HHS Public Access

Author manuscript

Ophthalmic Epidemiol. Author manuscript; available in PMC 2016 May 09.

Published in final edited form as:

Ophthalmic Epidemiol. 2016 April ; 23(2): 99–108. doi:10.3109/09286586.2015.1129426.

Dietary intake of lutein and diabetic retinopathy in the Atherosclerosis Risk in Communities (ARIC) Study

Michelle W. Sahli[2], **Julie A. Mares**[4], **Kristin J. Meyers**[4], **Ronald Klein**[4], **William E. Brady**[3], **Barbara E. K. Klein**[4], **Heather M. Ochs-Balcom**[2], **Richard P. Donahue**[2], and **Amy E. Millen**[1]

Amy E. Millen: aemillen@buffalo.edu

[1]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, 270 Farber Hall, Buffalo, NY 14214-8001. Telephone: (716) 829-5377, Fax: (716) 829-2979

[2]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, Buffalo, NY

[3]Department of Biostatistics and Bioinformatics, Roswell Park Cancer Institute, Buffalo, NY

[4]Department of Ophthalmology and Visual Sciences, The University of Wisconsin-Madison, Madison, WI

Abstract

Purpose—We tested the hypothesis that dietary intake of lutein is inversely associated with prevalence of diabetic retinopathy due to its antioxidant and anti-inflammatory properties and its location within the retina.

Methods—We used logistic regression to examine the association between prevalent DR and energy-adjusted lutein intake [by quartile (Q)] using data collected from 1,430 ARIC study participants with diabetes (n=994 White and n=508 Black). DR was assessed using a 45-degree nonmydriatic retinal photograph from one randomly chosen eye taken at visit 3 (1993–95). Dietary lutein intake was estimated using a 66-item food frequency questionnaire at visit 1(1987–89).

Results—The median estimated daily lutein intake was 1,370 μg/1000 kcals and the prevalence of DR was ~21%. We found a crude association between lutein and DR [OR (95% CI) for Q4 (high intake) vs. Q1 (low intake) =2.11 (1.45–3.09); p for trend<0.0001] which was attenuated after adjustment for race, duration of diabetes, glycosylated hemoglobin levels, field center and energy intake [1.41 (0.87–2.28); p for trend=0.01]. In analyses limited to persons with a short duration of diabetes (<6 years), the association no longer persisted [0.94 (0.31–2.16); p for trend=0.72] as compared to the association in those with a longer duration of diabetes (≥6 year) [1.58 (0.91–2.75); p for trend=0.01].

Correspondence to: Amy E. Millen, aemillen@buffalo.edu.

Proprietary interests or conflicts of interest: None of the authors have any proprietary interests or conflicts of interest related to this submission.

Statement: This submission has not been published anywhere previously and that it is not simultaneously being considered for any other publication.

Conclusion—Contrary to our hypothesis, we found that the odds of higher lutein intake were greater among those with DR than those without DR. However, after adjusting for confounders, intake of lutein was not associated with DR.

Introduction

The prevalence of diabetes and its complications are increasing worldwide[1, 2]. It is estimated that in 2030 there will be over 191 million people with diabetic retinopathy and vision will be compromised in over 55 million of these people[3]. While poor blood glucose control, high blood pressure and a long duration of diabetes are recognized as risk factors for diabetic retinopathy[4], other modifiable risk factors may exist.

Hyperglycemia, common in those with diabetes, can lead to retinal microvasculature damage indicative of diabetic retinopathy through a number of pathways that involve oxidative stress and inflammation. These include increased permeability of retinal blood vessels, loss of pericytes, increased endothelial cell production and neovascularization.[5, 6] Animal and human studies suggest that lutein, a carotenoid which is obtained through diet and found in the retina,[7] may reduce oxidative stress and inflammation.[8–12]

Animal studies have demonstrated that lutein supplementation lowers oxidative stress and inflammatory markers both in the eye and systemically.[9, 11] In humans, serum lutein levels are inversely associated with circulating markers of inflammation (leukocyte counts and C-reactive protein).[8] Lutein supplementation has also been shown to decrease levels of complement factor D, an important component of the alternative complement pathway, along with this pathway's activation products, C5a and C3d.[13] Further, the retina is highly susceptible to oxidative stress because its tissues (e.g., endothelial cells) have a high proportion of polyunsaturated fatty acids which are prone to peroxidation, high oxygen uptake, high glucose oxidation, and irradiation from visible light.[14]

Epidemiologic studies have shown protective associations between both dietary and supplemental lutein intake and chronic eye diseases such as age-related macular degeneration and cataract [15]. However, few studies have examined the association between lutein and retinopathy [16]. The few published studies on this relationship in humans have been small (n<125) [16, 17] and studies of antioxidant supplement use containing lutein alongside other antioxidants.[18] It is difficult to discern whether the effect of supplementation was due to lutein intake, other antioxidants within the supplement, or a synergistic effect of all antioxidants. Despite limitations in individual studies, the increasing body of scientific evidence suggests that lutein may be beneficial in preventing retinopathy and its progression.[10, 16–18]

We hypothesized that diets rich in lutein protect against development of diabetic retinopathy. We examined associations between dietary intake of lutein and diabetic retinopathy in a sample of individuals with diabetes enrolled in the Atherosclerosis Risk in Communities (ARIC) Study, a population-based cohort study.

Materials and Methods

Study Sample

Our data comes from the ARIC study, a prospective cohort that was designed to investigate the causes and natural history of atherosclerosis and variation in risk factors for cardiovascular disease [described in detail elsewhere].[19, 20] The study sample was drawn from the following four communities: Forsyth County, North Carolina, Jackson, Mississippi, the northwestern suburbs of Minneapolis, Minnesota and Washington County, Maryland. Participants were eligible for inclusion in the ARIC cohort if they were between 45 and 65 years old at visit 1 (1987–1989) and intended to remain in the area in which they lived.[21]

Our study sample was comprised of ARIC participants categorized as having diabetes at visit 3 (1993–1995), with readable fundus photographs, which were only available at visit 3, and completed food frequency questionnaires (FFQ) at visit 1. We restricted our study to just black and white subjects because only 8 participants (<0.5%) self-identified their race/ethnicity as neither black nor white.

There were 1,899 participants that were classified as having diabetes at visit 3. Participants were categorized as having diabetes at visit 3 if they had a non-fasting blood glucose concentration ≥200 mg/dl, a fasting blood glucose concentration of ≥126 mg/dl, reported being told by a physician that they had diabetes, or were on blood glucose lowering medication in the two weeks prior to the study visit.[22] Of these 350 were missing fundus photograph data (49 participants with no photographs taken and 301 with ungradable photographs) and were excluded from the study sample. We also excluded 39 participants who reported implausible caloric intakes (i.e., ≤500 or ≥3600 kcals for women and ≤600 or ≥4,200 kcals for men) or were missing ≥10 (15%) responses to food item questions on the food frequency questionnaire (FFQ).[23] An additional 72 participants were excluded from the analysis due to missing HbA1c data leaving a study sample of 1,430 participants. Signed informed consent was obtained for all participants and the study protocol was approved by the institutional review boards at each ARIC study site.

Dietary Intake of Lutein

At visits 1 and 3 dietary data was collected using an interviewer administered, previously validated, [24, 25] 66-item FFQ which was adapted from a 61 item FFQ developed by Willett et al.[21] Deviations from Willett's original 61 item FFQ were mainly due to the addition of questions about fish consumption and questions on cooking fats.[21] The food content of lutein and its isomer zeaxanthin were not differentiated in the FFQ's nutrient composition database and were supplied as one value which we refer to as "lutein". Lutein intake was adjusted for energy using the multivariate nutrient density method, standardizing nutrient values to 1000 kcals consumed.[26] We created quartiles (Q) of this energy-adjusted dietary intake of lutein. Lutein supplements were not on the market when the data were collected.

In our primary analyses, we used intake data from the FFQ administered at visit 1, six years prior to the assessment of retinopathy status with fundus photographs at visit 3. For some individuals, this assessment of diet is likely to have preceded the development of disease and may be more likely to represent dietary intake in the participant's life prior to knowledge of

diabetic complications. Data from the FFQ administered at visit 3 was used in additional analyses to explore whether averaging lutein intake at visits 1 and 3 might alter our findings and whether consistent lutein intake was more associated with retinopathy than intake at one point in time.

Assessment of Diabetic Retinopathy

As part of visit 3, one 45° stereoscopic color retinal photograph was taken of one random eye, centered on the optic disc and macula, from each participant with a fundus camera that allows for non-mydriatic photographs. Photographs were taken at all ARIC study sites and were sent to a central retinal reading center where they were assessed for abnormalities by graders masked to participants' diabetic and hypertensive status.[27]

Retinopathy was assessed using light box grading which was performed by examining the photos on a monocular 8× stand viewer (Agfa-Gevaert, Mortsel, Belgium) on a fluorescent box. Any potential abnormalities on the photographs were compared to standardized photographs to assist in determining the existence and severity of any irregularities. Graders noted the number of retinal microaneurysms and retinal hemorrhages along with soft exudates, hard exudates, intraretinal microvascular abnormalities, venous beading and/or optic disc swelling. Using the results of the grading, the presence and severity of retinopathy was calculated using the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale. Participants with photos graded as a 10 on the ETDRS were considered as having *no retinopathy*. Those with scores ranging from 14–35 were categorized as having *mild non-proliferative retinopathy* (NPDR), scores of 43–53 were categorized as having *moderate to severe NPDR* and participants with scores of 61 or higher as having or having had *proliferative retinopathy* (PDR).[27, 28]

Questionnaire Data, Physical and Other Measurements

At each ARIC study visit trained study personnel collected information on participants' age, health history, family health history, smoking, physical activity, demographic factors, medication use and other potential risk factors for cardiovascular disease.[20] A fasting blood draw obtained from each participant at each visit was used to measure blood glucose, total cholesterol, triglycerides and HDL cholesterol, and to calculate LDL cholesterol. HbA1c concentration was assessed in an ancillary study of the ARIC using blood samples collected during study visit 2 (1990–1992). The details of these measurements have been reported elsewhere. [29–31]

Statistical Analyses

We examined the distributions of demographics and other characteristics considered risk factors for diabetic retinopathy in earlier literature. Analyses of the distributions of these covariates, by quartile of lutein intake and prevalence (none/any) and severity (none, mild NPDR, moderate to severe NPDR and PDR) of diabetic retinopathy were performed using χ^2 tests for categorical variables and t-tests or ANOVA for continuous variables as appropriate. Differences in the distribution of these variables were considered significant at a p-value ≤ 0.05. We used this same strategy to compare characteristics of ARIC study

participants with diabetes who were excluded from our analysis due to missing data on retinopathy status, diet or pertinent covariates (n=469) with those included in the study.

The association between lutein intake at visit 1 and prevalence of retinopathy was investigated using logistic regression. We first created a univariate model using lutein intake as the independent variable and prevalence of any retinopathy as the dependent variable and calculated crude odds ratios (OR) and 95% confidence intervals (95% CI) comparing the participants in each quartile of lutein intake to those in the lowest quartile (Q1). We decided *a priori* to consider HbA1c, blood pressure and duration of diabetes as potential confounders of this association as they have been shown to be strong predictors of retinopathy.[4, 32] We also considered those covariates that differed between groups by both quartile of lutein intake and prevalence of retinopathy at the ≤ 0.20 α level as potential confounders. The adjusted model used in our analyses was fit using a stepwise process where potential confounders that changed the odds ratio by 10% or more were retained.

We also examined the association between prevalent retinopathy and lutein intake using lutein intake assessed at visit 3 and an average of lutein intake assessed at visits 1 and 3. It has been suggested that an estimate of nutrient intake may have less measurement error when obtained by averaging data from multiple FFQs than one FFQ alone.[26, 33] Additionally, in order to investigate this association in participants with more stable lutein intakes, we performed our analyses using data from only those participants who remained in the same quartile of lutein intake from visit 1 to visit 3.

We explored the association between lutein intake and severity of retinopathy by creating two additional models, one in which the odds of PDR or moderate to severe NPDR were modelled relative to the odds of mild NPDR or no retinopathy, and another in which the odds of PDR were modelled relative to the odds of less severe or no retinopathy. We adjusted for the same covariates as in our primary analysis.

In an additional exploratory analysis, we stratified by race, levels of glucose control at study visit 2 [adequate if HbA1c $\leq 7\%$ and inadequate if HbA1c $>7\%$ [34]], and duration of diabetes (<6 years and ≥ 6 years) to evaluate if the association between lutein intake and prevalence of retinopathy differed according to levels of these factors. The racial makeup of the ARIC cohort presented an opportunity to examine whether the association between lutein intake and diabetic retinopathy differs by race. We postulated that there may be differences in the antioxidant and anti-inflammatory effects of lutein with varying levels of blood glucose control. We also hypothesized that this association may differ with duration of diabetes because those with longer duration of diabetes may have subsequently changed their diet after the onset of diabetic complications and prior to assessment of diet in the study cohort. We tested the significance of a multiplicative interaction between dietary intake of lutein and these factors by adding an interaction term (dietary intake of lutein $\times$ factor of interest) to the adjusted model. P for interaction of ≤ 0.10 was considered statistically significant.

We also explored whether the associations between intake of lutein-containing foods and retinopathy were similar to those found in the primary analysis. The extent to which foods on the FFQ contributed to the variation in dietary intake of lutein was examined using

stepwise linear regression with lutein intake as the dependent variable and monthly servings of foods containing lutein intake as the independent variables (inclusion and exclusion criteria $p<0.15$). Food groups that explained greater than 10% of the variation in lutein intake (r^2) were considered as significant predictors of lutein intake. We used logistic regression to examine the associations between significant food group predictors of lutein (by categories of servings: "almost never", "twice/month", "once /week" and "> once/ week") and diabetic retinopathy. We adjusted for the same covariates as in the primary analysis.

Results

Distribution of Characteristics in the Study Sample

Among ARIC participants with diabetes at visit 3, those included in our analyses were on average, younger, had shorter durations of diabetes, lower blood glucose levels, lower HbA1c concentrations and lower intakes of lutein compared to those excluded (Supplementary Table 1). A greater proportion of those included was white and had a higher level of education. There were no statistically significant differences between the groups by gender, prevalence of retinopathy, smoking status, usual ethanol intake, body mass index (BMI), prevalence of hypertension (average systolic blood pressure ≥140 mm Hg, or diastolic ≥90 mm Hg, or blood pressure medication use in the 2 weeks prior to visit) or high serum total cholesterol (total cholesterol ≥200 mg/dL, or cholesterol lowering medication use in the 2 weeks prior to visit).

Dietary Lutein Intake and Prevalent Diabetic Retinopathy

Prevalence of retinopathy was greater in those with higher lutein intakes (Q1=14.3%, Q2=19.6%, Q3=23.5% and Q4=26.1%; $p<0.001$) (Table 1). Study participants with lutein intakes in Q4 tended to be older, more likely to have a duration of diabetes ≥six years and consumed less alcohol per week than those in Q1–Q3. There were significant differences in proportions of blacks, females and people with hypertension across quartiles of lutein intakes. Mean blood glucose and HbA1c levels also significantly differed between quartiles with those in higher quartiles tending to have greater concentrations of both blood glucose and HbA1c. Smoking status, BMI and high serum total cholesterol status was not significantly different between quartiles of lutein intake. Median lutein intakes were 434, 1016, 1791 and 4005 μg/1000kcal in Q1 to Q4, respectively (Table 2).

Study participants with retinopathy were older, consumed less alcohol and had higher BMIs, longer durations of diabetes, higher blood glucose levels, and higher HbA1c concentrations than those without retinopathy. There were greater proportions of blacks, females, individuals with less than a high school education, never smokers and people with hypertension among those with retinopathy compared to those without retinopathy. A lower percentage of people with retinopathy had high total cholesterol than those without retinopathy (Supplementary Table 2).

Dietary Lutein Intake and Prevalence of Retinopathy

In the crude analysis, high (Q3 and Q4) compared to low (Q1) lutein intakes were significantly associated with prevalence of any retinopathy (ORs for Q3 vs. Q1: 1.84; 95% CI: 1.25–2.70 and Q4 vs. Q1: 2.11; 95% CI: 1.45–3.09, p for trend<0.0001) (Table 2). After adjusting for study center, total energy consumption, race, duration of diabetes and HbA1c levels in our model, these ORs were attenuated and no longer statistically significant (adjusted ORs for Q3 vs. Q1: 1.54; 95% CI: 0.96–2.47 and Q4 vs. Q1: 1.41; 95% CI: 0.87–2.28), although the p for trend remained statistically significant at 0.01. Further adjustment for saturated fat intake (as a percentage of energy intake) did not substantially alter our results. When we repeated the analyses using lutein intake at visit 3, the adjusted OR for Q4 vs. Q1 was similar to what was seen with visit 1 (OR=1.63; 95% CI: 1.01–2.63, p for trend = 0.09) (Supplementary Table 3). We obtained similarly attenuated results when lutein was represented as an average of visits 1 and 3 and after removing those who did not have consistent intakes of lutein between visits 1 and 3 There were no statistically significant associations observed between lutein intake and the odds of moderate to severe NPDR or PDR (Table 2), although significant p for trends remained. We were unable to calculate adjusted ORs for proliferative retinopathy due to small cell sizes.

In the race-stratified analyses we found associations similar to the primary analysis but the association was stronger in blacks. (Table 3) The adjusted OR for Q4 vs. Q1 was 2.29 (95% CI: 0.53–9.86, p for trend = 0.14) for blacks and 1.36 (95% CI: 0.77–2.43, p for trend = 0.04) for whites. In our analyses limited to persons with a short duration of diabetes (<6 years), the increased odds of retinopathy with increasing lutein intake no longer persisted (adjusted OR for Q4 vs. Q1: 0.89; 95% CI: 0.31–2.50, p for trend = 0.72) as compared to the association in those with a longer duration of diabetes (≥6 year) (adjusted OR for Q4 vs. Q1: 1.58; 95% CI: 0.91–2.75, p for trend = 0.01). Associations were not substantially different between strata of HbA1c concentration. We found no evidence of statistically significant interactions between lutein and race, duration of diabetes, or HbA1c concentrations.

Servings of Food Sources of Lutein and Diabetic Retinopathy

Spinach and other leafy greens represented the only food group that predicted more than 10% of the variability in lutein intake (partial $r^2 = 0.80$). The cumulative r^2 for the model containing all foods retained in the model created using stepwise regression was 0.84. Similar to our analysis of lutein intake, ORs for the association between spinach and other leafy greens and retinopathy were attenuated and not statistically significant after adjusting for confounders (adjusted OR for > once/week vs. almost never: 1.21; 95% CI: 0.76–1.94, p for trend <0.0001).

Discussion

We examined associations between the history of dietary lutein intake and retinopathy in individuals with diabetes the ARIC study. Our study is the first study to investigate this association in a large, population-based cohort with a predominately biracial makeup. We found no significant difference in the odds of prevalent retinopathy among those with higher

dietary intakes of lutein compared to those with lower intakes after adjusting for study center, total energy consumption, race, duration of diabetes and HbA1c.

Previously published studies[10, 17, 18] suggest that an association between higher levels of lutein and decreased odds of retinopathy exists. In one such study, rats whose diets were supplemented with zeaxanthin, an isomer of lutein, had lower retinal levels of oxidative stress biomarkers (e.g., lipid peroxides, 8-hydroxy-2′-deoxyguanosine and nitrotyrosine) and higher levels of mitochondrial complex III (which is thought to be associated with decreased oxidative stress) compared to controls.[10] A cross-sectional study in 111 individuals with type 2 diabetes[17] found that a higher non-pro-vitamin A (including lycopene, lutein and zeaxanthin) to pro-vitamin A ratio was associated with a lower odds of retinopathy (OR=0.33, 95% CI: 0.12–0.95), independent of other risk factors.[17] Additionally, in a five year clinical trial (n=97), investigators found that retinopathy, assessed using a retinopathy degree score, did not significantly progress in participants assigned to antioxidant supplementation (p=0.08 for difference between baseline and follow-up) but did in the control group ($p \leq 0.01$ for difference between baseline and follow-up). Supplements used in this trial contained lutein and zeaxanthin, however, they also contained other antioxidants making it impossible to attribute the effect seen to one specific component.[18]

We explored whether the association between lutein and retinopathy was modified by race, glucose control or duration of diabetes. Although the association appeared to be stronger in blacks than whites, it was not statistically significant and we still found that higher intakes of lutein were associated with higher prevalence of retinopathy. The direction of the association also remained the same after stratifying by HbA1c levels. Interestingly, when the analysis was conducted stratified by duration of diabetes, the increased odds of retinopathy with high lutein intake persisted only in those with a long duration of diabetes. It is possible that those with longer durations of diabetes had started to eat healthier diets (i.e., increased their consumption of vegetable intake), perhaps due to complications of diabetes, prior to enrollment in the ARIC cohort.

We conducted our primary analyses using dietary intake of lutein at visit 1. Results from the examination of associations using dietary data from the same point in time as the eye photos (visit 3) or an average of these two time points, as often done in the literature [35, 36], did not substantially vary from our primary analysis. We also postulated that consistently high dietary lutein over time might be of greater importance in preventing retinopathy than intake at one single point in time. However, results of analyses limited to participants without extreme differences in lutein ranking between visits did not alter our study conclusions.

We repeated our analysis using servings of spinach and leafy green as the exposure variable and our results paralleled those of our primary analysis. This was expected since almost all variation in lutein intake was explained by this one food group. It is possible that the method of preparation, such as use of saturated fats during preparation, confounded the relationship between lutein intake and retinopathy. However, after we adjusted for saturated fat intake our findings remained the same. Fat intake may also not explain the association because it may be beneficial to lutein absorption as well.[37]

There are limited epidemiological studies on the association between lutein and retinopathy. We hypothesized that lutein is associated with decreased odds of retinopathy because it is highly concentrated in the eye, has antioxidant properties and was demonstrated as a safe and effective component in antioxidant supplements protective against progression AMD another retinal disease thought to be promoted by similar pathogenic mechanisms.[38] Epidemiological studies of associations between diabetic retinopathy and antioxidants other than lutein have inconsistent findings.[39–43] If diet is associated with diabetic retinopathy, it is possible that the synergistic effects of nutrients within a broader diet pattern would more accurately capture this.

Our analysis did not include 469 (~25%) ARIC study participants with diabetes at visit 3 for various reasons, which include missing eye data and missing or extreme data on other variables. It is likely that inclusion of these participants would not have attenuated our findings since those excluded had a higher lutein intake and were more likely to have retinopathy because they were older, had a longer duration of diabetes, higher blood glucose concentrations and HbA1C percentages than those included.

In the current study, we analyzed diet data collected from participants before lutein supplements were publically available. As a result we can be more confident that the participants' entire lutein intake was through diet alone. Future investigations of this association need to consider intake of lutein in supplements, which will also likely allow for a greater between-person variation in intake.

A limitation of this study was that only one photograph of one field was taken from one eye of each participant using a non-mydriatic camera. This likely led to outcome misclassification. It is possible that if photos were taken of both eyes, or more fields, we would have detected more retinopathy in our study sample. However, since the eye to be photographed was chosen at random, it would be expected that any misclassification of our outcome would be non-differential biasing our results toward the null. Furthermore, individuals with diabetes of 6 years or more made up more than half of our study sample. It is possible that their diagnosis of diabetes, and conceivably the onset of diabetic complications, may have resulted in an increase in their dietary intake of lutein before our assessment of diet at visit 1.

In conclusion, we observed no significant association between dietary intake of lutein and diabetic retinopathy in people with diabetes at visit 3 in the ARIC study. These findings may be due to measurement error in assessment of retinopathy or diet, increase in lutein intake after to the onset of retinopathy, or a true absence of an association. It is possible a protective effect of lutein on retinopathy exists, but the noted potential biases inherent in this study may have prevented us from observing such an association. Further prospective studies are needed to specifically investigate the association of lutein intake and diabetic retinopathy incorporating measurement of retinopathy at baseline, consideration of lutein intake from supplementation, and use of dietary measurement instruments validated in individuals with diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: This research is supported by the National Institute on Aging grant number 5R01AG041776-03

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).

Works cited

1. World Health Organization; Organization WH, editor. Diabetes Factsheet. 2012; 2012
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010; 87(1):4–14. [PubMed: 19896746]
3. Zheng YF, He MG, Congdon N. The worldwide epidemic of diabetic retinopathy. Indian J Ophthalmol. 2012; 60(5):428–31. [PubMed: 22944754]
4. Yau JWY, Rogers SL, Kawasaki R, et al. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. Diabetes Care. 2012; 35(3):556–64. [PubMed: 22301125]
5. Ciulla TA. Epidemiology and impact of diabetic retinopathy. Advanced Studies in Medicine. 2004; 4:694–701.
6. Ola MS, Nawaz MI, Siddiquei MM, et al. Recent advances in understanding the biochemical and molecular mechanism of diabetic retinopathy. J Diabetes Complications. 2012; 26(1):56–64. [PubMed: 22226482]
7. Bone RA, Landrum JT, Dixon Z, et al. Lutein and Zeaxanthin in the Eyes, Serum and Diet of Human Subjects. Exp Eye Res. 2000; 71(3):239–45. [PubMed: 10973733]
8. Hozawa A, Jacobs DR, Steffes MW, et al. Relationships of circulating carotenoid concentrations with several markers of inflammation, oxidative stress, and endothelial dysfunction: The Coronary Artery Risk Development in Young Adults (CARDIA)/Young Adult Longitudinal Trends in Antioxidants (YALTA) Study. Clin Chem. 2007; 53(3):447–55. [PubMed: 17234732]
9. Kim JE, Clark RM, Park Y, et al. Lutein decreases oxidative stress and inflammation in liver and eyes of guinea pigs fed a hypercholesterolemic diet. Nutrition Research and Practice. 2012; 6(2): 113–9. [PubMed: 22586499]
10. Kowluru RA, Menon B, Gierhart DL. Beneficial effect of zeaxanthin on retinal metabolic abnormalities in diabetic rats. Invest Ophthalmol Vis Sci. 2008; 49(4):1645–51. [PubMed: 18385086]
11. Shanmugasundaram R, Selvaraj RK. Lutein supplementation alters inflammatory cytokine production and antioxidant status in F-line turkeys. Poult Sci. 2011; 90(5):971–6. [PubMed: 21489941]
12. Kowluru RA, Kanwar M, Chan PS, et al. Inhibition of retinopathy and retinal metabolic abnormalities in diabetic rats with AREDS-Based micronutrients. Arch Ophthalmol. 2008; 126(9): 1266–72. [PubMed: 18779489]
13. Tian Y, Kijlstra A, Van der Veen RLP, et al. The Effect of Lutein Supplementation on Blood Plasma Levels of Complement Factor D, C5a and C3d. Plos One. 2013; 8(8)
14. Beatty S, Koh HH, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. Survey of Ophthalmology. 2000; 45(2):115–34. [PubMed: 11033038]
15. Mares, JA.; Millen, AE.; Meyers, KJ. Chapter 19. Diet and Supplements in the Prevention and Treatment of Eye Diseases. In: Coulston, AM.; Boushey, CJ.; Ferruzzi, MG., editors. Nutrition in the Prevention and Treatment of Disease. 3. London: Elsevier Academic Press; 2013. p. 341-371.

16. Hu BJ, Hu YN, Lin S, et al. Application of Lutein and Zeaxanthin nonproliferative diabetic retinopathy. International Journal of Ophthalmology. 2011; 4(3):303–6. [PubMed: 22553667]
17. Brazionis L, Rowley K, Itsiopoulos C, et al. Plasma carotenoids and diabetic retinopathy. Br J Nutr. 2009; 101(2):270–7. [PubMed: 18554424]
18. Garcia-Medina JJ, Pinazo-Duran MD, Garcia-Medina M, et al. A 5-year follow-up of antioxidant supplementation in type 2 diabetic retinopathy. Eur J Ophthalmol. 2011; 21(5):637–43. [PubMed: 21218388]
19. Atherosclerosis Risk in Communities (ARIC) Study Research Group. Response Rate for Annual Follow Up (AFU) CY2–CY23 AFU Versions A-M, V1. Chapel Hill: NC Collaborative Studies Coordinating Center, Department of Biostatistics, Gillings School of Global Public Health; 2012.
20. The ARIC Investigators. The Atherosclerosis Risk In Communities (ARIC) Study - Design And Objectives. Am J Epidemiol. 1989; 129(4):687–702. [PubMed: 2646917]
21. Atherosclerosis Risk in Communities (ARIC) Study Research Group. Manual 2 - Cohort Component Procedures Version 2.0. Chapell Hill, NC: The ARIC Coordinating Center; 1988.
22. Atherosclerosis Risk in Communities (ARIC) Study Research Group. Exam 3 Derived Variable Dictionary Version 37. Vol. 2012. Atherosclerosis Risk in Communities (ARIC) Study Research Group; 2010.
23. Atherosclerosis Risk in Communities (ARIC) Study Research Group. ARIC Data Book, Cohort, Exam 1 TOTNUTX Nutritional Data. Collaborative Studies Coordinating Center Department of Biostatistics Gillings School of Global Public Health University of North Carolina; Chapel Hill 137 E. Franklin Street Suite #203 Chapel Hill, NC 27514–4145:
24. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. American Journal of Epidemiology. 1985; 122(1):51–65. [PubMed: 4014201]
25. Stevens J, Metcalf PA, Dennis BH, et al. Reliability of a food frequency questionnaire by ethnicity, gender, age and education. Nutrition Research. 1996; 16(5):735–45.
26. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: A comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol. 1999; 149(6):531–40. [PubMed: 10084242]
27. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the atherosclerosis risk in communities study. Ophthalmology. 1999; 106(12):2269–80. [PubMed: 10599656]
28. Fundus photographic risk-factors for progression of diabetic-retinopathy - ETDRS report number-12. Ophthalmology. 1991; 98(5):823–33. [PubMed: 2062515]
29. Atherosclerosis Risk in Communities (ARIC) Study Research Group. Manual 7 Blood Collection. Chapell Hill, NC: Atherosclerosis Risk in Communities (ARIC) Study Research Group; 1988.
30. Folsom AR, Szklo M, Stevens J, et al. A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes - The atherosclerosis risk in communities (ARIC) study. Diabetes Care. 1997; 20(6):935–42. [PubMed: 9167103]
31. Selvin E, Steffes MW, Gregg E, et al. Performance of A1C for the Classification and Prediction of Diabetes. Diabetes Care. 2011; 34(1):84–9. [PubMed: 20855549]
32. Beck RW. The Burgeoning Public Health Impact of Diabetes The Role of the Ophthalmologist. Arch Ophthalmol. 2011; 129(2):225–9. [PubMed: 21320972]
33. Willett, W.; Simpson, L. Nutritional Epidemiology. 3. New York, NY: Oxford University Press; 2013. Foods and Nutrients.
34. American Diabetes Association. A1C and eAG. Vol. 2014. Alexandria, VA: American Diabetes Association; 2013.
35. Hu FB, Willett WC. Dietary fat and coronary heart disease: A comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. American Journal of Epidemiology. 2000; 151(1):106.
36. Willett W. Invited commentary: A further look at dietary questionnaire validation. Am J Epidemiol. 2001; 154(12):1100–2. [PubMed: 11744512]

37. Failla ML, Chitchumronchokchai C, Ferruzzi MG, et al. Unsaturated fatty acids promote bioaccessibility and basolateral secretion of carotenoids and alpha-tocopherol by Caco-2 cells. Food & Function. 2014; 5(6):1101–12. [PubMed: 24710065]

38. Chew EY, Clemons TE, Sangiovanni JP, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. JAMA ophthalmology. 2014; 132(2):142–9. [PubMed: 24310343]

39. Millen AE, Gruber M, Klein R, et al. Relations of serum ascorbic acid and alpha-tocopherol to diabetic retinopathy in the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2003; 158(3):225–33. [PubMed: 12882944]

40. Millen AE, Klein R, Folsom AR, et al. Relation between intake of vitamins C and E and risk of diabetic retinopathy in the atherosclerosis risk in Communities Study. Am J Clin Nutr. 2004; 79(5):865–73. [PubMed: 15113727]

41. Li Z-Z, Lu X-Z, Ma C-C, et al. Serum lycopene levels in patients with diabetic retinopathy. Eur J Ophthalmol. 2010; 20(4):719–23. [PubMed: 20099237]

42. Lonn E, Yusuf S, Hoogwerf B, et al. Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes - Results of the HOPE study and MICRO-HOPE substudy. Diabetes Care. 2002; 25(11):1919–27. [PubMed: 12401733]

43. Mayer-Davis EJ, Bell RA, Reboussin BA, et al. Antioxidant nutrient intake and diabetic retinopathy - The San Luis Valley Diabetes Study. Ophthalmology. 1998; 105(12):2264–70. [PubMed: 9855158]

Table 1

Characteristics of study participants by quartile of lutein intake (adjusted for energy intake) among Black and White ARIC Study participants classified as having diabetes and having gradable eye photos at visit 3 (1993–95) (**N=1430**)

Characteristic*	N 1430	Quartile 1 (n=357)	Quartile 4 (n=357)	p-value†
Energy adjusted lutein intake (μg/1000 kcal) mean (SD)		435.2 (165.1)	4853.1 (2695.3)	
Prevalence of retinopathy, n (%) *yes*	298	51 (14.3)	93 (26.1)	**<0.001**
Severity of retinopathy *				**0.004**
None	1132	306 (85.7)	264 (73.9)	
Mild NPDR	222	35 (9.8)	64 (17.9)	
Moderate to severe NPDR	47	9 (2.5)	18 (5.0)	
PDR	29	7 (2.0)	11 (3.1)	
Demographics				
Age (years), mean (SD)	1430	54.6 (5.7)	55.22 (5.4)	**0.05**
Self-reported age at diagnosis *	917	53.5 (9.9)	51.9 (10.4)	**0.004**
Race, n (%) *black*	473	26 (7.3)	186 (52.1)	**<0.001**
Gender, n (%) *female*	732	147 (41.2)	219 (61.3)	**<0.001**
Field center, n (%)				**<0.001**
Forsyth County, NC	332	60 (16.8)	97 (27.2)	
Jackson, MS	406	23 (6.4)	161 (45.1)	
Minneapolis, MN	299	141 (39.5)	21 (5.9)	
Washington County, MD	393	133 (37.3)	78 (21.8)	
Education, n (%)				**<0.001**
Basic or 0 years (high school or less)	397	81 (22.8)	127 (35.6)	
Intermediate (high school/vocational school)	594	183 (51.4)	125 (35.0)	
Advanced (college or higher)	436	92 (25.8)	105 (29.4)	
Health and Lifestyle				
Smoking status, n (%)				0.30
Current	311	77 (21.6)	70 (19.6)	
Former	511	140 (39.3)	120 (33.6)	
Never	607	139 (39.0)	167 (46.8)	
Usual ethanol intake (g/week), mean (SD)	1422	46.4 (127.2)	21.1 (61.5)	**0.002**
Body Mass Index (kg/m2), mean (SD)	1427	30.92 (5.1)	31.7 (6.1)	0.15
Physical activity at work index‡, mean (SD)	1428	2.2 (0.9)	2.1 (1.0)	0.29
Sports in leisure time index‡, mean (SD)	1427	2.3 (0.8)	2.4 (0.7)	0.89
Other leisure time physical activity index‡, mean (SD)	1428	2.3 (0.6)	2.3 (0.6)	0.25
Hypertension§, n (%) *yes*	657	118 (33.2)	192 (54.2)	**<0.001**
High blood cholesterol‖, n (%) *yes*	938	233 (65.4)	228 (64.4)	0.84
Duration of diabetes *, n (%)				**0.02**
< 3 years	319	97 (27.2)	73 (20.4)	
≥3 to <6 years	317	90 (25.2)	71 (19.9)	

Characteristic*	N 1430	Quartile 1 (n=357)	Quartile 4 (n=357)	p-value†
≥6 years	794	170 (47.6)	213 (59.7)	
Blood glucose (mg/dL), mean (SD)	1413	140.4 (51.2)	163.6 (81.9)	**<0.001**
HbA1c* (%), mean (SD)	1430	7.1 (1.9)	7.7 (2.1)	**0.0004**
Diet				
Total energy intake (kcals), mean (SD)	1430	1863.5 (684.9)	1509.5 (531.8)	**<0.001**
Total carbohydrate intake (% kcals), mean(SD)	1430	47.2 (9.4)	49.9 (9.6)	**0.0008**
Total protein intake (% kcals), mean (SD)	1430	17.1 (4.1)	20.0 (4.2)	**<0.001**
Total fat intake (% kcals), mean (SD)	1430	35.4 (7.3)	31.2 (7.0)	**<0.001**
Total saturated fat intake (% kcals), mean (SD)	1430	13.1 (3.2)	11.2 (3.0)	**<0.001**
Total monounsaturated fat intake (% kcals), mean (SD)	1430	13.6 (3.2)	11.9 (3.1)	**<0.001**
Total polyunsaturated fat intake (% kcals), mean (SD)	1430	5.3 (1.7)	4.8 (1.3)	**<0.001**
Total omega fatty acid w20:5 and w22:6 intake (% kcals), mean(SD)	1430	0.2 (0.3)	0.3 (0.3)	**<0.001**
Dietary zinc intake (mg), mean (SD)	1430	12.2 (4.8)	10.9 (4.4)	**<0.001**
Dietary Vitamin C intake (mg), mean (SD)	1430	110.0 (90.5)	156.3 (102.1)	**<0.001**
Dietary α-tocopherol intake (mg), mean (SD)	1430	4.9 (2.7)	5.2 (3.3)	**0.03**
Currently on a special diet, n (%) *yes*	456	81 (22.7)	146 (40.9)	**<0.001**

*All characteristics were assessed at visit 1 except HbA1c (visit2) and retinopathy, duration of diabetes, self-reported age at diagnosis (visit 3)

†p-value for χ^2 test for categorical variables and ANOVA test for continuous variables across all four quartiles of energy adjusted lutein intake

‡On index score ranging from 1–5 based on the ARIC/Baecke physical activity questionnaire[54]

§Average systolic blood pressure ≥140 mm Hg, or diastolic ≥90 mm Hg, or high blood pressure medication use in the past 2 weeks

//Total cholesterol ≥200 mg/dL, or cholesterol lowering medication use in the past 2 weeks (i.e. by medication codes)

Table 2

Crude and adjusted* odds ratios (OR) and 95% confidence intervals (95%CI) for the association between dietary intake of lutein, assessed at visit 1 (1987–89), and severity of diabetic retinopathy (DR) among White and Black ARIC Study participants classified as having diabetes and having gradable eye photos at visit 3 (1993–95) **(N=1430)**

Outcome	**Comparison group**	**Quartile(Q) of Energy Adjusted Dietary Intake of Lutein**				
		Q1 (n = 357)	**Q2 (n = 358)**	**Q3 (n = 358)**	**Q4 (n = 357)**	**p-value for trend†**
Median lutein intake (μg/1000 kcal)		434	1016	1791	4005	
Any retinopathy	**None**					
# with outcome		51	70	84	93	
Crude OR (95%CI)		1 (referent)	1.46 (0.98 – 2.17)	1.84 **(1.25 – 2.70)**	2.11 **(1.45 – 3.09)**	**<0.001**
Adjusted[1] OR (95%CI)		1 (referent)	1.10 (0.69 – 1.75)	1.54 (0.96 – 2.47)	1.41 (0.87 – 2.28)	**0.01**
Moderate/severe NPDR and PDR	**None and mild NPDR**					
# with outcome		16	17	14	29	
Crude OR (95%CI)		1 (referent)	1.06 (0.53 – 2.14)	0.87 (0.42 – 1.81)	**1.88 (1.01– 3.53)**	**<0.001**
Adjusted[1] OR (95%CI)		1 (referent)	0.83 (0.38 – 1.80)	0.68 (0.30 – 1.56)	1.31 (0.60 – 2.85)	**0.01**
Proliferative	**None, mild NPDR, and moderate/severe NPDR**					
# with outcome		7	5	6	11	
Crude OR (95%CI)		1 (referent)	0.71 (0.22 – 2.25)	0.85 (0.28 – 2.56)	1.59 (0.61 – 4.15)	**0.006**
Adjusted[1] OR (95%CI)		NA due to small cell sizes				

*Adjusted for study center, total energy consumption, race, duration of diabetes and HbA1c concentration

†p for trend calculated using energy adjusted lutein as a continuous variable

Ophthalmic Epidemiol. Author manuscript; available in PMC 2016 May 09.

Table 3

Stratified odds ratios * (OR) and 95% confidence intervals (95%CI) for the association between dietary intake of lutein, assessed at visit 1 (1987–89), and diabetic retinopathy (DR) among White and Black ARIC Study participants classified as having diabetes and having gradable eye photos at visit 3 (1993–95) **(N=1430)**

	Quartile(Q) of Energy Adjusted Dietary Intake of Lutein (Range in μg/1000 kcal)				
Group	**Q1 (4 – 715)**	**Q2 (716 – 1359)**	**Q3 (1364 – 2590)**	**Q4 (2605 – 19813)**	**p-value for trend‡**
Stratified by race					
Black (n=473)					
# with DR / # in group	3/26	28/105	44/156	58/186	
Adjusted * OR (95%CI)	1 (referent)	1.61 (0.37 – 7.06)	2.88 (0.65 – 12.67)	2.29 (0.53 – 9.86)	0.14
White (n=957)					
# with DR / # in group	48/331	42/253	40/202	35/171	
Adjusted * OR (95%CI)	1 (referent)	1.17 (0.69 – 1.97)	1.32 (0.76 – 2.30)	1.36 (0.77 – 2.43)	**0.04**
p for interaction					0.40
Stratified by HbA1c level †					
>7% (inadequate glycemic control) (n=629)					
# with DR / # in group	42/130	59/158	73/161	77/180	
Adjusted * OR (95%CI)	1 (referent)	1.10 (0.65 – 1.87)	1.47 (0.85 – 2.53)	1.22 (0.71 – 2.13)	**0.04**
≤7% (adequate glycemic control) (n=801)					
# with DR / # in group	9/227	11/200	11/197	16/177	
Adjusted * OR (95%CI)	1 (referent)	1.12 (0.44 – 2.83)	1.08 (0.41 – 2.87)	1.64 (0.65 – 4.15)	0.16
p for interaction					0.47
Stratified by duration of diabetes					
< 6 years (n=636)					
# with DR / # in group	11/187	8/157	6/148	8/144	
Adjusted * OR (95%CI)	1 (referent)	0.82 (0.31 – 2.16)	0.67 (0.22 – 2.04)	0.89 (0.31 – 2.50)	0.72
≥6 years (n=794)					
# with DR / # in group	40/170	62/201	78/210	85/213	
Adjusted * OR (95%CI)	1 (referent)	1.22 (0.71 – 2.08)	1.87 (**1.08 – 3.21**)	1.58 (0.91 – 2.75)	**0.01**
p for interaction					0.20

[*] All analyses are adjusted for study center, total energy consumption, race, duration of diabetes and HbA1c levels excluding the characteristic on which it is being stratified

[†] Glucose control defined as adequate if HBA1C ≤7% and inadequate if HBA1C >7% according to recommendations by the American Diabetes Association[55]

[‡] p for trend calculated using energy adjusted lutein as a continuous variable