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Healthy Lifestyles Related to Subsequent Prevalence of Age-Related Macular Degeneration

JA Mares, **R. Voland**, **SA Sondel**, **A.E. Millen**, **T LaRowe**, **SM Moeller**, **M.L. Klein**, **B.A Blodi**, **R. Chappell**, **L. Tinker**, **C Ritenbaugh**, **K Gehrs**, **G Sarto**, **E.J Johnson**, **M Snodderly**, and **RB Wallace**

Department of Ophthalmology and Visual Sciences (Drs Moeller, Voland, Blodi, and Mares, Ms. Sondel), the Department of Family Medicine (Dr. La Rowe), the Department of Statistics and Biostatistics (Dr. Chappell), and the Department of Obstetrics and Gynecology, Center for Women's Health Research (Dr. Sarto), University of Wisconsin, Madison, WI ; Oregon Health Science University, Casey Eye Institute (Dr. Klein), Tufts University (Dr. Johnson); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (Dr. Tinker); the Department of Social and Preventive Medicine, University at Buffalo, Buffalo, NY (Dr. Millen); KMG Center for Retina & Macular Disease (Dr. Gehrs); University of Texas-Austin, (Dr. Snodderly); and the Department of Epidemiology, University of Iowa, Iowa City, IA (Dr. Wallace).

Abstract

Purpose—The relationships between lifestyle behaviors of diet, smoking and physical activity and the subsequent prevalence of age-related macular degeneration (AMD) were investigated.

Methods—The population included 1,313 participants (55 to 74 years) in the Carotenoids in Age-Related Eye Disease Study (CAREDS), an ancillary study of the Women's Health Initiative Observational Study (WHIOS). Scores on a modified 2005 Healthy Eating Index (mHEI) were assigned using responses to a food frequency questionnaire administered at WHIOS baseline (1994-1998). Physical activity and lifetime smoking history were queried. An average of six years later, stereoscopic fundus photographs were taken to assess presence and severity of AMD; present in 202 women, 94% of whom had early AMD, the primary outcome.

Results—In multivariate models, women whose diets scored in the highest compared with the lowest quintile on the mHEI had a 46% lower odds for early AMD. Women in the highest vs. lowest quintile for physical activity (MET- Hrs/Wk) had 54% lower odds for early AMD. Although smoking, alone was not independently associated with AMD, having a combination of three healthy lifestyles (healthy diet, physical activity and not smoking) was associated with a 71% lower odds for AMD compared with having high risk scores (P=0.0004).

Conclusions—Modifying lifestyles might reduce risk for early AMD as much as 3-fold, lowering the risk for advanced AMD in a person's lifetime and the social and economic costs of AMD to society.

INTRODUCTION

The macula of the human eye progressively degenerates with age, more quickly in some people than in others, and can lead to advanced age-related macular degeneration (AMD), which involves the loss of photoreceptors in the macula of the eye. Treatment for advanced

To whom correspondence should be sent: Julie A. Mares, PhD Professor University of Wisconsin Department of Ophthalmology and Visual Sciences 610 N. Walnut Street; 1063 WARF Building Madison, Wisconsin 53726-2336 (608) 262-8044 FAX: (608) 265-9279 jmarespe@wisc.edu.

AMD is of limited effectiveness, is a costly disease to treat [1] and will become more so as the number of older Americans increase in the coming decades.[2] Moreover, it profoundly limits the ability of older adults to function independently. The loss of central vision associated with advanced AMD diminishes the ability to see and recognize other people's faces, and to read fine print such as in newspapers and on pill bottles and food packages.

Early and advanced stages of AMD are consistently more common in people who have specific genotypes (many of which function to mediate response to inflammation, oxidative stress, lipid metabolism and angiogenesis, as recently reviewed. [3]) Several modifiable aspects of lifestyle have been related to a lower occurrence of AMD, including smoking, physical activity and diet. AMD is also sometimes observed to be more common in people with a history of chronic diseases or conditions which can also be modified by lifestyle choices [4-7] such as cardiovascular disease, [5, 6] diabetes,[7] hypertension, [2,8] obesity, [9-11] and diseases of inflammation or elevated markers of inflammation.[12]

Smoking has been the most consistently reported risk factor for AMD.[13] However, these associations may reflect other unhealthy lifestyle habits which are more common in smokers; the associations of smoking to AMD are not often adjusted for other aspects of healthy lifestyles which are less common in smokers. Physical activity has been only recently studied in relation to AMD and was related to lower risk for advanced AMD in three past studies. [14-16]

AMD has often been associated with diets which are poor in one or more ways: It has been more common among people with low levels of carotenoids in the diet, serum or macula and diets or serum low in one or more other nutrients, or diets high in fat (reviewed [17]). However, associations of single nutrients to AMD are often inconsistent across studies and impossible to totally disentangle from other aspects of diet. Moreover, they do not account for synergistic relationships of food components. Recently, combinations of nutrients [18, 19] or a diet score which reflects 1990 US Dietary Guidelines have been related to lower risk of AMD. [20] Relationships of AMD to two currently recommended diet patterns (The 2005 US Dietary Guidelines or a Mediterranean diet pattern) have not been previously reported.

The common approaches to assessing relationships of healthy lifestyles to AMD in observational studies may give erroneous estimates of single aspects of healthy lifestyles. This is, in part, because single aspects of diet or lifestyle are difficult to disentangle from each other. We cannot measure the levels of these individual aspects of a healthy lifestyle perfectly across several decades of adult life when they are likely to influence AMD; any attempt to simply adjust one in consideration of the other(s) risks the likelihood of incomplete adjustment or residual confounding.

Moreover, adjustment of one healthy lifestyle for another may lead to misleading interpretations. This is because the mechanisms of protection of some healthy lifestyles are related. For example, the energy expenditure of physical activity permits a higher daily nutrient intake and may be protective in this way. Also, both physical activity and diet can contribute to better vitamin D status [21] which has been related to lower risk for AMD. [22]

If several aspects of lifestyle all protect through a common mechanism (such as reducing inflammation) then examination of risk associated with one healthy lifestyle can be underestimated. Single studies have not previously considered these risk factors, together with diet, concurrently. The objective of the present report was to describe relationships of AMD to a combination of healthy behaviors, including diet, physical activity and smoking history. This was possible in the Carotenoids in Age-Related Eye Disease Study because participants were recruited from a sample of women who provided detailed dietary and

lifestyle habit histories as part of the Women's Health Initiative (WHI) an average of six years before AMD was assessed.

METHODS

Design and Study Sample

Women (50 to 79 years of age) were recruited into the CAREDS from those who were enrolled in the Women's Health Initiative Observational Study Cohort (WHI-OS)[23] at 3 of 40 sites: the University of Wisconsin (Madison), the University of Iowa (Iowa City), and the Kaiser Center for Health Research (Portland). Women who had intakes of lutein plus zeaxanthin that were above the 78th and below the 28th percentiles (n=3143), as assessed at WHI baseline (1994-1998) were sent letters inviting them to participate in the eye study. Sampling women at the extremes of dietary intake maximized the statistical power available to detect associations between AMD and levels of lutein and zeaxanthin in the diet and serum. Because the intake of lutein and zeaxanthin is also correlated with intakes of many vitamins and minerals from foods (range of Spearman correlation coefficients = 0.27 for vitamin D to 0.77 for folate) and negatively correlated with fat intake (r = -0.36), this design would also be expected to maximize extremes in intake of other aspects of healthy diets and enhance the power available to detect associations with these related aspects of diet, relative to samples with similar ranges of intake of comparable sizes.

Of the 3,143 women recruited, 2,005 (64%) were enrolled and photographic evidence of AMD was determined in CAREDS examinations in 2001-2004, four to seven years (mean of 6.3 years) after WHIOS baseline. Gradable fundus eye photography was completed on 1,853 eligible women, of whom 1,787 provided full detail regarding covariates used in regression models of AMD. Based on evidence for selective mortality bias in associations of diet to AMD in women over 75 years of age,[24, 25] and similar findings in relation to the independent variables which are evaluated in the present analysis (data not shown), the present dataset includes only the 75% of women in this sample who were less than 75 years of age at the time of eye photography (N=1,325 women). All procedures conformed to the Declaration of Helsinki and were approved by the Institutional Review Board at each University.

A comparison of CAREDS participants and non-respondents in the full dataset has been previously described.[24, 25] Further, we compared CAREDS participants < 75 years (N= 1325) with WHIOS participants the same ages who were recruited, but did not participate, or were excluded from our analysis dataset because of missing covariate data (n=922). Four percent of women in this analysis reported having physician diagnosed AMD at WHIOS 3 year follow-up visits vs. 2 percent of the non- participating women (p=0.13). Women in this analysis were (after age-adjustment) more likely to have never smoked (53 vs. 49%; p=0.0002), and had diets that were slightly lower in fat (32 vs. 33% of energy; p = 0.001) and higher in lutein and zeaxanthin (1.8 vs. 1.6 mg/day; p <0.0001), reported higher levels of physical activity (15 vs.12 MET-Hr-Wk; P<0.0001), and had lower body mass index (BMI) (median =27.7 vs.28.4 Kg/M^2).

Eye Examinations and Photography

Measures of macular pigment density[26] and dilated fundus photography[27] taken at CAREDS baseline (2001-2004) have been described. Iris color was determined from retina photographs. Stereoscopic fundus photographs were graded for AMD by the University of Wisconsin Fundus Photography Reading Center, using methods based on those used in the Age-Related Eye Disease Study (AREDS).[27]

The primary outcome was the presence of early AMD in at least one eye. Early AMD was defined as the presence of either: large drusen (one or more large drusen (≥ 125μm) or extensive intermediate drusen (area ≥ 360μm when soft indistinct drusen is present; or, ≥ 650μm when soft indistinct drusen is absent) or pigmentary abnormalities of the retinal pigment epithelium (an increase or decrease in pigmentation accompanied with at least one druse (≥ 63μm)), consistent with previously established definitions. [28] This corresponds to stage 3 of the AREDS original AMD definitions, with the exception that, like other population-based studies, it includes, in the definition of early AMD, having pigmentary abnormalites (with drusen). All analyses were also performed separately for two components of early AMD (large drusen and pigmentary abnormalities).

There were only twelve women (n=12) with advanced AMD in the CAREDS sample <75 years of age (defined as geographic atrophy, neovascularization, or exudation in the center sub-field or receiving a physician diagnosis of advanced AMD, confirmed subsequently in writing by a physician.) Because this was too small of a number to analyze this endpoint separately, and to reduce the possibility of temporal bias influencing the estimates of relationships of healthy lifestyles to early AMD, we excluded these women from the main analyses.

Estimates of Dietary Intake

Daily levels of nutrients in diets were estimated from responses to a previously validated, semi-quantitative food frequency questionnaire (FFQ)[29] at WHI baseline. For this report, we primarily evaluated diets using the 2005 Healthy Eating Index (HEI-2005) which reflects adherence to the 2005 US Dietary Guidelines.[30]

The HEI-2005 assigns scores for the intake of specific food components (per 1000 kilocalories), as shown in Table 1. This score represents different aspects of a healthy diet, including the abundant intake of fruits and vegetables (including those which are particularly nutrient-rich) and whole grains, and low intake of discretionary calories from sugar, fat and alcohol and of saturated fat. We made one modification to the original 100-point HEI-2005 scoring system, herein referred to as the modified HEI-2005 (mHEI), by omitting the 10 points assigned for the intake of oils (non hydrogenated vegetable oils and oils in fish, nuts and seeds). The original intent for including points for oils in the scoring system was to ensure adequate intake of vitamin E and essential fatty acids. However, using this component, in evaluation of diets from Americans who otherwise consume adequate sources of these nutrients, may lead to higher scores for diets which are less nutrient dense. Indeed, omitting this score component (which largely reflected vegetable oil intake in this sample) improved correlations with several vitamins and minerals, while not influencing associations with blood levels of alpha-tocopherol (data not shown).

We also explored whether a similar association of AMD to another healthy diet pattern existed by assigning scores for adherence to a Mediterranean diet adapted for use in American people (aMED).[31] In a nine-point scoring system, a point was assigned for 1) servings of each of the following food components >75th percentile within the sample: fruits, vegetables, whole grains, legumes, nuts and fish, and ratio of monosaturated to saturated fat and; 2) <25th percentile for servings of red meat, and 3) alcohol intake of 5-25 g/day. These scores were associated with a wider distribution of intakes of many vitamins and minerals than the mHEI (data not shown).

While results are reported by both scoring systems, for the opportunity of greater insights, we focus on the mHEI and used the aMED scoring system for further exploratory analyses. This is because scores are spread more widely on the mHEI score (90 possible points) than the aMed score (9 possible points). Moreover, high scores on the aMED pattern were

uncommon in this sample; only 53 women had scores of 6-9. The mHEI has the added advantages of being based on established recommendations for reduction of chronic disease risk in Americans,[32] and being easier for the comparison of results across American study samples.

Physical Activity

At WHIOS baseline women were asked about participation in total and recreational physical activity which included household and yard work, walking and strenuous, moderate, and intensive activities.[33] Responses to these questions were used to estimate energy expenditure in metabolic energy task (MET)-Hrs/wk. These reflect the sum of METs multiplied by the duration and frequency of activity in a week. MET values are based on estimates of the intensity of the physical activity; for example, one hour of strenuous activity requires 7 METs, one hour of moderate activity or walking very fast requires 4-4.5 METs and one hour of low intensity or walking slow requires 3 METs.

Other Lifestyles and Covariates

At WHIOS baseline women were weighed and measured and their body mass indexes (BMIs) (Kg/M ^{2}) were computed and blood pressure measured. At the time of entry into the WHIOS women provided information about their smoking history. This was updated in CAREDS questionnaires, permitting the creation of a summary variable of lifetime smoking (pack years), further categorized as 1) never smoked, 2) smoked 0-7 pack years or 3) smoked > 7 pack years. Additional demographic, lifestyle, and health history data were available from questionnaires including: education, hormone replacement therapy use, alcohol use, pulse pressure, and history of diabetes, hypertension, and cardiovascular disease. At CAREDS visits, we also queried family history of macular degeneration (immediate family member age 65 years or older when diagnosed) and obtained updated histories of alcohol use and diabetes. WHI baseline serum samples, collected after a ≥ 10-hour fast, were stored at -80 degrees centigrade and analyzed in 2004-2005 for serum levels of lutein and zeaxanthin and tocopherols by a reverse phase HPLC analysis,[34] and in 2007 and 2008 for serum 25- hydroxyvitamin D by the Diasorin LIAISON® chemiluminescence method and high sensitivity C-reactive protein (CRP) by High sensitivity CRP Assay kit (DiaSorin, Stillwater MN) at Heartland Assays, Inc. (Ames, IA).

Healthy Lifestyle Score

We constructed a 6-point healthy lifestyle score (HLS) which gave equal weight to three levels of each of three health habits: diet, physical activity and smoking, based on our knowledge of the distribution of these variables. We assigned 2 possible points for healthy levels of each behavior: diet (mHEI score in lowest 20 percent= 0, 21- 80th percent= 1 and in the highest 20 percent = 2), physical activity (MET hrs/Wk) (lowest tertile= 0, second tertile = 1 and third tertile = 2) and smoking (>7 pack years = 0, >0-≤7 = 1 and none/never smoking = 2).

Statistical Analysis

We evaluated the relationships of quintile ranks for scores on mHEI and physical activity to other risk and protective factors for AMD using ANCOVA and Cochran-Mantel-Haenszel. Next, logistic regression (PROC LOGISTIC in SAS v.9.2, SAS Institute, Cary, NC) was used to compute odds ratios (OR) and 95 percent confidence intervals (95% CI) for specific AMD endpoints (early AMD, large drusen, pigmentary abnormalities, excluding women with advanced AMD from the reference groups (N=12), and any AMD). OR were described by quintile or categories, as shown in Table 3 and P values for trend across the continuous range of score values was also computed.

OR for AMD were first adjusted for age and multivariate models were further adjusted for other risk factors which were not explanatory or intermediary variables. Previous multiple variable models in this sample [24, 25] included age, pack-years smoked, history of diabetes, family history of AMD, iris color, history of cardiovascular disease, and use of hormone replacement therapy. These were included in the multivariate-adjusted models unless they were independent variables. Additional variables which were statistically significantly related ($p \leq 0.10$) to both AMD and healthy diet pattern or healthy lifestyle scores in CAREDS, or which were previously suspected to be biologically plausible confounders, were tested by adding them singly to age-adjusted models. (For mHEI score only non dietary-risk factors were tested.) Those covariates that changed the AMD odds ratio by ≥10% were retained in the final model. We tested for interactions to determine whether mHEI or physical activity associations with AMD differed (p for interaction <0.10) by age, study site, family history of AMD or levels of smoking or BMI.

RESULTS

Healthy Diets and AMD

Women whose mHEI diet scores were ranked in the highest, compared with the lowest quintile, had lower rates of early AMD (11% vs. 19%), (Table 2), diets significantly lower in fat (% energy) and higher in median servings of several food groups (fruits, vegetables, dairy, grains and meats or alternatives (including poultry, meat, fish, beans and eggs) (Table 3). Supplement use was fairly common: 56 vs. 37% of women in high, compared with low quintiles for mHEI used multivitamins. Being in high vs. low quintiles for mHEI score was also associated with reporting more physical activity, fewer years of smoking, a lower likelihood of having a history of hypertension, lower systolic blood pressure, and lower levels of BMI and serum CRP (Table 3. Associations with aMED scores and non nutritional AMD risk factors were generally similar (data not shown).

Women in the highest, compared to the lowest, quintile for mHEI score had 46% lowering of odds for early AMD multivariate-adjusted OR (95% CI) = 0.54 (0.33-0.88) (Table 4). The 58 women with aMED scores of 6-9 had a 66% lower odds for AMD, compared with many more women (n=490) in this sample who scored 0 or 1 on this pattern (Table 4). Further adjusting for physical activity attenuated ORs or early AMD in women with high compared to low scores for both diet patterns; Multivariate-adjusted OR (95%CI) for early AMD among women in high vs. low quintiles for mHEI = 0.64 (0.38-1.07) and among women with aMED scores of 6-9 vs. 0-1 = 0.44 (0.10-1.27), indicating that associations with diet is not totally independent from the association with physical activity.

The multivariate-adjusted OR for large drusen and pigmentary abnormalities among women in highest compared to lowest quintiles of the mHEI were similar to those for overall early AMD (multivariate-adjusted OR (95%CI) = 0.56 (0.31-0.97); P for trend = 0.049 and 0.58 (0.29 – 1.13); P for trend = 0.07), respectively. Associations of mHEI to total AMD (early plus advanced AMD) were also similar (multivariate-adjusted OR (95%CI) = 0.55 (033-0.88); P for trend = 0.012).

Consistency and interactions—The associations between mHEI score and early AMD were significantly different across study sites (P for interaction = 0.08), with stronger inverse associations between mHEI score and AMD in Portland (n=425) and Madison (N=436) than in Iowa City (N= 452), but all associations were inverse (data not shown). The inverse associations of mHEI score to AMD did not significantly differ (p > 0.20) by BMI, physical activity level, smoking history, macular pigment density level or having a family history of AMD (data not shown).

Physical Activity and AMD

Women in the highest quintile vs. lowest quintile for physical activity had a greater than two-fold lower multivariate-adjusted odds for AMD (OR (95%CI) = 0.46 (0.27-0.78); P for trend = 0.002). Associations with drusen, pigmentary abnormalities and any AMD were similar (data not shown). Despite a significant correlation between level of physical activity and mHEI score (Spearman correlation coefficient = 0.30; p<0.0001), adjusting for mHEI only slightly attenuated this association (OR (95%CI) = 0.52 (0.30-0.89); P for trend = 0.009). The association also remained consistently inverse in women with mHEI scores above and below the median (P for interaction = 0.90). Physical activity was also correlated with BMI (r=-0.26; p<0.001). However, the association of physical activity to early AMD was also consistently inverse across all levels of BMI (<25, 25-29 and >30; P-value for interaction = 0.33).

The association of physical activity to early AMD appeared to reflect the weekly time spent in physical activity rather than any specific type or intensity. For example, multivariate-adjusted OR (95%CI) for women in highest vs. lowest tertiles (minutes/week) for total recreational activity were 0.56 (0.37-0.84); P for linear trend=0.004, for moderately strenuous activity were 0.78 (0.52-1.16); P for linear trend = 0.01, and for strenuous activity were 0.67 (0.46-0.96); P for linear trend = 0.004.

Smoking and BMI

The OR for early AMD by smoking history and BMI are also given in Table 4. Women who smoked more than 7 pack-years had a 45 % increase in odds for AMD in multivariate-adjusted models, but the association across all levels of smoking was only marginally significant (P=0.07) and was attenuated after adjusting for mHEI and physical activity. Only the 10% of women who were extremely obese had 58% higher odds for early AMD and after further adjustment for multiple variables, mHEI and physical activity, BMI was no longer associated with AMD (Table 3).

Overall Healthy Lifestyles

Women who had a HLS of 6, which reflected healthiest (lowest risk levels) of all three score components (diet, physical activity and smoking), had a 71% lower odds for early AMD, compared with women who had scores of 0-2 (Table 4). Obesity (BMI >30) was much less common in women with a HLS of 6 (9%) vs. 0-2 (43%) (P=<0.0001). However, adjusting for BMI did not influence associations. We explored the consistency of the HLS associations with early AMD in women who were obese (BMI ≥30) vs. not obese (BMI < 30). (In these analyses we grouped women with scores of 5-6 because too few women with a HLS of 6 were obese.) The associations were somewhat, but not statistically, stronger in obese women (P for interaction =0.17). The multivariate – adjusted OR (95% CI) were 0. 26 (0.06-0.78); P trend = 0.004 in women who were obese and 0.60 (0.34-1.06); P trend = 0.02 in women who were not.

COMMENT

The results of the present study indicate that broadly healthy diets and lifestyles in women 50-69 years of age were associated with a lower prevalence of early AMD an average of 6 years later. A three-fold lowering of odds was associated with having a combination of healthy lifestyles which included healthy diets, physical activity and not smoking. Specifically, in this particular sample, the 5 % of women with highest lifestyle score (equal to 6) never smoked (<0.1 packyear), reported the equivalent of about 10 hours of low intensity physical activity/d (such as walking or gardening) or 8 hours of moderate activity/ week and had the following diet qualities: daily servings of fruits (3.5/day) and vegetables

(about 5/day; 2 of which were dark green, orange or legumes), dairy (2.3/day) meat or alternatives (meat, poultry, fish, beans or eggs) (2.7 ounces/day) and grains (3.5 servings/day of which 1 serving/day is whole grain). These lifestyle habits are interrelated in practice and in biological effect (discussed below) so that the degree to which they might contribute independently to associations cannot be accurately assessed in this study.

These associations, like those generated from data in prospective studies, are not likely to reflect temporal biases, which are possible in studies in which lifestyle and AMD are assessed at the same point in time. This is because 1) lifestyle was assessed an average of 6 years before photographs documented AMD and 2) most women who had AMD at this point in time were in early stages (77% of women who had not previously told they had AMD) and 3) because of their young ages, the women who had AMD were also not likely to have had AMD for many years.

Healthy Diets

These analyses provide the first estimate of associations between AMD and the dietary patterns [35] recommended by the 2005 U.S. Dietary Guidelines. [32] Associations with mHEI were stronger than associations for individual aspects of diet previously studied in this sample[24, 25] Results are consistent with a recently reported association between an alternative version of the 1990 Dietary Guidelines and advanced AMD in a case-control study.[20] Further, results extend the protective nature of broadly healthy diet patterns to early AMD which dramatically increases risk for eventually developing advanced AMD in Caucasian populations.[36-38]

The shift in odds ratio towards unity after adjusting for physical activity suggests some of this effect could be due to physical activity. Both healthy diets and physical activity improve nutritional status. (Recommendations for both are included in the 2005 US Dietary Guidelines.[32]) Physical activity might contribute to better nutritional health by 1) increasing energy expenditure, allowing a larger absolute intake of phytochemicals and micronutrients and 2) increasing moderate exposure to sunlight, when outdoors, as was common in this sample. Walking outdoors was a strong predictor of blood vitamin D levels in this sample (M. Kluczynski, unpublished manuscript) and a separate sample of WHI participants. [21] Low levels of vitamin D were associated with higher odds for AMD in a sub sample of CAREDS [39] and in a separate sample.[22]

Having a high score (6-9) on the aMED diet pattern, which is more plant- food focused than the U.S Dietary Guidelines, and predicts somewhat higher intake of several nutrients in the diet and serum than the mHEI score (data not shown), was associated with lower odds for AMD than scores in the top quintile for mHEI (66 vs.46% reduction, respectively in odds). Few women in this sample (4%) had aMED scores in this range. Intake of three foods groups which contribute to higher scores on the aMED, whole grains (Table 3), nuts and fish (previously described[25]) were limited in this sample. These foods could contribute to the intake of short (grains and nuts) and long-chain (fatty fish from cold water) omega-3 polyunsaturated fatty acids (PUFAs). The intake of fish or omega-3 PUFAs has been associated with lower risk for AMD in many previous studies.[40, 41]

The protective association of mHEI to AMD in this sample is likely to reflect the fact that high scores were associated with an intake of high levels of several single nutrients which have been related to low prevalence or progression of AMD in previous studies (antioxidants,[18, 42] B-vitamins,[43] zinc[18, 44, 45] and lutein plus zeaxanthin[24, 45-49]). Previous investigators have found that combinations of nutrients from food are more strongly associated with AMD risk than single nutrients.[18, 19] The protective association of mHEI to

early AMD is also likely to reflect direct relationships of dietary fat to AMD, as previously reported in this sample [25] other samples.[50-53]

Physical Activity

This was the first observation of a relationship between physical activity and early stage of AMD. Protective associations with physical activity were reported in relation to the incidence of diagnosed AMD or photographically evident advanced AMD in three previous studies.[14-16] Evidence from the present study indicates that the association of physical acitivity is independent of diet. The degree to which associations of physical activity to AMD might have reflected better diets in people with higher levels of physical activity had not been previously assessed, except in one study with limited dietary data.[15]

Smoking and Obesity

Smoking has been the one risk factor most consistently associated with a higher risk for AMD.[13] The association between lifelong smoking and AMD in the present study was only marginal and further attenuated after further adjusting for diet and physical activity. Obesity has been associated with a higher prevalence or incidence of AMD less consistently, [9] but weight loss has been associated with reduced AMD presence.[10] Only extreme obesity was associated with AMD in the present sample; this was not significant after multivariate adjustment and was almost completely attenuated after adjusting for the potential explanatory variables of mHEI and physical activity. It is unclear how much of the associations of these risk factors in past studies may have been attributed to that fact that smoking and obesity are more common among people with poor diets and people who exercise less. Previous studies did not adjust for both diet and physical activity. Moreover, even when adjusted for, statistically, some residual confounding can be expected due to imperfect measurement and failure to capture these exposures over long periods in adult life.

A Combination of Healthy Lifestyles

In the present study, the three-fold lowering of odds for AMD among women with a combination of healthy, compared with unhealthy, lifestyles suggests that a combination of healthy lifestyle practices might be more important in reducing AMD risk than a focus on one. These changes, collectively, may contribute to lowering of oxidative stress, inflammation, blood pressure and improving blood lipids all of which are thought to be pathogenic mechanisms which promote AMD. It is well known that smoking increases oxidative stress[54] and expected that stopping smoking lessens it. Physical activity can also up-regulate antioxidant protection enzyme systems, so that it reduces oxidative stress, despite the fact that bouts of physical activity can increase oxidative stress in the short-term (reviewed [55]). Improvements in diet and physical activity alone or in conjunction with a reduction in obesity can lessen oxidative stress as well (reviewed[56]).

Healthy lifestyles may lower AMD risk by lowering systemic inflammation which is widely thought to contribute to AMD pathogenesis. Healthy diet patterns and physical activity have been related to lower blood levels of CRP, a marker of systemic inflammation in other samples, [31,57] as they were in the present sample (Table 3).

Healthy lifestyles may also lower AMD risk by reducing blood pressure(related to AMD risk in some past studies (previously reviewed [8]). Intervention trials have demonstrated that reductions in blood pressure can result from healthy diets,[58] physical activity,[59] and weight loss.[59, 60] A history of hypertension was less common in women in the highest quintiles for mHEI, physical activity and HLS-score (Table 3) .

In addition to these mechanisms, we speculate that healthy diets and physical activity might lower risk for AMD by improving status of macular pigment. Macular pigment density was associated with healthy diets, physical activity and HLS (Table 3) . The carotenoids which comprise macular pigment can block the frequencies of blue light that are known to damage the retina directly; they may also quench reactive oxygen species that form as a result of the light and oxygen rich environment (previously reviewed[61]) and they could reduce the formation of a toxic metabolite of retinal recycling (A2E) which is stimulated by blue light[62] by blocking blue light from reaching the retina. Clearly, lutein and zeaxanthin supplementation from foods can increase macular pigment density, but the ability to increase macular pigment varies considerably among persons.[63-65] As, we have previously discussed[66 67] several aspects of diet, such as the overall intake of fruits, vegetables, whole grains, and fat may contribute to the uptake and turnover of these carotenoids. Physical activity might contribute to more dense macular pigment by reducing inflammation and oxidative stress, directly, or by reducing obesity. Obesity is related to lower macular pigment in this and other samples[66, 68, 69] and may increase oxidative stress and carotenoid turnover, as well.[56]

LIMITATIONS

Confirmation of these associations of healthy diets and lifestyles to AMD in intervention studies and long-term population-based studies which include men and a broader sample of ethnic backgrounds would provide additional evidence and more reliable risk estimates for the strong associations we observed in the present study among women. Our estimates in this primarily white sample may overestimate the overall impact in people from Hispanic, African and Asian origins who seem to be at lower risk for developing advanced stages of AMD, despite similar levels of early AMD.[70] Conversely, estimates in the present study could be underestimated because women with less healthy lifestyles were less likely to participate in this study, weakening the power to estimate AMD rates among those with unhealthy lifestyle habits.

The HLS was not constructed a priori and needs to be further studied in separate samples. Healthy diets or lifestyles that we evaluated might reflect other unknown and unmeasured aspects of lifestyle. Socioeconomic status can be a surrogate for some such unknown factors. The socioeconomic status of women in this sample is high, limiting the extent to which this may be a confounder. For example, 78% of women had more than a high school education. Further adjustment for education or income levels did not influence associations in this sample (data not shown).

The size of this sample and of any single sample available today are not large enough, nor the sample diverse enough, to evaluate associations of each healthy lifestyle behavior to AMD independently. For example, we could not evaluate the potential benefit of healthy diets in women who were overweight compared with those who were lean. Exploratory analyses indicated stronger associations of mHEI-score to AMD among women with BMI>30, compared to <25, but these associations were not significant, nor were the interactions between diet and BMI significant. Larger studies or pooled samples across many studies might be useful to estimate interactions between these healthy habits and their influence on the occurrence of AMD.

Finally, it may be that the impact of healthy habits is more or less important in people who have high risk genotypes for AMD. In several recent studies healthy lifestyles have been more strongly associated with risk lowering among people with high variants of CFH Y402H [71 , 72-75] and ARMS2 A69S. [71] In the present study, having a family history for AMD did not modify the association of healthy diet or lifestyle with AMD, but genotyping

will better characterize a person's susceptibility for the disease and improve the ability to examine the possibility that diet and lifestyle modifies genetic risk.

CONCLUSIONS

A combination of healthy lifestyle behaviors that includes healthy diets, physical activity and not smoking was associated with markedly lowered prevalence of early AMD, an average of six years later, in postmenopausal women. Adopting these healthy habits may markedly lower the prevalence of early stages of AMD, the number of people who develop advanced stages of AMD in their lifetime and health care costs associated with treatment for this condition.

These results also serve to remind us that risk for AMD is passed to subsequent generations not only through genes, but possibly also through the lifestyle habits we model and encourage. Specifically, we believe that these results, together with current scientific evidence for chronic disease prevention, support recommendations to exercise (“move” at least a low intensity for one to two hours per day; outside when possible), avoid smoking and follow a healthy diet pattern diets which is 1) abundant in plant foods (vegetables that include dark leafy green and orange, fruits and whole grains) 2) contains daily protein sources in moderation and variety (beans, nuts, fish, dairy, eggs , meat and poultry) and 3) limits foods which are high in sugar, fat, alcohol, refined starches and oils.

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WHI Investigators

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg; (Medical Research Labs, Highland Heights, KY) Evan Stein; (University of California at San Francisco, San Francisco, CA) Steven Cummings.

Clinical Centers: (Albert Einstein College of Medicine, Bronx, NY) Sylvia Wassertheil-Smoller; (Baylor College of Medicine, Houston, TX) Haleh Sangi-Haghpeykar; (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (Brown University, Providence, RI) Charles B. Eaton; (Emory University, Atlanta, GA) Lawrence S. Phillips; (Fred Hutchinson Cancer Research Center, Seattle, WA) Shirley Beresford; (George Washington University Medical Center, Washington, DC) Lisa Martin; (Los Angeles Biomedical Research Institute at Harbor- UCLA Medical Center, Torrance, CA) Rowan Chlebowski; (Kaiser Permanente Center for Health Research, Portland, OR) Erin LeBlanc; (Kaiser Permanente Division of Research, Oakland, CA) Bette Caan; (Medical College of Wisconsin, Milwaukee, WI) Jane Morley Kotchen; (MedStar Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Northwestern University, Chicago/Evanston, IL) Linda Van Horn; (Rush Medical Center, Chicago, IL) Henry Black; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (State University of New York at Stony Brook, Stony Brook, NY) Dorothy Lane; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Alabama at Birmingham, Birmingham, AL) Cora E. Lewis; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of California at Davis, Sacramento, CA) John Robbins; (University of California at Irvine, CA) F. Allan Hubbell; (University of California at Los Angeles, Los Angeles, CA) Lauren Nathan; (University of California at San Diego, LaJolla/Chula Vista, CA) Robert D. Langer; (University of Cincinnati, Cincinnati, OH) Margery Gass; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Hawaii, Honolulu, HI) J. David Curb; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Massachusetts/Fallon Clinic, Worcester, MA) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark, NJ) Norman Lasser; (University of Miami, Miami, FL) Mary Jo O'sullivan; (University of Minnesota, Minneapolis, MN) Karen Margolis; (University of Nevada, Reno, NV) Robert Brunner; (University of North Carolina, Chapel Hill, NC) Gerardo Heiss; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (University of Tennessee Health Science Center, Memphis, TN) Karen C. Johnson; (University of Texas Health Science Center, San Antonio, TX) Robert Brzyski; (University of Wisconsin, Madison, WI) Gloria E. Sarto;

(Wake Forest University School of Medicine, Winston-Salem, NC) Mara Vitolins; (Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI) Michael S. Simon.

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker.

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REFERENCES

1. Smiddy WE. Relative cost of a line of vision in age-related macular degeneration. Ophthalmology. May; 2007 114(5):847–854. [PubMed: 17306878]
2. Schneider EL, Guralnik JM. The Aging of America. Impact on Health Care Costs. JAMA. May 2.1990 :2335–2340. [see comment]. 1990. [PubMed: 2109105]
3. Ding X, Patel M, Chan C-C. Molecular pathology of age-related macular degeneration. Progress in Retinal and Eye Research. 2009; 28(1):1–18. [PubMed: 19026761]
4. Hoffmann K, Zyriax B-C, Boeing H, Windler E. A dietary pattern derived to explain biomarker variation is strongly associated with the risk of coronary artery disease. Am J Clin Nutr. September 1; 2004 80(3):633–640. 2004. [PubMed: 15321803]
5. Sun C, Klein R, Wong TY. Age-related Macular Degeneration and Risk of Coronary Heart Disease and Stroke: The Cardiovascular Health Study. Ophthalmology. 2009; 116(10):1913–1919. [PubMed: 19592102]
6. Tan JS, Mitchell P, Smith W, Wang JJ. Cardiovascular risk factors and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology. Jun; 2007 114(6):1143–1150. [PubMed: 17275090]
7. Feke GT. Cardiovascular disease, its risk factors and treatment, and age-related macular degeneration: women's health initiative sight exam ancillary study. Am J Ophthalmol. Sep; 2007 144(3):482–483. author reply 483. [PubMed: 17765447]
8. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. Am J Ophthalmol. Mar; 2004 137(3):486–495. [PubMed: 15013873]
9. Cheung N, Wong TY. Obesity and Eye Diseases. Survey of Ophthalmology. 2007; 52(2):180–195. 2007/4//. [PubMed: 17355856]
10. Peeters A, Magliano DJ, Stevens J, Duncan BB, Klein R, Wong TY. Changes in Abdominal Obesity and Age-Related Macular Degeneration: The Atherosclerosis Risk in Communities Study. Arch Ophthalmol. November 1; 2008 126(11):1554–1560. 2008. [PubMed: 19001224]
11. Schaumberg DA, Christen WG, Hankinson SE, Glynn RJ. Body Mass Index and the Incidence of Visually Significant Age-Related Maculopathy in Men. Arch Ophthalmol. September 1; 2001 119(9):1259–1264. 2001. [PubMed: 11545630]
12. Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N. Association between C-reactive protein and age-related macular degeneration. JAMA. Feb 11; 2004 291(6):704–710. [see comment]. [PubMed: 14871913]
13. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. Eye. 2005; 19(9):935–944. [PubMed: 16151432]
14. Knudtson MD, Klein R, Klein BEK. Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. British Journal of Ophthalmology. December; 2006 90(12):1461–1463. 2006. [PubMed: 17077116]
15. Williams PT. Prospective Study of Incident Age-Related Macular Degeneration in Relation to Vigorous Physical Activity during a 7-Year Follow-up. Invest. Ophthalmol. Vis. Sci. January 1; 2009 50(1):101–106. 2009. [PubMed: 18566466]

16. Seddon JM, Cote J, Davis N, Rosner B. Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio. Arch Ophthalmol. Jun; 2003 121(6):785–792. [PubMed: 12796248]

17. Mares, JA.; Millen, AE. Nutrition in the Prevention and Treatment of Disease. 2nd ed. Elsevier, Inc.; San Diego, CA: 2008. Diet and Supplements and the Prevention and Treatment of Eye Diseases..

18. van Leeuwen R, Boekhoorn S, Vingerling JR, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. Jama. Dec 28; 2005 294(24):3101–3107. [PubMed: 16380590]

19. Chiu CJ, Milton RC, Klein R, Gensler G, Taylor A. Dietary compound score and risk of age-related macular degeneration in the age-related eye disease study. Ophthalmology. May; 2009 116(5):939–946. [PubMed: 19410952]

20. Montgomery MP, Kamel F, Pericak-Vance MA, et al. Overall diet quality and age-related macular degeneration. Ophthalmic Epidemiol. Jan-Feb; 2010 17(1):58–65. [PubMed: 20100101]

21. Millen AE, Wactawski-Wende J, Pettinger M, et al. Predictors of serum 25-hydroxyvitamin D concentrations among postmenopausal women: the Women's Health Initiative Calcium plus Vitamin D Clinical Trial. Am J Clin Nutr. Mar 10.2010

22. Parekh N, Chappell RJ, Millen AE, Albert DM, Mares JA. Association between vitamin D and age-related macular degeneration in the Third National Health and Nutrition Examination Survey, 1988 through 1994. Arch Ophthalmol. May; 2007 125(5):661–669. [PubMed: 17502506]

23. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials. Feb; 1998 19(1):61–109. [PubMed: 9492970]

24. Moeller SM, Mehta NR, Tinker LF, et al. Associations between intermediate age-related macular degeneration and lutein and zeaxanthin in the Carotenoids in Age-Related Eye Disease Study (CAREDS), an ancillary study of the Women's Health Initiative. Arch Ophthalmol. Aug.2006 124:1–24.

25. Parekh N, Voland RP, Moeller SM, et al. Association Between Dietary Fat Intake and Age-Related Macular Degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS): An Ancillary Study of the Women's Health Initiative. Arch Ophthalmol. November 1; 2009 127(11): 1483–1493. 2009. [PubMed: 19901214]

26. Snodderly DM, Mares JA, Wooten BR, et al. Macular pigment measurement by heterochromatic flicker photometry in older subjects: the carotenoids and age-related eye disease study. Invest Ophthalmol Vis Sci. Feb; 2004 45(2):531–538. [PubMed: 14744895]

27. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6. Am J Ophthalmol. Nov; 2001 132(5):668–681. [PubMed: 11704028]

28. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. Survey of Ophthalmology. 1995; 39(5):367–374. /4//. [PubMed: 7604360]

29. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Annals of Epidemiology. Apr; 1999 9(3):178–87. [PubMed: 10192650]

30. Guenther, P.; Reedy, J.; Krebs-Smith, S.; Reeve, B.; Basiotis, P. Development and evaluation of the healthy eating index-2005: Technical report. Center for Nutrition Policy and Promotion, United States Department of Agriculture; 2007.

31. Fung TT, McCullough ML, Newby PK, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr. July 1; 2005 82(1):163–173. 2005. [PubMed: 16002815]

32. USDA. Key Recommendations for the General Population, Dietary Guidelines for Americans 2005. 2005 [May 9, 2005]. 6th:www.health.gov/dietaryguidelines/dga2005/recommendations.htm.

33. Meyer AM, Evenson KR, Morimoto L, Siscovick D, White E. Test-retest reliability of the Women's Health Initiative physical activity questionnaire. Med Sci Sports Exerc. Mar; 2009 41(3): 530–538. NIHMSID: NIHMS107793, PMCID: PMC2692735. [PubMed: 19204598]

34. Yeum KJ, Booth SL, Sadowski JA, et al. Human plasma carotenoid response to the ingestion of controlled diets high in fruits and vegetables. Am J Clin Nutr. Oct; 1996 64(4):594–602. [PubMed: 8839505]
35. Gao X, Wilde PE, Lichtenstein AH, Tucker KL. The 2005 USDA Food Guide Pyramid is associated with more adequate nutrient intakes within energy constraints than the 1992 Pyramid. J Nutr. May; 2006 136(5):1341–1346. [PubMed: 16614427]
36. Klein R, Klein BE, Tomany SC, Meuer SM, Huang GH. Ten-year incidence and progression of age-related maculopathy: The Beaver Dam eye study. Ophthalmology. Oct; 2002 109(10):1767–1779. [PubMed: 12359593]
37. Klein R, Klein BEK, Knudtson MD, Meuer SM, Swift M, Gangnon RE. Fifteen-Year Cumulative Incidence of Age-Related Macular Degeneration: The Beaver Dam Eye Study. Ophthalmology. 2007; 114(2):253–262. [PubMed: 17270675]
38. Wang JJ, Rochtchina E, Lee AJ, et al. Ten-year incidence and progression of age-related maculopathy: the blue Mountains Eye Study. Ophthalmology. Jan; 2007 114(1):92–98. [PubMed: 17198852]
39. Millen, AEVR.; Sondel, S.; Parekh, N.; Horst, RL.; Hageman, GS.; Wallace, RB.; Klein, ML.; Blodi, BA.; Gehrs, KM.; Chappell, RJ.; Sarto, G.; Mares, JA. Relationships Between Vitamin D status and Age-related Macular Degeneration (AMD) in the Carotenoids and Age-Related Eye Disease Study, an Ancillary Study of the Women's Health Initiative Observational Study (WHIOS). 2010. In review
40. Chong EWT, Kreis AJ, Wong TY, Simpson JA, Guymer RH. Dietary {omega}-3 Fatty Acid and Fish Intake in the Primary Prevention of Age-Related Macular Degeneration: A Systematic Review and Meta-analysis. Arch Ophthalmol. June 1; 2008 126(6):826–833. 2008. [PubMed: 18541848]
41. SanGiovanni JP, Agron E, Clemons TE, Chew EY. Omega-3 long-chain polyunsaturated fatty acid intake inversely associated with 12-year progression to advanced age-related macular degeneration. Arch Ophthalmol. Jan; 2009 127(1):110–112. NIHMSID: NIHMS163830, PMCID: PMC2812062. [PubMed: 19139352]
42. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. Oct; 2001 119(10):1417–1436. [PubMed: 11594942]
43. Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. Arch Intern Med. Feb 23; 2009 169(4):335–341. [PubMed: 19237716]
44. VandenLangenberg GM, Mares-Perlman JA, Klein R, Klein BE, Brady WE, Palta M. Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol. 1998; 148(2):204–214. [PubMed: 9676703]
45. Tan JSL, Wang JJ, Flood V, Rochtchina E, Smith W, Mitchell P. Dietary Antioxidants and the Long-term Incidence of Age-Related Macular Degeneration: The Blue Mountains Eye Study. Ophthalmology. 2008; 115(2):334–341. [PubMed: 17664009]
46. Mares-Perlman JA, Fisher AI, Klein R, et al. Lutein and zeaxanthin in the diet and serum and their relation to age- related maculopathy in the third national health and nutrition examination survey. Am J Epidemiol. 2001; 153(5):424–432. [PubMed: 11226974]
47. Cho E, Hankinson SE, Rosner B, Willett WC, Colditz GA. Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration. Am J Clin Nutr. June 1; 2008 87(6):1837–1843. 2008. [PubMed: 18541575]
48. Seddon JM, Ajani UA, Sperduto RD, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. JAMA. 1994; 272(18):1413–1420. [PubMed: 7933422]
49. SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: AREDS Report No. 22. Arch Ophthalmol. Sep; 2007 125(9):1225–1232. [PubMed: 17846363]

50. Seddon JM, Cote J, Rosner B. Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake. Arch Ophthalmol. Dec; 2003 121(12):1728–1737. [PubMed: 14662593]
51. Mares-Perlman JA, Brady WE, Klein R, VandenLangenberg GM, Klein BE, Palta M. Dietary fat and age-related maculopathy. Arch Ophthalmol. Jun; 1995 113(6):743–748. [PubMed: 7786215]
52. Cho E, Hung S, Willett WC, et al. Prospective study of dietary fat and the risk of age-related macular degeneration. Am J Clin Nutr. Feb; 2001 73(2):209–218. [PubMed: 11157315]
53. Delcourt C, Carriere I, Cristol JP, Lacroux A, Gerber M. Dietary fat and the risk of age-related maculopathy: the POLANUT study. Eur J Clin Nutr. Nov; 2007 61(11):1341–1344. [PubMed: 17299457]
54. Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. Ann N Y Acad Sci. May 28.1993 686:12–27. discussion 27-18. [PubMed: 8512242]
55. Ji LL, Gomez-Cabrera MC, Vina J. Role of free radicals and antioxidant signaling in skeletal muscle health and pathology. Infect Disord Drug Targets. Aug; 2009 9(4):428–444. [PubMed: 19689384]
56. Vincent HK, Innes KE, Vincent KR. Oxidative stress and potential interventions to reduce oxidative stress in overweight and obesity. Diabetes Obes Metab. Nov; 2007 9(6):813–839. [PubMed: 17924865]
57. Tomaszewski M, Charchar FJ, Przybycin M, et al. Strikingly low circulating CRP concentrations in ultramarathon runners independent of markers of adiposity: how low can you go? Arterioscler Thromb Vasc Biol. Sep 1; 2003 23(9):1640–1644. [PubMed: 12869354]
58. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997; 336(16):1117–1124. [PubMed: 9099655]
59. Elmer PJ, Obarzanek E, Vollmer WM, et al. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. Ann Intern Med. Apr 4; 2006 144(7):485–495. [PubMed: 16585662]
60. Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. Ann Intern Med. Jan 2; 2001 134(1):1–11. [PubMed: 11187414]
61. Landrum, JT.; Bone, RA. Mechanistic Evidence for Eye Diseases and Carotenoids.. In: Krinsky, NI.; Mayne, ST.; Sies, H., editors. Carotenoids in Health and Disease. Marcel Dekker, Inc.; New York: 2004. p. 445-472.
62. Sparrow JR, Boulton M. RPE lipofuscin and its role in retinal pathobiology. Exp Eye Res. May; 2005 80(5):595–606. [PubMed: 15862166]
63. Hammond BR Jr. Johnson EJ, Russell RM, et al. Dietary modification of human macular pigment density. Investigative Ophthalmology & Visual Science. 1997; 38(9):1795–1801. [PubMed: 9286268]
64. Bone RA, Landrum JT, Guerra LH, Ruiz CA. Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. Journal of Nutrition. 2003; 133(4):992–998. [PubMed: 12672909]
65. Bowen PE, Herbst-Espinosa SM, Hussain EA, Stacewicz-Sapuntzakis M. Esterification does not impair lutein bioavailability in humans. Journal of Nutrition. 2002; 132(12):3668–3673. [PubMed: 12468605]
66. Mares JA, LaRowe TL, Snodderly DM, et al. Predictors of optical density of lutein and zeaxanthin in retinas of older women in the Carotenoids in Age-Related Eye Disease Study, an ancillary study of the Women's Health Initiative. Am J Clin Nutr. Nov; 2006 84(5):1107–1122. [PubMed: 17093164]
67. Moeller SM, Voland R, Sarto GE, Gobel VL, Streicher SL, Mares JA. Women's Health Initiative diet intervention did not increase macular pigment optical density in an ancillary study of a subsample of the Women's Health Initiative. J Nutr. Sep; 2009 139(9):1692–1699. NIHMSID: 2728692, PMCID: 19587126. [PubMed: 19587126]
68. Hammond BR Jr. Ciulla TA, Snodderly DM. Macular pigment density is reduced in obese subjects. Invest Ophthalmol Vis Sci. Jan; 2002 43(1):47–50. [PubMed: 11773011]

69. Nolan J, O'Donovan O, Kavanagh H, et al. Macular pigment and percentage of body fat. Invest Ophthalmol Vis Sci. Nov; 2004 45(11):3940–3950. [PubMed: 15505040]

70. Moeller SM, Mares JA. Ethnic differences in diet and age-related maculopathies. Int Ophthalmol Clin. 2003; 43(4):47–59. Fall. [PubMed: 14574201]

71. Schaumberg DA, Hankinson SE, Guo Q, Rimm E, Hunter DJ. A Prospective Study of 2 Major Age-Related Macular Degeneration Susceptibility Alleles and Interactions With Modifiable Risk Factors. Arch Ophthalmol. January 1; 2007 125(1):55–62. 2007. [PubMed: 17210852]

72. Wang JJ, Rochtchina E, Smith W, et al. Combined effects of complement factor H genotypes, fish consumption, and inflammatory markers on long-term risk for age-related macular degeneration in a cohort. Am J Epidemiol. Mar 1; 2009 169(5):633–641. [PubMed: 19074778]

73. Seddon JM, Francis PJ, George S, Schultz DW, Rosner B, Klein ML. Association of CFH Y402H and LOC387715 A69S with progression of age-related macular degeneration. Jama. Apr 25; 2007 297(16):1793–1800. [PubMed: 17456821]

74. Seddon JM, Reynolds R, Maller J, Fagerness JA, Daly MJ, Rosner B. Prediction model for prevalence and incidence of advanced age-related macular degeneration based on genetic, demographic, and environmental variables. Invest Ophthalmol Vis Sci. May; 2009 50(5):2044–2053. [PubMed: 19117936]

75. Baird PN, Robman LD, Richardson AJ, et al. Gene-environment interaction in progression of AMD: the CFH gene, smoking and exposure to chronic infection. Hum Mol Genet. May 1; 2008 17(9):1299–1305. [PubMed: 18203751]

Table 1

Components and Scoring System for the 2005 Modified Healthy Eating Index

	Maximum Points	Criteria for Maximum Score For Each 1000 Kilocalories	Servings needed to receive maximum points in 1500 kcalories[a]
Components that contribute to high scores			
Total Grain	5	≥3 oz	4.5
Whole Grain	5	≥ 1.5 oz.	2.3
Total Vegetables	5	≥ 1.1 cup	3.3
Dark Green, Orange, and Legume Vegetables	5	≥ 0.4 cup	1.2
Total Fruit	5	≥ 0.8 cup	2.4
Whole Fruit	5	≥ 0.4 cup	1.2
Milk	10	≥ 1.3 cup	2
Meat, Beans, Fish, Eggs	10	≥ 2.5 oz	3.8
Components that contribute to low scores			
Saturated Fat (% of energy)	10	≤7% of energy	<11.6 gm
Sodium (g/day)	10	≤ 0.7 gm[a]	≤1 gm
Energy from Solid Fat, Alcohol, and Added Sugar (Kcal/day)	20	≤ 20% of energy	≤ 300 kcal

[a]Serving equivalents are as follows: grains: 1 slice bread, 1 cup cereal, ½ cup pasta; vegetables: ½ cup raw or cooked, 1 cup raw leafy; fruit: 1 medium or ½ cup; milk:1 cup milk, 2 oz. cheese; meat: 1 oz meat, 1 egg, ¼ cup cooked lentils, tofu

Table 2

Prevalence of early and advanced AMD among Women in the Carotenoids in Age-Related Eye Disease Study <75 years of age (n=1325) by High and Low Quintiles for modified Healthy Eating Index and Level of Physical Activity and Healthy Lifestyle Score

	Modified Healthy Eating Index Score		**Physical Activity MET-hrs/week**		**Healthy Lifestyle Score**	
	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Low	High
Range	42-59	70-80	0-2	25-119	0-2	6
Percent with AMD						
Early	19	11	19	9	18	6
Advanced	1.1	0.8	1.4	0	1.1	0
Age at photography (years)	65.7	66.2	66.4	66.2	66.1	65.9
P-value[a]	0.24		0.94		0.10	

[a] p-values are for associations across continuous values

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Table 3

Potential Risk Factors[a] among Women in the Carotenoids in Age-Related Eye Disease Study < 75 years of age (n=1325) by High and Low Quintiles for modified Healthy Eating Index Score (mHEI) and Level of Physical Activity and Healthy Lifestyle Score

	Modified Healthy Eating Index Score		**Physical Activity MET-hrs/week**		**Healthy Lifestyle Score**	
Estimated Servings:	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Quintile 1	Quintile 5
Vegetables						
Total	3.0	4.6	3.2	4.9	3.3	4.9
Dark Green, Orange, and Legumes	0.7	1.8	1.0	1.8	0.9	1.9
Fruit (total)	1.5	3.1	1.9	2.9	1.8	3.5
Milk or dairy	1.2	2.1	1.4	1.9	1.4	2.3
Meat, Beans, Fish or Eggs	2.1	2.6	2.1	2.4	2.1	2.7
Grains						
Total	2.5	3.4	2.7	3.2	2.6	3.5
Whole	0.48	1.11	0.66	0.84	0.56	1.13
Nutrients From Food:						
Total Fat (% energy)	42	24	36	29	37	23
Polyunsaturated Fatty Acids (% energy)	8.2	5.3	7.4	6.0	7.5	5.1
Monounsaturated Fatty Acids (% energy)	15	9	13	10	15	9
Lutein + Zeaxanthin (mg)	1.0	1.7	1.1	1.8	1.1	1.8
Vitamin C (mg)	60	118	75	118	73	123
Vitamin D (mcg)	4.0	5.0	4.3	4.9[b]	4.2	5.1
Vitamin E (mg)	7.3	7.4[b]	7.2	8.0[b]	7.2	7.7
Zinc (mcg)	8.8	11.1	9.2	11.3	9.1	11.6
Nutrients From Food and Supplements Combined						
Vitamin C (mg)	151	302	188	291	176	315
Vitamin D (mcg)	6.8	10.6	7.8	12.8	7.3	11.6
Vitamin E (mg)	56	69[b]	52	231[b]	54	82[b]
Zinc (mcg)	13.1	18.4	14.6	17.8[b]	14.1	18.9
Multivitamin User (%)	37	56	41	53[b]	39	60

	Modified Healthy Eating Index Score		Physical Activity MET-hrs/week		Healthy Lifestyle Score	
Nutrient Levels in Serum						
Lutein+Zeaxanthin (trans) (umol/L)	0.26	0.36	0.26	0.38	0.26	0.40
Alpha-tocopherol (umol/L)	42	49	45	49[b]	44	51
Vitamin D (nmol/L)	51	60	51	66	52	67
Macular Pigment Optical Density	0.34	0.40	0.34	0.39[b]	0.34	0.42
Non-nutritional Risk Factors						
Physical Activity MET-hrs/week	9	22	1	39	5	36
Body Mass Index (mm/Kg2)	29.4	26.2	29.7	25.5	29.8	25.7
Smoking Packyears	10.0	6.4	9.3	7.2	18.3	0.1
Diabetes Status (%)	3.6	1.9[b]	5.0	0.7[b]	3.9	0.0[b]
Family History of AMD (%)	16	15[b]	15	14[b]	15	11[b]
Iris Pigment Color						
% Blue/Green	66	70[b]	64	70[b]	62	66
%Brown	34	30[b]	36	30[b]	38	34
History of Cardiovascular Disease (%)	22.2	20.6[b]	23.2	21.1[b]	23.2	21.5
History of Hypertension (%)	30	19	31	21	29	16
Systolic Blood Pressure in women not taking hypertension medication[c] (mm Hg)	124.9	121.2	121.8	120.6[b]	122.3	117.2[b]
C-Reactive Protein[d] (mg/liter)	5.6	3.7	5.5	3.6	5.6	3.6

[a] All numbers are age-adjusted least squared means (or age-adjusted percentages) of values determined at WHI baseline, except for macular pigment optical density which was measured in CAREDS in 2001-2004 and histories of smoking, hormone use, diabetes and cardiovascular disease which were updated in CAREDS. Lutein, vitamin and zinc estimates from food and supplements combined were log-transformed in the calculation because of skewed distributions.

[b] All associations between potential risk factors and mHEI score, level of physical activity and Healthy Lifestyle Score were significant ($p<0.05$) except for these.

[c] In women not taking hypertension medication (N=988)

[d] CRP values were available in 903 women in this dataset.

Table 4

Odds Ratios (95% CI's) for Early Age-Related Macular Degeneration (AMD) by Healthy Diet Patterns and Lifestyles among women<75 years old in the Carotenoids in Age-Related Eye Disease Study (n=1313).

Diet Pattern/Life Style Factor	Number at Risk/Number with AMD	Age-Adjusted OR (95% CI)	Multiple-Variable Adjusted OR (95% CI)[a]	Multiple Variable Further Adjusted OR (95% CI)
Modified Healthy Eating Index				
Quintiles				
1 (42-59 points)	275/52	1.0	1.0	1.0[e]
2 (60-63 points)	256/36	0.64(0.40-1.01)	0.65(0.40-1.04)	0.68(0.42-1.10)[b]
3 (64-66 points)	253/38	0.68(0.43-1.08)	0.71(0.44-1.13)	0.77(0.48-1.24)[b]
4 (67-69 points)	264/32	0.54(0.33-0.88)	0.58(0.35-0.93)	0.63(0.38-1.03)[b]
5 (70-80 points)	265/29	0.51(0.31-0.82)	0.54(0.33-0.88)	0.64(0.38-1.07)[b]
P value for trend[c]		0.006	0.014	0.099
Alternative Mediterranean Diet				
Categories				
1 (0-1 points)	490/69	1.0	1.0	1.0[e]
2 (2-3 points)	518/88	1.20(0.85-1.69)	1.17(0.83-1.67)	1.24 (0.87-1.78)[b]
3 (4-5 points)	247/27	0.76(0.47-1.21)	0.77(0.47-1.24)	0.89(0.54-1.43)[b]
4 (6-9 points)	58/3	0.32(0.08-0.89)	0.34 (0.08-0.98)	0.44(0.10-1.27)[b]
P value for trend[c]		0.032	0.046	0.230
Total Physical Activity (Met-hours/week)				
Quintiles				
1 (0-2.2)	275/49	1.0	1.0	1.0[f]
2 (2.4-8)	253/38/	0.80(0.50-1.26)	0.80(0.50-1.28)	0.8390.51-1.32)[d]
3 (9-13)	252/33	0.63(0.39-1.02)	0.65(0.39-1.06)	0.71(0.43-1.17)[d]
4 (14-24.5)	270/43	0.83(0.53-1.29)	0.88(0.55-1.39)	0.97(0.60-1.56)[d]
5 (24.7-119)	263/24	0.44(0.26-0.73)	0.46(0.27-0.78)	0.52(0.30-0.89)[d]
P-value for trend[c]		<0.001	0.002	0.009
Body Mass Index kg/m^2				
Categories				
Very Lean (16-22)	232/28	0.86(0.50-1.47)	0.86(0.50-1.48)	0.89(0.52-1.53)[e]
Lean (23-25)	238/36	1.0	1.0	1.0[g]
Overweight (26-29)	478/67	0.91(0.59-1.44)	0.88(0.56-1.39)	0.81(0.52-1.29)[e]
Obese (30-34)	233/30	0.81(0.47-1.37)	0.78(0.45-1.33)	0.67(0.38-1.15)[e]
Extremely Obese (35-62)	132/29	1.58(0.91-2.75)	1.36(0.76-2.41)	1.06(0.58-1.92)[e]
P-value for trend		0.29	0.65	0.49
Smoking				
Packyears				
0	726/102	1.0	1.0	1.0[g]
1-7	315/41	1.01(0.67-1.48)	1.06(0.70-1.57)	1.10(0.73-1.64)[e]
8-125	272/49	1.45(0.99-2.10)	1.45(0.98-2.12)	1.42(0.96-2.08)[e]

Diet Pattern/Life Style Factor	Number at Risk/Number with AMD	Age-Adjusted OR (95% CI)	Multiple-Variable Adjusted OR (95% CI)[a]	Multiple Variable Further Adjusted OR (95% CI)
P-value for trend[c]		0.043	0.072	0.11
Healthy Living 6 Point Scale				
Categories				
1 (0-2 points)	355/64	1.0	1.0	1.0[h]
2 (3 points)	348/56	0.84(0.56-1.25)	0.85(0.56-1.27)	0.84(0.56-1.27)[f]
3 (4 points)	307/40	0.63(0.40-0.96)	0.62(0.40-0.96)	0.64(0.40-1.00)[f]
4 (5 points)	233/26	0.53(0.32-0.85)	0.53(0.32-0.87)	0.54(0.32-0.90)[f]
5 (6 points)	70/4	0.27(0.08-0.68)	0.29(0.09-0.75)	0.29(0.08-0.76)[f]
P-value for trend[c]		<.001	<.001	<.001