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Association between dietary fats and age-related macular degeneration (AMD) in the Carotenoids in Age-Related Eye Disease Study (CAREDS), an ancillary study of the Women's Health Initiative[1,2,3]

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Abstract

Objective—Evaluating relationships of amount and type of dietary fat to intermediate AMD.

Design—Women, ages 50–79, from the Women's Health Initiative-Observational Study, with high and low lutein intakes, were recruited into the Carotenoids in Age-Related Eye Disease Study (CAREDS). Fat intake in 1994–1998 was estimated using food frequency questionnaires. AMD was assessed in 2001–2004 from stereoscopic fundus photographs.

Results—Intakes of omega-6 and omega-3 polyunsaturated fats (ω-6 and ω-3 PUFA), which were highly correlated (r=0.8), were associated with higher prevalence of intermediate AMD. Significant age-interactions were noted for associations with total fat, monounsaturated and saturated fat (p= 0.01–0.02). In women <75 years (n=1,325), diets high in total fat (% energy) were associated with increased prevalence of AMD (OR (95% CI) for quintile five vs. one = 1.73 (1.02–2.7; p-trend=0.10); the association was reversed in older women. Monounsaturated fat (MUFA) intakes in quintiles three through five vs. one were associated with lower prevalence of AMD in the whole population.

Conclusions—Overall associations of dietary fat to AMD differed by type of fat and, often, by age in this cohort. These findings contribute insights about sources of inconsistencies of fat to AMD in epidemiological studies.

Keywords

total fat; saturated fats; omega-6 polyunsaturated fats; monounsaturated fats; omega-3 polyunsaturated fats; age-related macular degeneration

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INTRODUCTION

Age-related macular degeneration (AMD), is the third leading cause of blindness, worldwide[1] and leading cause of legal blindness in the United States, where 8% of people over 65 years have intermediate AMD and 12% of people over 80 years of age have advanced AMD.[2] With increasing longevity, and with the projected doubling of people 65 years and older by 2020, advanced AMD is expected to increase in prevalence by 50%.[3] For this reason, it is important to identify modifiable aspects of lifestyle that can lower the impact of this condition.

Although genetics appears to explain a large proportion of variability in risk (as recently reviewed[4, 5]) epidemiological studies consistently suggest the influence of smoking[6] (or associated lifestyles) and cardiovascular disease or its risk factor.[7, 8] Dietary factors that lower oxidative stress and/or inflammation are sometimes related to AMD, as well.[4, 9, 10] Results of the AREDS trial demonstrated that high-dose antioxidant and zinc supplements reduced progression of intermediate to late AMD,[11] although not necessarily in people with certain known genetic risk factors.[12] There is a need to better understand modifiable dietary risk factors, particularly for earlier stages.

Previous epidemiological studies generally indicate a higher prevalence or progression of AMD among people with diets high in total fat,[13–18] although associations are not always statistically significant. However, the associations with individual types of fats have been less consistent with the exception of ω-3 polyunsaturated fatty acid (PUFA) or fish intake, which were generally reported to decrease risk for AMD.[14–16, 18–21] Previous studies,[13–16, 18, 19, 21] which examined associations of saturated fatty acid, (SFA), PUFA, and monounsaturated fatty acid (MUFA) intakes with AMD, observed an increased risk (not always statistically significant) for the highest versus lowest level of intakes of these fats. While all previous studies addressed advanced AMD, few studies[13, 16, 17, 19] addressed earlier stages detectable photographically, and in only one of these studies[19] was diet assessed prior to photographic ascertainment of AMD.

We investigated the amount and specific type of dietary fat intake in relation to the prevalence of intermediate AMD, in the Carotenoids in Age-Related Eye Disease Study (CAREDS), in which estimates of diet were available 4–7 years prior to AMD ascertainment and lifetime histories of suspected and known AMD risk factors were available.

SUBJECTS AND METHODS

The Carotenoids in Age-Related Eye Disease Study (CAREDS) population

CAREDS was an ancillary study of the Women's Health Initiative-Observational Study (WHI-OS), among women at 3 of 40 nationwide study sites, at the University of Wisconsin-Madison (Madison, WI), the University of Iowa (Iowa City, IA), and the Kaiser Permanente Center for Health Research in collaboration with Oregon Health and Science University (Portland, OR). Women eligible for WHI-OS were aged 50–79 years at baseline (1994–98), postmenopausal, and reported assurance of residence in the area for at least 3 years after enrollment. Exclusion criteria for WHI-OS were presence of medical conditions predictive of a survival time of less than three years, high alcohol consumption, drug dependency, and/or diagnosed mental illness. Women were recruited by direct mailing and media campaigns.[22] The participants received a questionnaire each year to gather information on diet, medical history, and/or lifestyle characteristics, and the health of the WHI-OS participants was tracked over an average of nine years.[23]

Women from WHI-OS at the three study sites were invited to participate in CAREDS if they were above the 78th percentile or below the 28th percentile of dietary lutein and zeaxanthin intake, as recorded on the WHI-OS baseline (1994–1998) food frequency questionnaire (FFQ) (N = 3,143 women), in order to study the impact of these dietary carotenoids on AMD.[24] Of the 3,143 women, 93 women died or were lost to follow-up between selection in year 2000 and enrollment in CAREDS from 2001–2004. A total of 1,045 women declined participation and 2,005 women were enrolled in CAREDS. Of the 2,005 enrolled, 1,894 participated in study visits, and gradable fundus photographs were available for 1,853 participants; an additional 4 participants who had physician confirmed diagnosis of macular degeneration were added to the analyses dataset. Of the 1,857 women, 70 were excluded from the analysis dataset because of missing covariate data. Thus, there were 1,787 women in the final analysis dataset.

The CAREDS sample was enhanced with women at the two extremes of intake of lutein and zeaxanthin in order to maximize statistical power to evaluate these aspects of diet. CAREDS participants are comparable to women in the larger WHI-OS cohort in the distribution of age, education, income, employment and the distribution of most potential risk factors (blood pressure, body mass index, high cholesterol, diabetes, history of cancer, smoking, alcohol intake, and physical activity). However, the fat intake (as percentage of energy) was lower ($p<0.05$) in CAREDS participants, median of 31 percentile vs. 37 percentile in the overall WHI-OS cohort.

Differences between those included and those excluded in the analyses were evaluated to assess potential biases that may have arisen from non-participation of the excluded individuals. Briefly, women included in the final dataset (N = 1,787) had similar rates of self-reported AMD at the WHI three-year follow-up in 1997–2000 (4% versus 5%), as women excluded from our analysis dataset (N = 1,356). Women included in the final analysis dataset were younger (median age: 63 versus 65 years; $p = 0.0005$), had greater than high school education (77% versus 69%; $p < 0.0001$), and had lower median intakes of total fat (31 vs. 32% energy; $p = 0.0009$) and higher intakes of zinc (10 vs. 8 mg/d) than women excluded.

Data collection

Diet and other covariate data—The 122 item semi-quantitative WHI-food frequency questionnaire (WHI-FFQ),[25] was administered at entry into the WHI study (1994–1998). Participants were queried on types of fats added to foods and food preparation techniques. The correlation coefficient between fat intake (% energy) estimated using this questionnaire and using eight days of records/recalls was 0.62.[25]

The CAREDS participants completed additional mailed FFQs in 2001–2004 on their diets in the recent (2001–2004) and long-term past (1986–1988) to use in exploratory analyses of stable diets over time. Responses to all FFQs were used by the Fred Hutchinson Cancer Research Center to compute nutrient estimates using their nutrient database, designed using the Minnesota Nutrient Data System (version 2.6). Data regarding other risk and protective factors for AMD (Figure) were collected at WHI baseline visits (smoking, physical activity, height, weight, use of hormone replacement therapy, alcohol, and history of chronic diseases) or collected at CAREDS study visits (history of sunlight and updated histories of diabetes mellitus and supplement use, iris color, family history of AMD).

Ascertainment of AMD and definitions of AMD endpoints—Stereoscopic fundus photographs were obtained during CAREDS-baseline study visits in 2001–2004 and graded for AMD at the University of Wisconsin Fundus Reading Center using slight modifications of the protocols established in the Age-Related Eye Disease Study (AREDS)[26] as previously

described.[24] Overall intermediate AMD was the primary endpoint and was defined similar to AREDS, as the presence of extensive drusen (AREDS stage 3), but also included the presence of pigmentary abnormalities with at least 63 microns of drusen. There were too few cases of advanced AMD (those with exudative/neovascular macular degeneration and/or geographic atrophy) (n=34) to describe associations with fat intake reliably. The non-diseased referent group included women without intermediate AMD or advanced AMD.

STATISTICAL ANALYSES

Fat intake evaluated at WHI-baseline (1994–98), which is about 4–7 years prior to AMD ascertainment, was used in all statistical analyses. Total dietary fat, ω-6 PUFA, SFA and MUFA intake, expressed as a percentage of energy, and ω-3 PUFA (long-chain, short-chain and total), expressed as a nutrient density in mg/1000 kilocalories, were divided into quintiles.

Odds ratios and 95% confidence intervals (CIs) for AMD, adjusted only for age, were first computed for overall intermediate AMD, large drusen, and pigmentary abnormalities using logistic regression, by quintile of dietary fat intake (amount and type) with quintile 1 as the reference group. P-trends were calculated using quintile medians of fat intake. We tested medical, lifestyle, ocular and dietary factors as potential confounders by entering these additional variables singly into the regression models. If the addition of the variable singly in the model changed the OR for intermediate AMD by 10% or more, the variable was added to the final regression model (using a criteria of inclusion of changing the OR by 5 % or more does not alter the observations (data not shown)). The variables tested as potential confounders included age (years); cigarette smoking history (pack-years smoked: 0, 0 to <7, ≥7); alcohol consumption (g/d); body mass index (kg/m^2); hormone replacement therapy (never, past, current); current physical activity (METS/d); high dose antioxidant supplement use less than five years versus more than five years; self-reported presence or absence of hypertension, cardiovascular disease and diabetes; family history of AMD (at least one first degree relative diagnosed over age 55); iris color (blue versus other). We also tested the impact of adjusting for the following dietary attributes: lutein plus zeaxanthin (μg/d); vitamin C (mg/d); vitamin A (μg/d); vitamin E (mg/d); vitamin D (μg/d); energy (kcals/day); protein (percent of total energy); carbohydrates (percent of total energy); beta-carotene (μg/d); and zinc (mg/d).

In a combined model, we further tested associations including all statistically significant risk factors of any type of AMD in this sample: pack-years (0, 0≤7, and >7), history of diabetes (yes/no), family history of AMD (yes/no, at least one immediate family member suspected), blue iris color (yes/no), history of cardiovascular disease (yes/no), and postmenopausal hormone therapy use (never, past, current). However, additional adjustment for these risk factors combined, did not change the odds ratios. Final models were adjusted for the 'lutein intake group' variable, to control for the unique participant selection strategy, since the CAREDS sample was selected from the WHI-OS parent population of participants with only high and low lutein intakes.

We tested for potential interactions (considered significant for the purpose of these analyses at alpha value of 0.10 or less) to explore whether the associations between total and specific types of fat intake and intermediate AMD differed by age, and variables that might reflect susceptibility to AMD: personal history of cardiovascular disease and family history of AMD. Further, in exploratory analyses, we restricted analyses to a subgroup of women who had stable fat intakes, from 1986–88 to 1994–98 to ascertain whether the associations were consistent with the analyses done with diets assessed at WHI baseline. Women were classified as having stable fat diets if their quintile ranking for total or specific type of fat

intake at WHI-baseline differed from their ranking for total or specific fat intake at 6–7 years previous, by no more than one quintile.

Additionally, in order to further interpret associations of dietary fats to AMD, we computed ORs for intermediate AMD by intake of food sources of fats foods that were top contributors of total or specific type of fats consumed in the diet, in this sample. We also evaluated the relationship between AMD and the intake of foods which have been suggested to confer protection in other samples: fish and nuts. For these analyses, the number of monthly servings of each food group was divided into tertiles. Odds ratios and 95% CI were computed for intermediate AMD for tertiles 2 and 3 versus tertile 1 (lowest level of intake), of food servings for each food group. All analyses were conducted using SAS (SAS Institute, Inc; Cary, North Carolina) version 9.1.

RESULTS

We evaluated the distribution of risk factors for AMD and other participant characteristics by quintile of total fat and specific type of dietary fat intake. These data are summarized in Table 1 for quintile 1 and 5 of total fat, ω-6 and ω-3 PUFA. (Data is not presented separately for SFA and MUFA, since the characteristics are very similar to those for total fat intake.) Higher intakes of these and total fats were associated with higher BMI, rates of hypertension and diabetes, and intake of energy and vitamin E, but lower intakes of lutein plus zeaxanthin, vitamin C, vitamin D, vitamin A and zinc.

We next evaluated the interrelationships of total and specific types of fats. Total fats were positively and significantly correlated with SFA(r=0.90), MUFA (r=0.97), ω-6 PUFA (r=0.75) and ω-3 PUFA (r=0.70). Similarly, all the specific types of fats were positively and significantly correlated with each other (data not shown). Briefly, ω-6 PUFA intake was most correlated with ω-3 PUFA (r=0.8) and least with SFA (r=0.4); MUFA intake was most correlated with SFA (r=0.8) and least with ω-3 PUFA intake (r=0.6).

Overall intermediate AMD

Total dietary fats—Age-adjusted OR for intermediate AMD did not differ among women across the different levels of total fat intake in the overall population (Table 2). Because we noted significant age interactions (p= 0.02) when age was treated as a continuous variable in the model, and inspection of risk ratios across strata indicated associations differed most for all aspects of diet among women <75 vs. 75 years of age or older, the associations were evaluated separately for the two age-groups. Data are shown in Table 2 for women <75, because these associations are considered to be more reliable estimates of associations with true AMD risk because they would be less likely, than data in women >75y to be influenced by selective mortality bias or biases caused due to recent diet and lifestyle changes, possibly in response to chronic illnesses. OR for the specific endpoints of extensive drusen and pigmentary abnormalities, which were generally consistent with those observed for overall intermediate AMD (not shown).

After stratification by age groups above and below 75 years at CAREDS-baseline, (Table 2), associations were significantly direct among women <75 years of age and inverse among women 75 years of age or older. In the younger age group, women in the highest quintile for dietary total fat had 73% higher odds for overall intermediate AMD, compared with those in the lowest quintile, although the linear trend was only marginally significant across all quintiles (p=0.10). In contrast, among women >75 years in the highest quintile for dietary total fat had about 50% lower odds for overall intermediate AMD, compared with those in the lowest quintile (p-trend =0.02).

We could not identify explanations for the differing inverse associations of fat intake with AMD in older women within this sample. Relationships of dietary fat intake with other dietary, lifestyle and medical characteristics were similar to those reported in Table 1 for both groups, except for larger prevalence of chronic diseases among older women compared to the younger women across all levels of fat intake (data not shown). Adjusting for other possible risk or protective factors of AMD including histories of cardiovascular disease, hypertension, current or past use of hormone therapy, personal or family history of AMD, dietary zinc or antioxidants, and recent dietary change, did not explain the inverse associations seen only in the older age group.

Types of dietary fats

1) SFA: As summarized in Table 2, the age-adjusted OR for overall intermediate AMD did not differ among women across levels of SFA intake (p-trend = 0.98). However, a non-significant 35% higher odds for intermediate AMD was associated and intakes of SFA in high, compared with low, quintiles (p=0.36) after additional adjustment for PUFA, MUFA and lutein intake group. Additional adjustment for individual risk factors singly or all risk factors for AMD simultaneously, did not influence the associations in this sample, a significant interaction (p=0.01) between SFA and age (continuous variable) was observed. Higher SFA intake was associated with higher prevalence of overall intermediate AMD in women younger than 75, the group at risk of developing AMD, (similar to findings for total fats) (Table 2), but not in women 75 years or older (Multivariate OR (95%CI) = 0. 9 (0.3–2.6).

2) MUFA: Age-adjusted OR for overall intermediate AMD did not differ among women across quintiles of MUFA intake. However, after adjusting for ω-6 PUFA, SFA and lutein intake group, MUFA intake was associated with a significantly decreased risk of overall intermediate AMD among women in quintiles 3–5 compared to quintile 1, but the overall linear trend across all levels of intake was not significant (p=0.12). Additional adjustment for individual risk factors singly or simultaneously, did not change the OR, and associations were similar in women with stable MUFA intakes. Associations, again, differed by age (p for interaction=0.02): Although inverse in both women <75 (Table 2) and >75, associations in the older age group were stronger (Multivariate OR for AMD in quintile 5 vs 1 (95%CI)= 0.21 (0.1–0.8); p trend = 0.02).

3) ω-6 PUFA: The age-adjusted OR for overall intermediate AMD was greater than 1.0 among women in the highest versus the lowest quintile of ω-6 PUFA (p-trend = 0.20). After adjustment for MUFA, SFA, and lutein intake group, increasing levels of ω-6 PUFA were associated with a two-fold linearly (p-trend=0.02) increased risk for overall intermediate AMD in the whole population. Additional adjustment for individual risk factors for AMD in this sample, singly or simultaneously in the model, did not change the ORs.

Similar to other fats, we stratified analyses by age due to the presence of age interactions (p=0.10). However, the association remained direct in both younger (Table 2) and older age groups (Multivariate OR (95%CI)= 2.7 (1.1–6.9); p trend = 0.04). When we restricted the analyses to women with stable ω-6 PUFA intakes, the ORs were even further from unity.

4) ω-3 PUFA: The intake of ω-3 and ω-6 PUFAs were highly correlated in this sample (r=0.82; p<0001). The associations with shorter chain (α-linolenic acid, stearidonic acid and docosapentanoic acid) and long-chain ω-3 PUFA (docosahexanoic acid and eicosapentanoic acids) analyzed separately, were similar in direction (data not shown); therefore, data are presented for total ω-3 PUFAs intake. Higher intakes of ω-3 PUFA, measured in mg/1000 kilocalories, adjusted for age and energy only, were directly associated with AMD (Table 2).

Additional adjustment for lutein intake group and other potential confounders or repeating analysis among women with stable ω-3 PUFA intake did not influence ORs.

Previous investigations have observed a protective influence of ω-3 PUFA or fish to be stronger among people with lower intakes of ω-6 PUFA,[14, 18, 20] possibly because ω-6 PUFA replace ω-3 PUFA in membranes as well as compete with ω-3 PUFA for cyclooxygenases to form pro-inflammatory eicosanoids.[27] Therefore, we computed associations of ω-3 PUFA intake to AMD, separately, stratifying by level of intake of ω-6 PUFA (above and below the median intake of 6% as a percent of total energy). The odds ratios remained direct, regardless of level of dietary ω-6 PUFA: The OR's (95%CI) were 1.2 (0.8–1.9) vs. 1.8 (1.2–2.7) for women below vs. above the median for ω-6 PUFA intake. Because a deleterious influence of ω-6 PUFAs could reflect the fact that foods high in these fats can also be sources of trans-fatty acids, there were no associations between trans fat intake and intermediate AMD (OR=0.9, 95% CI=0.6–1.4 adjusting for age, energy and lutein intake group).

Food sources of fats—In order to interpret associations of fat to AMD, we explored associations of AMD with specific food sources of fat. In Table 3, we list associations in the youngest age group at risk for AMD (women <75 years of age) because these associations are least likely to reflect biases due to selective mortality or diet change. The majority of fat in the CAREDS sample was provided by dairy foods (26%), added fats (24%) and meats (16%). Intake of added animal or vegetable fats, or high-fat versions of dairy foods or meats was consistently associated with higher prevalence of AMD, although the associations with the intake of no one food group was statistically significant. Although the intake of low-fat dairy foods supplied 39% of total dairy fat, intake in high vs. low tertile was related to almost two-fold lower risk for AMD. No associations of AMD with food sources of omega-3 fatty acids, nuts and dark fish were observed, but the consumption frequency of these foods was low. Moreover, the predominant intake of dark fish was in the form of tuna salad, and most fat (about 70 to 90%) in tuna salad comes from added vegetable fat (mayonnaise) which was directly (although non-significantly) associated with AMD.

DISCUSSION

Types of dietary fats

In the present study, in which diet was assessed approximately 4 to 7 years prior to the ascertainment of AMD in postmenopausal women, the intake of ω-6 PUFA, primarily provided by added vegetable fats (salad dressing, mayonnaise, margarine), were associated with an increased prevalence in intermediate AMD. Similar associations with overall omega- 6 PUFAs or with the intake of the major ω-6 PUFA (linoleic acid) have been observed in five[13–15, 18, 20] previous investigations in American samples, although in some, the association was most direct in women[13, 15] (possibly reflecting that this is a more important contributor to fat intake than in men). In another American sample[28] and an Australian cohort[16, 19] and French cohort,[29] odds ratios for AMD among persons with high, compared with low intakes of omega- 6 PUFAs or linoleic acid were close to unity. Nevertheless, more studies than not suggest direct associations of vegetable fats to AMD. The present findings extend these associations to include earlier stages.

These direct associations of ω-6 PUFAs with AMD could reflect simply the fact that this is a common source of fat in this sample, and that fat simply replaces calories spent on eating more nutrient dense foods. This is discussed further below. It could also reflect a deleterious influence of these fats, specifically. ω-6 PUFA might promote inflammation (reviewed in[30]) which is thought to contribute to retinal pathology that promotes AMD[31] and/or the promotion of atherosclerosis, which some have found to be related to AMD risk in some

studies.[8, 32] Although PUFAs lower atherogenetic blood lipids (reviewed in[33])ω-6 PUFA, may be atherogenic because they promote inflammatory processes.[30] The overall effect of fatty acids on the inflammatory process appear to depend on the level of other fatty acids from which pro and anti-inflammatory cytokines and eicosanoids are synthesized. ω-6 and ω-3 fatty acids have been found to have antagonist effects on inflammation, which may be explained by competition for shared enzymes (previously reviewed[27]).

However, the effects of ω-6 PUFAs on inflammation and atherosclerosis are complex and appear to depend on levels of other fatty acids, as well. Levels of other fatty acids, such as omega-9 fatty acids, may also influence the overall inflammatory effect of omega- 6 PUFAs (reviewed in[30]). It has been suggested that the low ratio of omega- 6 to the sum of omega 3 plus omega-9 fatty acids (the most abundant of which is oleic acid, a monounsaturated fatty acid) in Mediterranean diets may explain the low prevalence of CVD and chronic inflammatory diseases in populations that follow these diet patterns.[30]

Another potential explanation for the direct association of ω-6 PUFAs with AMD in this and some other samples could be that solid vegetable fats-- in America--are also a source of trans fatty acids, which may be atherogenic. Trans-fatty acid intake in three American samples was associated with high risk for AMD.[14, 15, 18] However, in the present study, the intake of trans-fatty acids was not associated with AMD.

An adverse effect of ω-6 could reflect the possibility that PUFAs may enhance oxidative damage of the retina.[34–36] The unsaturated fat, because of double bonds, are more susceptible to attack by reactive oxygen species. It is well-known that photoreceptors concentrate ω-6 PUFAs,[37] accrued partially from the diet.[38] There is evidence to suggest that peroxidized lipids that increase in retinal membrane with age could promote AMD progression.[36, 39]

Contrary to results of several previous studies,[14, 16, 18–20, 28] we did not find inverse associations between AMD and higher intakes of ω-3 PUFA or fish. In fact, associations with ω-3 intake were direct. This may be due to that fact that the intake ofω-3 PUFA consumption in this sample was highly related to the intake of ω-3 PUFAs in this sample. This is likely to be because the intake of fatty fish was low and the major sources of ω-3 PUFA were tuna salad, which also supplies high levels of ω-6 PUFAs as mayonnaise. Direct associations between the intake of ω-3 fat intake and progression of AMD were observed in once previous study,[40] but the authors state that this is likely due to recent diet change in study participants, given that diet was assessed after baseline AMD was assessed. In three past studies in which ω-6 PUFAs were associated with higher risk, a protective association on long chain ω-3 PUFA was only observed in conjunction with high levels of these fats.[14, 18, 20] In the present study, ω-6 PUFA levels did not significantly modify associations with ω-3 PUFA intake, but such an observation would have been difficult to observe in this sample because ω-6 PUFA consumption was highly correlated with ω-3 PUFA consumption. Thus, it may be that levels of ω-6 PUFA levels were too high and PUFA ω-3 fatty acid levels too low and strongly related to ω-6 PUFA levels to observe such interactions in the present study. Overall, the body of epidemiological evidence suggests that the intake of ω-3 fats and/or fish is related to lower risk for AMD and the impact of long chain omega-fats on AMD is currently being tested in a large multicenter clinical trial.

The direction of associations of AMD to the intake of other specific types of fats were in a similar direction to PUFAs (direct) except for the intake of MUFAs, raising the possibility that these fats, or other food components they are associated with, may not increase the risk of AMD or may protect against it. Associations of MUFA to AMD across other studies are quite inconsistent. This could reflect, in part, different strategies for the adjustment of these

associations for other aspects of diet, in general, or fat, in particular. MUFAs in this and other samples contribute the most or second most to total fat intake and could reflect associations with the level of fat intake. The direction of associations between MUFAs and AMD changed, in this sample and in one previously reported study,[15] only after adjusting for the intake of other fats that were significant sources of energy (PUFAs, SFA), a strategy which was done so that associations better reflect the relative contributions of fat types rather than the level of fat in diets. Direct (albeit not always significant) associations were observed in three previous studies in which the intake of other energy yielding fats were not adjusted for.[13, 14, 16, 28, 29] Only in one previous study was an association of MUFA intake to AMD direct, even after adjusting for the intake of other fats.[18]

Lower prevalence of AMD among women in quintiles 3–5, compared to quintile 1, in the present could reflect the fact that these foods provide other nutrients that could protect against AMD. For example, dairy and meat products, which are important contributors of MUFA in American diets[41] are also important sources of zinc.[42] In the present study, while high fat versions of these foods were associated with high prevalence of AMD, the lower-fat versions either reduced risk (low-fat dairy)or were not associated with risk (medium or low fat meat) (Table 3). However, zinc intake was not related to AMD in the present study, nor did it influence associations with MUFAs (not shown). The level of intake of foods which provide MUFAs in Mediterranean diets (nuts and olive oil) were too low in this population to adequately evaluate the associations with the intake of these foods.

It is conceivable that MUFA may be protective against AMD via its anti-atherogenic role. It has been hypothesized that atherosclerosis and its risk factors are related to the development of AMD.[8, 32, 43–46] Previous epidemiologic studies and intervention trials of diets high in MUFA suggest a protective effect towards atherosclerosis and coronary heart disease (reviewed in[47]). Since olive oils[48] and nuts[49] that are rich in MUFA are also rich in vitamin E and other plant antioxidants, high MUFA intake may be a marker of other aspects of diet that may be associated with lower risk of AMD in some samples.

Total dietary fats

In this sample, total fat intake was not associated with overall intermediate AMD; However, associations varied with age. Direct associations of total fat to AMD in the younger women (three-fourths of our sample), were consistent with the large body of evidence that suggests AMD risk is directly associated with the level of total fat intake. High levels of fat have been significantly associated with higher prevalence, incidence or progression in several studies.[14, 15, 29] In several additional studies, associations with fat have been direct, even if not statistically significant.[13, 14, 16–18, 29] Data from the present study extended the body of evidence to include intermediate AMD. It is common knowledge that high-fat diets are often micronutrient-poor and this trend can be observed in Table 1. Consequently, high fat diets might be a marker for diets which are poor in many micronutrients that could protect against AMD. Although associations in this study persisted, despite adjusting for level of lutein in the diet, and despite adjustment for other protective micronutrients, some level of residual confounding is likely to persist due to imperfect measurement of diet and the fact that diet over a short time is queried, relative to the decades of adult life, over which diet could influence the health of the retina.

The inverse associations between AMD and total fat, in the older segment of the population, could be the result of selective mortality bias. Similar reversals of associations in old compared with younger persons were observed with the intake of lutein and zeaxanthin in the same sample[24] and a separate sample.[50] Moreover, the older women who enrolled in this study were more likely to have healthier diets and lifestyles than women in their birth cohorts who did not survive. Additionally, there is evidence that having AMD is associated

with increased risk for mortality.[51–54] Thus, potentially adverse relationships between diets high in fat and AMD could be masked in older segments of the sample. These biases are likely to contribute to the inconsistency in nutrition and other modifiable risk factors for AMD observed across epidemiological studies.

In addition to those already discussed, additional limitations of the present study must be considered. Although we had the ability to adjust for a large number of potential risk or protective factors (smoking, history of diabetes and cardiovascular disease, family history of AMD, iris color, and postmenopausal hormone therapy use), we did not have information about genetic risk for AMD. (We did have self-reports of family history of AMD and adjusting for this did not influence or modify the associations we observed.)

Second, there may be limitations in the ability to generalize the results of this study to the larger US population of women or to men. Different from the overall US population in NHANES III, at a similar time period to WHI recruitment, women in the CAREDS sample are primarily white (98%). Women in CAREDS are more educated, have higher incomes and are generally healthier than American women overall, except for being more likely to be overweight (37 vs. 26 %) or obese (26 vs. 19%). Fewer CAREDS participants currently smoke (4 vs. 19%), but a larger proportion smoked in the past (39% vs. 31%). Overall, 43% of CAREDS participants and 50% of US women over 40 years of age ever smoked.

We were unable to ascertain whether AMD antedated recruitment into the WHI study. However, retinal photographs were taken 4 to 7 years after dietary assessments were done in WHI-baseline study visits. It is unlikely that knowledge of having large drusen would influence diet patterns, because it was assessed photographically at a stage not often associated with being aware of the condition; the majority (72%) of women with intermediate AMD in this sample reported not having been told by a doctor that they had it. However, changes in diet just prior to entry into WHI, which are associated with the presence of other chronic diseases that may increase risk for AMD (cardiovascular diseases, diabetes or hypertension), could bias findings. Next, the unavoidable imprecision of the food frequency questionnaire may have attenuated our study findings toward the null. Further, given the number of comparisons made in analyzing amount and type of fat in relation with AMD, some borderline significant results may be by chance, in the absence of a real association.

Conclusions

Associations of the intake of total and specific types of fat to AMD are complex in this sample and across different study populations. However, some generalities can be made: Our study adds to the growing body of evidence that diets that are high in fat may influence the development of AMD and extends the adverse associations reported in past studies to earlier stages of AMD. Inconsistencies in relationships of specific fats to AMD across study samples and age-strata may also reflect different patterns of fat intake, other dietary characteristics for which fat intake is a marker, selective mortality bias and different strategies used to adjust for other aspects of diet across studies.

In this particular sample, adverse associations were particularly attributed to diets high in ω-6 PUFAs, which may have masked potential protective influences of consuming diets high in ω-3 PUFA.

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Table 1

Characteristics of 1,787 CAREDS participants in quintile five versus one of total and specific types of fats at WHI baseline[1]

	Total Fats			ω-6 polyunsaturated fats			ω-3 polyunsaturated fats		
Quintile	**1**	**5**	**p-value**	**1**	**5**	**p-value**	**1**	**5**	**p-value**
Demographics									
Income >$75,000 (%)	24	12	0.0009	20	14	0.0007	17	18	0.04
Race (% white)	97	98	0.46	96	97	0.24	97	96	0.06
Education									
High school	15	34	<0.0001	16	31	<0.0001	19	25	0.31
College	48	51		48	46		48	48	
Graduate	37	15		36	23		33	27	
Age (years)[2]	70±0.37	69±0.36	0.4	70±0.36	69±0.36	0.7	70±0.36	69±0.36	0.7
Intake From Foods									
Energy, kcals/d	1552±33.5	1682±33	0.009	1549±33	1628±33	0.02	1591±33	1623±33	0.04
Total fat, % kcals	20±0.14	44±0.14	<0.0001	23±0.31	41±0.31	<0.0001	24±0.35	39±0.35	<0.0001
Polyunsaturated fat, % kcals	4±0.08	9±0.08	<0.0001	4±0.05	10±0.05	<0.0001	4±0.08	9±0.08	<0.0001
Saturated fats, % kcals	7±0.10	15±0.09	<0.0001	9±0.17	13±0.17	<0.0001	8±0.16	13±0.16	<0.0001
Monounsaturated fats, % kcals	7±0.07	16±0.07	<0.0001	8±0.13	15±0.13	<0.0001	9±0.15	14±0.15	<0.0001
Lutein, μg/d	3032±85	1526±84	<0.0001	2566±88	1886±87	<0.0001	2174±88	2329±88	0.5
Vitamin C, mg/d	152±3.3	74±3.2	<0.0001	140±3.4	89±3.4	<0.0001	128±3.5	101±3.5	<0.0001
Vitamin A, μg/d	1134±26.7	875±26.3	0.002	1087±26.5	875±26.5	<0.0001	1031±26.5	922±26.5	0.01
Vitamin E, mg/d	8±0.23	9±0.23	<0.0001	7±0.23	9±0.23	<0.0001	7±0.23	9.5±0.23	<0.0001
Vitamin D, μg/d	6±0.20	5±0.20	0.0045	6±0.19	5±0.19	0.044	7±0.20	5±0.20	<0.0001
Zinc, mg/d	11±0.28	10±0.28	0.001	11.5±0.27	10±0.27	<0.0001	11±0.27	10±0.27	0.04
Lifestyle									
Pack-years ≥7, % smokers[2]	20	21	0.5	19	22	0.9	21	24	0.3
Physical activity, METS/wk	21±0.77	9±0.76	<0.0001	19±0.78	11±0.77	<0.0001	17	12	<0.0001
High dose antioxidant users (%)[2,4]	12	6	<0.0001	9	8	<0.0001	11	7	<0.0001
Medical History									
Body mass index (kg/m^2)	26±0.31	29±0.30	<0.0001	27±0.31	29±0.30	<0.0001	27±0.31	29±0.31	<0.0001

	Total Fats			ω-6 polyunsaturated fats			ω-3 polyunsaturated fats		
Quintile	**1**	**5**	**p-value**	**1**	**5**	**p-value**	**1**	**5**	**p-value**
Waist-to-hip ratio	0.78±0.004	0.81±0.004	<0.0001	0.79±0.004	0.82±0.004	<0.0001	0.79±0.004	0.81±0.004	<0.0001
Cardiovascular disease (%)	22	25	0.9	22	24	0.5	24	25	0.9
Hypertension (%)	21	34	0.005	24	33	0.05	24	34	0.006
Diabetes (%)	1	6	0.009	2	6	0.004	2	6	0.03
Family history of AMD (%)[2]	16	17	0.8	13	16	0.21	15	19	0.1
Ocular Outcomes (%)[2]									
Intermediate AMD	18	19	0.7	17	21	0.6	16	25	0.01
Large drusen	16	17	0.3	13	18	0.4	12	21	0.01
Pigmentary abnormalities	9	11	0.7	9	12	0.5	10	15	0.07

[1] Data represent age-adjusted least squares means (SE) or percentage of participants, directly standardized for age groups: ≤69, 70–74, ≥75), except for age

[2] Assessed at WHI-baseline in 1994–1998,

[3] Assessed in CAREDS questionnaires or study visits

[4] Daily intake of at least 2 of the following 3 antioxidants from supplements containing ≥120 mg vitamin C, ≥60 IU (40 mg) vitamin E, or ≥10,000 μg beta-carotene at CAREDS-baseline for 10 or more years

[5] p-values were calculated using regression coefficients from the analyses of covariance, for continuous variables the Cochran-Mantel-Haenszel Statistic for general association for categorical variables

Table 2

Odds Ratios (95% CI) for overall intermediate AMD by quintiles of total and specific type of dietary fat intake in CAREDS participants, 2001–2004 (n=1,787)

	1	2	3	4	5	p-trend[1]	p-interaction
TOTAL FATS							
Median intake (% of energy)	21	26	31	36	43	-	
No. with outcome/No. at risk	65/339	72/355	61/360	62/346	67/353	-	
Age-adjusted OR	1.0	1.07 (0.7–1.6)	0.84 (0.6–1.2)	0.87 (0.6–1.3)	1.03 (0.7–1.5)	0.89	
Multivariate OR [3]							
Whole Sample	1.0	1.06 (0.7–1.6)	0.83 (0.6–1.3)	0.87 (0.6–1.3)	1.0 (0.7–1.5)	0.79	
Women with stable fat intake[4]	1.0	1.29 (0.8–2.0)	0.81 (0.5–1.3)	0.91 (0.6–1.5)	1.0 (0.6–1.7)	0.72	
<75 years							
Median Intake (% of energy)	21	26	31	36	43	-	
No. with outcome/No. at risk	29/262	38/262	39/264	36/263	48/262	-	
Age-Adjusted OR	1.0	1.35 (0.8–2.3)	1.38 (0.8–2.3)	1.24 (0.8–2.2)	1.83 (1.1–3.0)	0.05	
Multivariate OR[3]							
Whole Sample	1.0	1.34 (0.8–2.2)	1.35 (0.8–2.3)	1.20 (0.7–2.0)	1.73 (1.02–2.7)	0.1	
Women with stable fat intake[4]	1.0	1.65 (0.8–3.2)	1.24 (0.6–2.5)	1.48 (0.7–2.9)	1.80 (0.9–3.7)	0.19	
≥75 years							
Median Intake (% of energy)	20	26	30	35	42	-	0.02
No. with outcome/No. at risk	34/86	33/88	24/88	24/89	22/89	-	
Age-Adjusted OR	1.0	0.92 (0.5–1.7)	0.57 (0.3–1.1)	0.56 (0.3–1.1)	0.50 (0.3–1.0)	0.008	
Multivariate OR[3]	1.0	0.93 (0.5–1.7)	0.58 (0.3–1.1)	0.58 (0.3–1.1)	0.53 (0.3–1.0)	0.02	
SATURATED FATS							
Median intake (% of energy)	7	9	10	12	15	-	
No. with outcome/No. at risk	64/340	68/361	63/345	70/350	62/357	-	
Age-Adjusted OR	1.0	1.00 (0.7–1.5)	0.96 (0.6–1.4)	1.12 (0.8–1.6)	0.96 (0.6–1.4)	0.98	
Multivariate OR[3]							
Whole Sample	1.0	1.08 (0.7–1.7)	1.21 (0.7–2.0)	1.53 (0.8–2.7)	1.35 (0.7–2.5)	0.36	
Women with stable SFA intake[4]	1.0	1.02 (0.6–1.8)	1.45 (0.8–2.6)	1.70 (0.9–3.4)	1.31 (0.6–2.8)	0.39	

	1	2	3	4	5	p-trend[1]	p-interaction
<75 years							
Median Intake (% of energy)	7	9	10	12	15	-	0.01
No. with outcome/No. at risk	30/263	36/261	35/265	45/262	45/262	-	
Age-Adjusted OR	1.0	1.22 (0.7–2.2)	1.17 (0.6–2.3)	1.63 (0.8–3.3)	1.65 (0.7–3.7)	0.02	
Multivariate OR[3]							
Whole Sample	1.0	1.21 (0.7–2.2)	1.15 (0.6–2.3)	1.60 (0.8–3.3)	1.60 (0.7–3.6)	0.23	
Women with stable SFA intake[4]	1.0	1.41 (0.7–3.1)	1.75 (0.7–4.1)	2.42 (1.0–6.1)	2.41 (.9–6.7)	0.12	
MONOUNSATURATED FATS							
Median intake (% of energy)	7	10	11	13	16		
No. with outcome/No. at risk	66/338	71/350	60/359	62/349	68/357		
Age-Adjusted OR	1.0	1.09 (0.7–1.6)	0.84 (0.6–1.2)	0.91 (0.6–1.3)	1.01 (0.7–1.5)	0.87	
Multivariate OR[3]							
Whole Sample	1.0	0.89 (0.5–1.4)	0.54 (0.3–0.97)	0.49 (0.2–0.9)	0.47 (0.2–1.0)	0.12	
Women with stable MUFA intake[4]	1.0	0.96 (0.6–1.8)	0.46 (0.8–2.6)	0.41 (0.2–0.9)	0.41 (0.2–1.1)	0.11	
<75 years							0.02
Median Intake (% of energy)	8	10	11	13	16	-	
No. with outcome/No. at risk	29/245	35/261	38/266	38/269	50/272	-	
Age-Adjusted OR	1.0	1.17 (0.7–2.0)	1.24 (0.7–2.1)	1.21 (0.7–2.0)	1.69 (1.0–2.8)	0.04	
Multivariate OR[3]							
Whole Sample	1.0	0.89 (0.5–1.7)	0.78 (0.4–1.7)	0.64 (0.3–1.5)	0.77 (0.3–2.1)	0.67	
Women with stable MUFA intake[4]	1.0	0.79 (0.4–1.7)	0.50 (0.2–1.3)	0.35 (0.1–1.1)	0.49 (0.2–1.7)	0.29	
OMEGA-6 PUFA							
Median intake (% of energy)	3	4	5	6	8		
No. with outcome/No. at risk	58/347	53/355	65/354	62/342	73/355		
Age-Adjusted OR	1.0	1.20 (0.8–1.8)	1.11 (0.7–1.6)	1.10 (0.7–1.6)	1.35 (0.9–2.0)	0.20	
Multivariate OR[3]							
Whole Sample	1.0	1.35 (0.9–2.1)	1.45 (0.9–2.2)	1.55 (0.9–2.5)	2.01 (1.1–3.5)	0.20	
Women with stable ω-6 PUFA intake[4]	1.0	1.27 (0.8–2.1)	1.77 (1.1–3.1)	1.66 (0.9–3.0)	2.28 (1.2–4.4)	0.02	
<75 years							
Median Intake (% of energy)	3	4	5	6	8	-	0.10

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	1	2	3	4	5	p-trend[1]	p-interaction
No. with outcome/No. at risk	28/261	39/264	35/250	38/255	50/283	-	
Age-Adjusted OR	1.0	1.46 (0.8–2.6)	1.43 (0.8–2.6)	1.47 (0.8–2.8)	1.66 (0.8–3.3)	0.04	
Multivariate OR[3]							
Whole Sample	1.0	1.48 (0.8–2.6)	1.47 (0.7–2.7)	1.49 (0.8–2.9)	1.68 (0.8–3.4)	0.07	
Women with stable ω-6	1.0	1.51 (0.7–3.1)	2.32 (1.1–5.0)	2.14 (0.9–4.8)	2.14 (0.9–5.2)	0.17	
PUFA intake[4]							
OMEGA-3 PUFA							
Median intake (mg/1000 kcals)	501	634	748	879	1103		0.01
No. with outcome/No. at risk	57/351	62/351	59/344	61/352	88/355		
Age-Adjusted OR[5]	1.0	1.15 (0.8–1.7)	1.08 (0.7–1.6)	1.10 (0.7–1.6)	1.80 (1.2–2.6)	0.003	
Multivariate OR[3]							
Whole Sample	1.0	1.15 (0.8–1.7)	1.08 (0.7–1.6)	1.10 (0.7–1.7)	1.80 (1.2–2.6)	0.003	
Women with stable ω-3 PUFA intake[4]	1.0	1.15 (0.7–1.8)	1.00 (0.6–1.6)	1.11 (0.7–1.8)	1.82 (1.1–2.9)	0.005	
<75 years							
Median Intake (mg/1000 kcals)	500	634	748	880	1,106	-	
No. with outcome/No. at risk	26/232	35/227	30/226	36/229	63/209	-	
Age-Adjusted OR[5]	1.0	1.54 (0.9–2.6)	1.22 (0.7–2.1)	1.58 (0.9–2.7)	2.68 (1.6–4.4)	<0.0001	
Multivariate OR							
Whole Sample	1.0	1.53 (0.9–2.6)	1.22 (0.7–2.1)	1.56 (0.9–2.7)	2.65 (1.6–4.4)	<0.0001	
Women with stable ω-3 intake[4]	1.0	1.79 (0.9–3.6)	1.23 (0.6–2.5)	1.83 (0.9–3.6)	3.45 (1.8–6.6)	<0.0001	

[1] P-trend was calculated using quintile medians of the fats

[2] P-interaction for age and total and specific fats were calculated with age as a continuous variable in the model

[3] Model for total fats included age and lutein intake group (high versus low); For SFA, PUFA, MUFA analyses, models contained MUFA, PUFA, SFA, age, and lutein intake group (low versus high)

[4] Women were considered to have stable fat intakes for total and specific fats if their quintile ranking for total or specific type of fat intake at WHI-baseline (1994–98) differed from their ranking for total fat intake at 1986–88 by no more than one quintile N=1325.

[5] Adjusted for age and energy

Table 3

Multivariate[1] adjusted odds ratios and 95% confidence intervals for intermediate AMD by tertiles of food sources of dietary fat among CAREDS participants <75 years of age (n= 185 cases in 1313 total)

	% of Total Fat	Tertile 1	Tertile 2	Tertile 3
Dairy Foods	26			
High Fat Dairy[2] (61% of dairy fat)				
median servings/month		9	18	36
OR (95%CI)		1.0	1.28 (0.9–1.9)	1.14 (0.8–1.7)
Low Fat Dairy[3] (39% of dairy fat)				
median servings/month		11	36	87
OR (95%CI)		1.0	1.15 (0.8–1.6)	.54 (0.3–0.8)
Added Vegetable Fats[4] (79% of added fats	24			
median servings/month		10	26	54
OR (95%CI)		1.0	1.15 (0.8–1.7)	1.35 (.9–2.0)
Animal Fats[5]				
median servings/month		1.0	4.0	21
OR (95%CI)		1.0	0.90 (0.6–1.3)	1.25 (0.9–1.8)
Meats	16			
High Fat Meats[6] (20% total meat fat)				
median servings/month		0.0	1.0	4.5
OR (95%CI)		1.0	1.03 (0.7–1.5)	1.24 (0.9–1.8)
Low Fat Meats[7] (80% total meat fat)				
median servings/month		9	18	34
OR (95%CI)		1.0	.82 (0.6–1.2)	.98 (0.7–1.4)
Candy/High Fat Desserts[8]	8			
median servings/month		3	12	32
OR (95%CI)		1.0	1.10 (0.8–1.6)	.94 (0.6–1.4)
Peanuts, Nuts	5			
median servings/month		.5	2.3	11.0
OR (95%CI)		1.0	.87 (0.6–1.3)	1.06 (0.7–1.5)

	% of Total Fat	Tertile 1	Tertile 2	Tertile 3
Salty Snacks[9]	2			
median servings/month		1	6	20
OR (95%CI)		1.0	.98 (0.7–1.4)	1.08 (0.7–1.6)
Fish				
Total	1			
median servings/month				
OR (95%CI)		1.0	1.00 (0.7–1.5)	1.04 (0.7–1.6)
Fried or White fish				
median servings/month		0.0	2.3	5.3
OR (95%CI)		1.0	.91 (0.6–1.3)	.92 (0.6–1.3)
Dark Fish (20% Fat from Fish)				
median servings/month		1.0	2.5	6.7
OR (95%CI)		1.0	1.13 (0.8–1.7)	1.26 (0.8–1.9)

[1] Adjusted for age and lutein intake group (high vs low)

[2] High fat dairy includes: cheese and cheese dishes, butter, ice cream and custards, cream and dishes made with cream and whole milk.

[3] Low fat dairy includes: skim or 2% milk, low fat cheeses, yogurt, low fat dairy, desserts.

[4] Added vegetable fat includes: margarine, mayonnaise, salad dressing, vegetable oils.

[5] Added animal fat includes: butter, gravy, lard

[6] High fat meats include hot dogs, sausages, luncheon meat, fried chicken, organ meats, gravy and lard.

[7] Low fat meats include: beef, pork, lamb, poultry and mixed dishes containing them. (This represents 80% of fat from meats).

[8] Candy and high fat desserts include: chocolate candy, donuts and pastries, cookies and pies

[9] Salty snacks include popcorn (popped-oil), potato and snack chips.