Relationship of Dietary Fat to Age-Related Maculopathy in the Third National Health and Nutrition Examination Survey

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Objective: To evaluate the associations between dietary fat and age-related maculopathy (ARM) in persons 40 years or older who participated in the Third National Health and Nutrition Examination Survey.

Methods: We used a single, nonmydriatic, fundus photograph of 1 eye to ascertain ARM status in 7883 of 11,448 survey participants. Intake of fat was estimated from 24-hour recall, and specific sources of dietary fat were estimated from responses to food frequency questionnaires. Logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs) that accounted for complex survey design, nonresponse, and potential risk factors for ARM (age, smoking, race, sex, body mass index, history of cardiovascular disease or hypertension, eye color, and sedentary lifestyle). Persons aged 40 to 79 years (n=7405) were included in analyses for early ARM (n=644); those 60 years or older (n=4294) were included in analyses for late ARM (n=53).

Results: After adjustment for age, race, eye color, and sedentary lifestyle, OR for early ARM was 1.4 (95% CI, 0.9-2.2; P for trend, .10) among persons in high vs low quintiles of total fat intake (percentage of total energy). Associations for specific types of fatty acids (as percentages of caloric intake) were in the same direction and unrelated to ARM. The OR for late ARM was 0.7 (95% CI, 0.2-2.6; P for trend, .60) in persons 60 years or older. Further adjustments for other potential confounders did not significantly affect the ORs.

Conclusion: Age-related maculopathy was not significantly associated with dietary fat in this large cross-sectional survey.

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A GE-RELATED maculopathy (ARM) is the most frequent cause of severe visual impairment in the elderly.1,2 Atherosclerosis is a suspected risk factor for the development of ARM.3,4 Vascular disease has been associated with ARM in some epidemiological studies,5,6 whereas other studies found overall negative7,8 or inconclusive9-12 results. Vingerling et al13 reported that the prevalence of exudative ARM was 4.7-fold higher in an aged cohort when plaques in the carotid bifurcation were present. Impaired choroidal circulation due to atherosclerosis14 and hypertension15 has been hypothesized to act as a possible pathogenic factor for the development of maculopathy.16 Risk factors for atherosclerotic disease, such as smoking,17,18 hypercholesterolemia,19 and decreased estrogen exposure,20 have also been associated with ARM in previous studies.

Dietary fat has long been associated with risk for atherosclerotic change by way of alterations in blood cholesterol levels,21 influence on visceral adiposity,22 and influence on the inflammatory cascade.23 Dietary fat increases circulating levels of low-density lipoprotein (LDL), and saturated fat intake decreases LDL cholesterol receptor activity. Elevated LDL cholesterol levels and subsequent oxidation of circulating LDL cholesterol have been shown to increase risk for cardiovascular events. For these reasons, atherosclerosis has been hypothesized to be related to ARM, and greater intake of saturated animal fat has been associated with atherosclerotic risk. Therefore, investigation into the relationship of dietary fat to the development of ARM remains of interest.

Specific fatty acids have been associated with positive and negative effects on the vasculature, thus possibly affecting atherosclerotic risk and ARM. The retina may require ω-3 fatty acids to remain physiologically intact. The retina concentrates ω-3 fatty acids,24 believed to be required for maintaining photoreceptor membrane fluidity25 and retinal integrity.26 Thus, fish oils, specifically ω-3 and very-
SUBJECTS AND METHODS

STUDY POPULATION

The Centers for Disease Control and Prevention and the National Center for Health Statistics conducted the NHANES III from January 1, 1988, through December 31, 1994, among a nationally representative sample of the civilian noninstitutionalized US population. The survey method included 2 phases and used a stratified probability sample with oversampling of non-Hispanic black subjects, Mexican Americans, and adults older than 60 years, the details of which are published elsewhere.31 For the analyses presented herein, the sample was limited to persons aged 40 to 79 years to limit the impact of selectable mortality bias and confounders due to diet changes. Results of previous analyses in this population32 and of the relationships reported within (data not shown) indicate that relationships in the older groups differ from those in younger groups. The survey included results of a household interview, a medical examination that took place in a mobile examination center, and phlebotomy. During the household interview, demographic, socioeconomic, health history, and dietary data were collected. Information regarding food intake was gathered using a 24-hour diet recall method and a 60-item food frequency questionnaire (FFQ). The medical examination included a physical examination, fundus photography, urine collection, and collection of blood samples for the measurement of a number of hematologic factors.

Nonmydriatic fundus photographs were taken at the mobile examination center for participants 40 years or older. One eye was randomly selected, and a single color photograph was taken. Photographic fields were subsequently graded using modified Wisconsin Age-Related Macular Degeneration Grading System criteria, described in detail elsewhere.33,34 Two lesions of early ARM were quantified (soft drusen and pigmentary abnormalities) with the categorization of early and late ARM. The consistency of the masked grading has been described elsewhere.35

Total dietary fat and saturated, polyunsaturated, and monounsaturated fat levels were calculated as percentage of total calories from 24-hour recalls that had been analyzed for nutrient composition using standard nutrient analysis software and US Department of Agriculture food composition data. High-fat foods were categorized from responses to a 66-item FFQ, which was not adequately comprehensive to permit estimations of total levels of dietary fat. The following categories represented composite values for monthly consumption: fats, dressings, and oils; high-fat snack foods (salty and sweet); high-fat dairy foods; processed, high-fat meats; and fish. Fish consumption was estimated by response to a single item on the FFQ.

STATISTICAL METHODS

Participants’ dietary intake of fat from 24-hour recalls was rank ordered, and the distribution was divided into quintiles. Relationships between potential risk factors for ARM and total fat intake, high-fat food category, and fish intake were assessed using analysis of variance for continuous variables and the Cochran-Mantel-Haenszel test for trend for categorical variables. Variables were adjusted for age and race groups in these comparisons.

Logistic regression was used to compute odds ratios (ORs) for ARM within each quintile relative to the lowest quintile for dietary fat or among people consuming various numbers of servings of high-fat food compared with a low reference category. The Wald test for trend was performed on all continuous variables. Age-adjusted and multivariate analyses were performed by race and with all race groups combined. For analyses using all race groups combined, the jackknife replication method of variance estimation was used to account for complex sampling methods used in the NHANES III.36 Sample weights were applied to all analyses.37

The following variables were considered as potential confounders: age, sex, smoking status (none, current, or past), hypertension (blood pressure of >140/90 mm Hg or use of medications to treat hypertension), high-density lipoprotein (HDL) cholesterol level, physical activity (times per month), eye color, and estrogen use. In a first step, potentially important variables were added to the model when a change of 10% or greater was observed in the ORs for serum quintiles. A second step consisted of the evaluation of potentially explanatory variables on ORs. These included serum levels of C-reactive protein, fibrinogen, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, carotenoids, and vitamins E, C, and A; results of other laboratory measures; examination results; demographic and lifestyle variables; and dietary micronutrients. Additional analyses were performed excluding persons with comorbid conditions (cardiovascular disease, hypertension, and diabetes mellitus) in an attempt to remove any potential biases from recent dietary modifications due to disease status. Further analyses were stratified by age (40-59, 60-79, ≥80, 40-79, and ≥60 years) and race (non-Hispanic white, non-Hispanic black, and Mexican American) to account for possible selective mortality biases and to investigate potential effect modification. Commercially available software (SAS, Version 6.02; SAS Institute Inc, Cary, NC) was used for all statistical analyses.

Previous experiments indicate that endothelial response to ingesting high-fat meals can be attenuated by antioxidant intake.38 This raises the possibility that antioxidant availability modifies the effects of dietary fat. To investigate the possibility of effect modification by antioxidant status, participants were categorized into high and low antioxidant status on the basis of serum levels of several nutrients (α-carotene to represent carotenoids and vitamins E and C). The sample was divided into 2 groups on the basis of the median serum levels of all 3 nutrients. Persons falling into the low category of antioxidant status had serum values that were below the sample medians for vitamin E, vitamin C, and carotenoid levels.

long-chain polyunsaturated fatty acids, may be associated with ARM outside of their anti-inflammatory, antiatherosclerotic, and antithrombotic effects.

The epidemiological evidence regarding the relationship between dietary or serum lipid levels and age-related macular degeneration has been inconsistent. In 4 previous studies,37-40 higher intake of total dietary fat has been associated with a higher rate of ARM, but the type of fat associated with ARM has been inconsistent, and relationships are sometimes only marginally stas-
tically significant. Higher intake of fish oils was also associated with lower prevalence of ARM in 2 studies, 28,29 whereas total fish intake was not associated with ARM in 2 other studies. 27,30 The purpose of our study is to describe the relationships between fat and ARM in the racially diverse, nationally representative sample of the Third National Health and Nutrition Examination Survey (NHANES III).

RESULTS

The distribution of risk factors for ARM in high and low quintiles of saturated and total fat intake, after standardization for age and race, is depicted in Table 1. Relationships of the potential risk factors to the intake of polyunsaturated and monounsaturated fats were similar to those seen for total and saturated fats (data not shown). People in the highest vs lowest quintiles of percentage of total and saturated fat intake more often had higher rates of current smoking and were male (Table 1). Although they were less often physically active or had brown eyes, on average they also had lower serum vitamin E levels, lower serum lutein and/or zeaxanthin levels, and lower serum β-carotene levels. In addition, those classified as being in the higher quintiles of fat consumption reported lower dietary lutein and/or zeaxanthin and β-carotene intakes, on average.

Relationships of dietary fat to overall early ARM were direct but not significant (Table 2). Results were similar for specific types of fat (saturated fat, polyunsaturated fat, and monounsaturated fat) (data not shown). The ORs did not reach statistical significance for any of the specific lesions tested (drusen, pigmentary abnormalities) (data not shown). There were no relationships of total fat intake to late ARM, and the confidence intervals (CIs) were wide, reflecting the small number of advanced cases in this sample.

Exclusion of persons with comorbid conditions (who may have changed diets as a result) resulted in a more direct relationship, but did not achieve statistical significance in any age or race group tested. The intake of any specific type of high-fat food was not associated with an increased risk for ARM in this sample (Table 3).

We also investigated the relationships of total fat to any ARM stratified by serum antioxidant status. The ORs for early ARM by very low and very high serum antioxidant levels were 3.0 (95% CI, 0.8-11.3; P for trend, .10) and 0.8 (95% CI, 0.2-3.5; P for trend, .70), respectively. Nonsignificant results were seen when using this strati-
We investigated the relationship of fish intake, as a proxy for the consumption of ω-3 fatty acids, to ARM (Table 4). Consuming fish more than once a week...
pared with once a month or less was associated with ORs of 1.0 for early ARM (95% CI, 0.7-1.4) and 0.4 for late ARM (95% CI, 0.2-1.2) after adjusting for age and race. Adjusting for other possible risk factors did not influence these relationships. Similarly, no significant relationships were seen between the frequency of fish intake and the presence of the specific lesions of soft drusen or retinal pigment abnormalities.

**COMMENT**

Previous evidence in the Beaver Dam population suggested that the prevalence of early ARM was associated with the intake of animal fats. More recently, in the Blue Mountains Eye Study, a direct but marginally significant relationship was observed between the intake of total fat and ARM. More recently, total dietary fat intake was associated with a 50% higher risk for ARM in a large population study. In another recently published study, dietary intake of vegetable fat, but not animal fat, was associated with a significantly lower risk for advanced macular degeneration. In the NHANES III population, the relationships observed between total fat intake and early ARM were in similar directions to those seen in these previous studies, but were not statistically significant. Therefore, the epidemiological data usually indicate direct associations between the risk of ARM and dietary fat, but the results are not always statistically significant and the type of dietary fat most strongly related to ARM differs across populations studied.

The use of a 24-hour recall method to classify fat intake may be associated with misclassification of usual intake that could have limited our ability to detect a significant relationship between dietary fat and ARM. However, we did not observe any direct relationships between the frequency of eating high-fat foods (as noted on the FFQ) and ARM. A further limitation of this investigation is the possibility of misclassification of the status of specific lesions of ARM, because photographs of only 1 eye were obtained and because non-mydriatic fundus photographs were used. Nonresponse bias may have also contributed to an inability to observe an association. Subjects who are visually impaired may have been less likely to participate in the full NHANES III examination that included the retinal photography.

The cross-sectional nature of the study design is limited by estimation of food intake at the time of retinal photography, which may differ from intake during most of adult life. Greater dietary change in the years before the examination may have occurred to a greater extent among persons with ARM or other comorbid conditions. In support of this assumption, associations with fat intake became more direct after excluding people who had comorbid conditions associated with recent dietary change. We could not identify persons likely to have changed their diets for other reasons, such as having family members with chronic conditions or the presence of conditions not queried.

We considered the possibility that antioxidant status could affect whether high-fat diets might increase atherosclerosis and other pathogenic mechanisms for ARM.

Low serum levels of antioxidants have been shown to increase the level of endothelial damage that occurs after the intake of high-fat food. Poor antioxidant status, in conjunction with a high-fat diet, might be required to contribute substantially to the pathogenesis of ARM. We observed direct relationships between fat intake and ARM in persons classified as having low antioxidant status. However, the results were not statistically significant. A larger sample would be required to conclusively rule out this possibility.

One mechanism by which dietary fat could alter the risk for ARM is by enhancing the atherosclerotic process. Atherosclerotic lesions have been related to ARM in a past epidemiological study in which plaques present in the carotid bifurcation were associated with increased odds of ARM in persons younger than 85 years. In recent laboratory studies, C57BL/6 mice (mouse models of human arteriosclerosis) were fed a high-fat diet to investigate retinal changes over time. Investigations have shown accumulations of lipidlike droplets and atrophy of the retinal pigment epithelium of this strain. Degenerative changes in Bruch’s membrane were also seen when comparing same-strain mice fed Chow diets differing in fat content. The investigators suggest that a high-fat diet may interfere with lysosomal processing, perhaps by influencing the rate of fatty acid oxidation. However, demonstration of direct relationships between fat intake and ARM in human populations is inconsistent.

The inconsistent epidemiological evidence may reflect the possibility that fat itself is unrelated to the pathogenesis of this condition. The inconsistent findings could reflect that fat, related to ARM in some studies, is a marker for other conditions that influence risk for ARM. For example, high-fat diets also tend to be lower in levels of other micronutrients like zinc, vitamin E, and carotenoids, which are associated with lower risk for ARM in some studies. Simple adjustment for influence of other nutrients in regression models will not necessarily remove the possibility of influence by the other relationships because of the residual confounding if these other nutrients are imperfectly measured.

No associations were observed between fish intake, the primary source of ω-3 fatty acids in this popu-
lation, and ARM. However, associations with late ARM, while not statistically significant, were in the inverse direction, consistent with observations of inverse associations reported in 2 previous populations, in which a decreased risk for late ARM was observed in persons consuming fish or fish oils. Sanders et al found no relationship between levels of individual ω-3 fatty acids in the blood and early ARM, and Mares-Perlman et al found no relationship between fish intake and ARM in the Beaver Dam Eye Study, albeit levels of fish intake in the Beaver Dam population were lower than in the present study or other studies. Results of a recently published study indicate that the intake of fish was associated with advanced ARM only in persons who also had low intake of linoleic acid. At this time, relationships between the intake of fish and ARM remain inconsistent.

**CONCLUSIONS**

The results of the present investigation in a large, representative sample of the American population contribute to the overall inconsistency of relationships of fat to ARM in human populations to date. Thus, at this time, there is insufficient evidence to make recommendations regarding the level of fat or specific fatty acid intake for the prevention of ARM. However, there is sufficient biological data to support the plausibility of associations of ARM with fat intake. Limitations in epidemiological investigations conducted to date warrant continued evaluation in long-term prospective studies in which estimates of fat intake over extended periods are available.

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