an ophthalmological examination, and gave a blood sample. Information collected by the interviewers included quantified smoking and alcohol use and a brief medical history, detailed questionnaire on outdoor exposure throughout working life and in retirement, and a dietary assessment (described in detail next).

Dietary Assessment Methodology

During the interview, dietary intake during the previous 12 months was assessed by using a semiquantitative food-frequency questionnaire (FFQ). We used the UK European Prospective Investigation into Cancer and Nutrition (EPIC) Study FFQ,[27] which was derived from the original FFQ devised by Willett.[28] For each non–United Kingdom country in the study, we modified the FFQ for food items that were redundant or relevant using the EPIC country-specific questionnaires to identify additional food items or the local variety of a food item. In Estonia, where there was no equivalent EPIC questionnaire, we devised the FFQ after consultation with local nutrition researchers. Validation studies have been carried out on country-specific EPIC questionnaires, for example, for the United Kingdom.[27] In addition, among the Spanish participants, we explored the relation between energy-adjusted dietary carotenoid and vitamin C intakes and serum concentration. Significant Pearson correlations were observed for alpha-carotene 0.21, β-carotene 0.19, lycopene 0.18, β-cryptoxanthin 0.20, and vitamin C 0.36, which support an acceptable performance of the dietary intakes estimated from the FFQ.[29] Information on habitual consumption of foods during the previous year included portion size and was recorded in 9 different frequency categories, from never or less than once a month to 6 times/day or more. Intake of food items was recorded into portions per day. Nutrient intake was estimated using the food-composition tables of Holland et al,[30] and eicosapentaenoic acid and docosahexaenoic acid intake were estimated using US Department of Agriculture tables,[31] because eicosapentaenoic acid and docosahexaenoic acid were not available in the tables of Holland et al.[30] For each study participant, the nutrient intake was calculated by multiplying the intake frequency for each food item by the nutrient content for the portion size. Dietary intakes were adjusted by energy using the residual method.

Assessing Adherence to Mediterranean Diet Score

We used a previously published MDS to classify participants according to their responses on the FFQ.[32] The composite score (range, 0–9) captures consumption of key food items, such as olive oil (1 point for ≥1 spoon/day), wine (1 point for ≥1 glass/day), fruit (1 point for ≥1 serving/day), vegetables or salad (1 point for ≥1 serving/day), fish (1 point for ≥3 servings/week), legumes (1 point for ≥2 servings/week), and low consumption of meat or meat products (1 point for <1 serving/day). A further point was awarded for a daily serving or more of both fruits and vegetables, and a final point was awarded when consumption of both white bread (<1 serving/day) and rice (<1 serving/week) was low or when consumption of whole-grain bread was high (>5 servings/week).

Assessment of Age-Related Macular Degeneration

After pupillary dilation with tropicamide 0.5% and phenylephrine 5%, two 35° nonsimultaneous stereoscopic digitized color fundus images were obtained of each eye, centered on the fovea.

The fundus images were sent to a single reading center (Erasmus University Rotterdam) and graded using the International Classification System for Age-Related Maculopathy[33] and then categorized into 5 mutually exclusive grades. Grade 0 was defined as a macula free of drusen or pigmentary irregularities or with hard drusen (<63 μm) only. Early AMD was subdivided as follows: Grade 1 was defined as soft distinct drusen (≥63 μm) or pigmentary abnormalities; grade 2 was defined as soft indistinct drusen (≥125 μm) or reticular drusen only or soft distinct drusen (≥63 μm) with pigmentary abnormalities; and grade 3 was defined as soft indistinct drusen (≥125 μm) or reticular drusen with pigmentary abnormalities; Grade 4 was defined as the presence of neovascular age-related macular degeneration (nvAMD) (presence of any of the following: serous or hemorrhagic retinal or retinal pigment epithelial detachment, subretinal neovascular membrane, periretinal fibrous scar) or