ARIC Manuscript Proposal #2186

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1.a. Full Title: Associations between dietary intake of lutein and zeaxanthin and diabetic retinopathy in a biracial cohort

b. Abbreviated Title (Length 26 characters): Lutein and diabetic retinopathy

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MS **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Analyses are planned to be completed between August 2013 and May 2014.

4. Rationale:

Diabetic retinopathy

Dramatic increases in diabetes are taking place both across the world and locally. Along with these increases in prevalence of diabetes, it can be expected that complications due to diabetes will increase as well. (1, 2) Data originating from 35 studies of diabetic retinopathy in multiple countries extrapolated to the global diabetic population approximated that, in 2010, there were 93 million people with some type of diabetic retinopathy worldwide (~35% of all people with diabetes). This same analysis estimated that ~10% of the world's diabetic population had retinopathy advanced enough to endanger their vision. (3) Applying this data to future projections for global prevalence of diabetes, Zheng et al. estimates that, in 2030, there will be over 191 million people with diabetic retinopathy over 55 million of which will have compromised vision. (4) Poor blood glucose control, high blood pressure and longer duration of diabetes have been shown to be risk factors for diabetic retinopathy, however, they do not account for a large part of the variability in developing this complication of diabetes. Identification of additional risk factors, and particularly modifiable risk factors, may help reduce the burden of diabetic retinopathy.

Diabetic retinopathy, oxidative stress and inflammation

In people with diabetes excess glucose accumulates in the blood due to an inability to produce insulin and/or the inability to use insulin. There are a number of proposed pathways by which excess glucose, or the state of hyperglycemia, can lead to damage to the microvasculature of the retina indicative of diabetic retinopathy, such as increased permeability due to disruption of the blood brain barrier, loss of pericytes, increased endothelial cell production and neovascularization.(5) Many of these proposed pathways, along with additional pathways involving hypertension and hyperlipidemia involve oxidative stress, inflammation, cell death or a combination of these factors to induce damage to cells in the retinal vasculature, the cumulative effect of which may be severe enough to threaten or cause loss of sight.(5, 6)

The retina is highly susceptible to oxidative stress because its tissues have a high proportion of polyunsaturated fatty acids which are prone to peroxidation, high oxygen uptake, high glucose oxidation, and irradiation from visible light.(7) Reactive oxygen species (ROS) are regularly produced by cells by way of the mitochondrial transport chain, cytochrome P450, the NAD(H) oxidases and nitric oxide synthases during normal cell functioning. (8) Additional ROS can originate from outside sources such as light exposure.(7) ROS are normally destroyed by the cell's antioxidant defensive system but an overproduction of ROS, or an inefficient ROS scavenging system could lead to an overabundance of ROS described as oxidative stress. Prolonged oxidative stress can harm molecules within a cell such as DNA, RNA, and macromolecules. This damage, if not repaired, can lead to production of even more ROS which, if persistent, can result in retinal tissue damage and possibly disease. (8)

Inflammation is a response to tissue damage or what the immune system perceives as foreign substances. This response involves complex chemical reactions (i.e. release of inflammatory agents) that result in the seepage of fluid from the blood vessels into the surrounding tissue and recruitment of leukocytes to the area of damaged tissue.(9) In the diabetic state, inflammation is a hallmark of a diabetic state.(10) This is supported by evidence showing increased circulation of inflammatory agents, such as tumor necrosis factor α (TNF-α), interleukin (IL)-6 and C-reactive protein (CRP), in people with type 2 diabetes.(10) Leukocytes, associated with this inflammation, may play an important role in the pathogenesis of retinopathy. Presence of these leukocytes, along with changes to the endothelial cells of the microvasculature due to hyperglycemia, are thought to result in blocked capillaries that results in decrease retinal blood flow through them.(11) This process is thought to lead to hypoxia and the resultant angiogenesis seen in diabetic retinopathy.

Lutein and Zeaxanthin

Lutein and zeaxanthin are the only carotenoids found in the retina. These carotenoids prevent damaging blue light from reaching structures in the back of the eye because their chemical structure is such that they absorb blue light. This reduction in the intensity of blue light may reduce oxidative stress on the retina.(12) Lutein and zeaxanthin may also reduce oxidative stress by being preferentially oxidized to form a radical cation then reacting with ascorbate to regain its lost electron and return to its original state ready to be oxidized again in place of substances such as polyunsaturated fatty acids, nucleic acids and proteins that are integral to cell structure.(12) Results of both animal and human studies suggest that lutein is associated with decreased oxidative stress and inflammation, both in the eye and systemically.

Animal studies have shown that lutein supplementation decreases oxidative stress and inflammatory markers.(13, 14) Among nineteen Guinea pigs fed a high cholesterol diet known to induce oxidative stress and inflammation, animals supplemented with lutein for 12 weeks, versus those not supplemented, were found to have significantly lower levels of both hepatic and ocular malondialdehyde, a marker of oxidative stress concentrations and lower hepatic and ocular levels of the inflammatory cytokines (TNF-α, IL-1β and monocyte chemotactic protein-1).(13) Similarly, spleens of turkeys that were administered lutein were found to have lower levels of IL-10, an anti-inflammatory cytokine, and higher levels of IL-1 β, a pro-inflammatory cytokine, than those not given lutein.(14)

In humans, serum lutein and zeaxanthin levels were inversely associated with circulating leukocyte counts and CRP, both markers of inflammation, in a cross-sectional analysis of data collected from 4,580 black and white, females and males aged 18-30 years in the Coronary Artery Risk Development in Young Adults study. This same study found a positive association between lutein and zeaxanthin and superoxide dismutase, an enzyme with antioxidant properties, and inverse associations between circulating lutein and zeaxanthin and F2-isoprostane (a marker of oxidative stress), p-selectin (though non-

significantly) and soluble intercellular adhesion molecule-1 (both cell adhesion molecules that are also markers of inflammation).(15)

Epidemiologic Evidence of an Association between Lutein and Zeaxanthin, and Diabetic Retinopathy,

Although there have been studies investigating the association between the carotenoids lutein and zeaxanthin and eye diseases such as age-related macular degeneration and cataract, there have been few studies regarding the association between lutein and zeaxanthin and diabetic retinopathy (16). The few published studies investigating this relationship have been done in animal models (17), small studies in humans (n<125) (16, 18) and in studies using supplements containing more than lutein and zeaxanthin (19). Despite their limitations, the results of these studies suggest that lutein and zeaxanthin may be beneficial in preventing retinopathy and its progression.

One such study was conducted in rats with streptozotocin induced diabetes.(17) The authors found higher concentrations of zeaxanthin in the retinas of rats fed a diet supplemented with zeaxanthin from 3 days to 8 weeks of age than in the retinas of unsupplemented, control rats. The retinas of the supplemented compared to unsupplemented rats were also found to have lower levels of certain markers of oxidative stress (e.g., lactoperoxidase, 8-hydroxy-2'-deoxyguanosine and nitrotyrosine) and higher levels of mitochondrial complex III. Suppression of mitochondrial complex III is thought to increase superoxide, a free radial, in the retina.

A cross-sectional study investigated the associations between plasma carotenoids and diabetic retinopathy among 78 individuals with diabetes and no retinopathy and 33 persons with diabetes and retinopathy (18). They found that, while higher plasma pro-vitamin A levels were associated with higher odds of retinopathy (OR=2.97, 95% CI: 1.00-8.79), a higher non-pro-vitamin A to pro-vitamin A ratio (including lycopene, lutein and zeaxanthin) was associated with a lower odds of retinopathy independent of other risk factors (OR=0.33, 95%CI: 0.12-0.95). This suggests that increasing plasma levels of lycopene, lutein and zeaxanthin may be protective against retinopathy.

A five year clinical trial conducted among 105 people with diabetes having non-proliferative retinopathy investigated the effects of antioxidant supplementation on diabetic retinopathy and found that retinopathy did not significantly progress in the supplemented group (p=0.08) but did in the control group (p=<0.01).(19) Supplements used in this trial contained lutein and zeaxanthin, however they also contained other antioxidants making it impossible to attribute the effects seen to one specific component.

In a small clinical trial (n=90) researchers compared serum concentrations of lutein and zeaxanthin between three groups: healthy volunteers, a control group of persons with diabetes that had non-proliferative diabetic retinopathy (NPDR) and a group of persons with diabetes given lutein and zeaxanthin supplementation with NPDR (16). At baseline, those with NPDR had significantly lower serum lutein and zeaxanthin levels (lutein = 0.07 μg/mL and zeaxanthin = 0.014 μg/mL) than healthy subjects (lutein = 0.23 μg/mL and zeaxanthin = 0.05 μg/mL). After three months of supplementation with 6mg/d lutein

and 0.05mg/d zeaxanthin the test group's mean serum concentration increased to 0.54 μg/mL of lutein and 0.28 μg/mL of zeaxanthin while the control group with NPDR remained the same as at baseline.(16).Using optical coherence tomography, they found that foveal thickness, shown to be greater in those with retinopathy (20), was reduced in 83% of those who underwent lutein and zeaxanthin supplementation than in persons with diabetes that were not supplemented.(16).

In the Atherosclerosis Risk in Communities (ARIC) Study we have the opportunity to investigate associations between dietary intake of lutein and zeaxanthin, assessed from 1987-89) and diabetic retinopathy, assessed from 1993-96) in a large population-based cohort of Caucasian and African American men and women with primarily Type 2 diabetes (n=1,572). Supplements containing lutein and/or zeaxanthin were not on the market at this time and thus exposure to lutein and zeaxanthin is coming exclusively from the diet. Diabetic retinopathy was assessed from grading of a single fundus photograph of one randomly chosen eye taken approximately three years after the collection of dietary intake. We also have the availability of numerous medical and lifestyle variables to explore as potential confounding factors or effect modifiers of this relationship.

5. Main Hypothesis/Study Questions:

Main Study Question
Is there an association between intake of lutein and zeaxanthin, assessed at Visit 1 (1987-1989), and the presence of diabetic retinopathy assessed at Visit 3 (1993-1995) among 1,572 individuals with prevalent diabetes at Visit 3?

Main Hypotheses

Hypothesis 1: The odds of diabetic retinopathy are higher in those with low, as compared to high, dietary intake of lutein and zeaxanthin.

Hypothesis 2: The odds of more severe diabetic retinopathy are higher in those with low as compared to high dietary intake of lutein and zeaxanthin.

Additional Study Questions
Does race, gender, or blood glucose control modify the association between lutein and zeaxanthin and diabetic retinopathy?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Sample
Our study sample will include those participants categorized by ARIC as having diabetes at visit 3 with readable fundus photographs (i.e., retinal photographs) and having completed a food frequency questionnaires at visit 1 (n=1572). Participants were categorized as having diabetes if they had a non-fasting blood glucose concentration

≥200 mg/dl, a fasting blood glucose concentration of ≥ 126mg/dl, reported being told by a physician that they had diabetes and/or were on blood glucose lowering medication in the two weeks prior to the study visit.(21)

Prevalent retinopathy was determined from grading of a retinal photographs taken at Visit 3 (1993-1995) of one randomly selected eye. Participants sat in a dark room for 5 minutes to allow for non-pharmocological pupil dilation (22). One 45-degree nonmydriatic retinal photograph was taken with a Canon CR-45UAF nonmydriatic film camera (Canon USA, Itasca, IL) and was centered to include the optic disc and the macula (22). Retinal photographs were graded for the presence and severity of diabetic retinopathy at the University of Wisconsin Fundus Photograph Reading Center using a standard grading system for participants, the modified Arlie House classification scheme (23). The eyes were graded for presence or absence of retinopathy as well as its severity when present.

Assessment of Dietary Intake of Lutein and Zeaxanthin

At Visits 1 (1987-89) and Visit 3 (1993-1995) a "Dietary Intake Form" was administered to participants and inquired about diet habits and included a 66 food frequency questionnaire (FFQ). This FFQ was adapted from a 61 FFQ developed by Willet et al. Deviations from Willett's original 61 item FFQ were mainly due to the addition of questions about fish consumption and questions on cooking fats. (24) This FFQ was previously validated by Willet et al in 173 women from the Nurse's Health Study. (25) The FFQ was administered by an interviewer using props to assist participants in selecting the portion sizes usually consumed. Lutein and zeaxanthin intake was determined using information from the 66 item FFQ and was supplied as a sum of both carotenoids. Participants' lutein and zeaxanthin intakes will be adjusted for energy intake using the multivariate nutrient density method, as described by Hu et al.(26) in which nutrient values are standardized to 1000 kcals consumed. The validity of self-reported nutrient intake from FFQs has been shown to improve after adjustment is made for energy intake. (27)

For our primary analyses we will examine the association between lutein and zeaxanthin intake assessed at Visit 1 and prevalent retinopathy assessed at Visit 3. While temporality between exposure and outcome cannot be established, we will use the FFQ at Visit 1 as a measure of diet 6 years prior to assessment of prevalent retinopathy status. Additionally, diet at this visit was chosen to be used as the primary exposure because it may be more likely to represent usual diet in the participant's life prior to knowledge of diabetic complications.

Proposed analysis

Assessing the distribution of characteristics in the study sample

We will create quartiles of dietary intake of lutein and zeaxanthin which will result in ~400 participants in each quartile and give us ~0.80 power to observe an OR of 0.60 at a p-value of 0.05 when comparing the highest to the lowest quartile of lutein and zeaxanthin intake (power calculations shown on **table 1)**. We chose quartiles for this analysis to obtain a balance between power and the ability to differentiate between high and low intake of lutein. The distribution of characteristics and potential risk factors in the study sample, most of which were assessed at Visit 1, will also be examined

according to quartile of lutein and zeaxanthin intake and prevalence and severity of retinopathy (none, mild NPDR, moderate to severe NPDR and proliferative diabetic retinopathy (PDR)).

Analyses of the distribution of covariates within the study sample by quartile of lutein and zeaxanthin intake and prevalence or severity of diabetic retinopathy will be performed using χ^2 tests for categorical variables and t-tests or ANOVA for continuous variables as appropriate. Those covariates whose distributions do not meet the assumptions of these tests will be investigated using nonparametric tests. Differences in the distribution of these variables will be considered significant at a p-value of 0.05 or lower.

Analysis of the association between dietary intake of lutein and zeaxanthin and prevalence of retinopathy

The association between lutein and zeaxanthin intake and prevalence of retinopathy will be investigated using a logistic regression model. We will first create a univariate model using dietary lutein and zeaxanthin, adjusted for total energy intake, as the independent variable and retinopathy (no = 0 and yes = 1) as the dependent variable and calculate crude odds ratios (OR) and 95% confidence intervals (95% CI) comparing the highest quartile of lutein and zeaxanthin intake to the lowest quartile of lutein and zeaxanthin intake.

Next, using the tables created when characterizing the population, we will consider those characteristics statistically significantly different between groups at the 0.20 α level for both the exposure and outcome for evaluation as potential confounders, along with hemoglobin A1c (HbA1c), blood pressure and duration of diabetes as these are strong predictors of retinopathy. HbA1c was assessed at Visit 2 only.

We will create bivariate models introducing each potential confounder into the crude model separately, again calculating ORs and 95% CIs for each model. We will adjust for potential confounders that change the crude OR, comparing the highest quartile of lutein and zeaxanthin intake to the lowest quartile, by at least 10%. Assumptions for use of the logistic model will be tested in this adjusted model. This final adjusted model will be the model used in the analysis of the association between lutein and zeaxanthin intake and prevalence of retinopathy as well the analysis of the association between lutein and zeaxanthin intake and severity of retinopathy.

Table 1. Power (%) to detect noted odds ratio for prevalent diabetic retinopathy when comparing the odds of retinopathy among 1,572 participants (n=338 with retinopathy) in the highest compared to the lowest quartile of dietary intake

Odds Ratio	**0.60**	**0.65**	**0.70**	**0.75**	**0.80**	**0.85**	**0.90**
Power (%)	0.80	0.66	0.50	0.35	0.23	0.15	0.09

Limitations and possible solutions

Although we will be using dietary data and data on potential confounders collected at the first ARIC study visit ~6 years prior to the assessment of diabetic retinopathy temporality cannot be established since participants' retinopathy status was unknown at baseline.

Another limitation of our data is the availability of retinal photographs in only one eye using film at Visit 3 for classification of retinal eye disease. Therefore, there may be misclassification of retinopathy status. As the eye chosen to be photographed at Visit 3 was done so randomly, we would expect non-differential misclassification of our endpoint which would bias our observed risk estimates toward the null.

Our study sample consists of participants that were classified as having diabetes by the ARIC investigators at visit 3. This classification was based on self-report of diagnosis of diabetes, medication use and/or one fasting or non-fasting blood glucose measurement. There is the potential for misclassification of diabetes status in the study that could result in people without diabetes being included in the sample or those with diabetes being excluded from the sample. This misclassification is likely to be non-differential and could result in an underestimation of the association between lutein and zeaxanthin intake and retinopathy. We will explore the potential effects of this misclassification by conducting a sensitivity analysis in which those participants that were classified as having diabetes at only one visit (e.g., Visit 1, 2 or 3) are removed.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?
__X__ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ Yes __ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___x___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11.

Other relevant proposals are those that focus on diabetic retinopathy and would involve Dr. Ronald Klein. Dr. Klein is a co-author on this work.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study

_X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.15)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

Works Cited

1. World Health Organization. Diabetes Factsheet. In: Organization WH, editor.; 2012. p. WHO Diabetes Factsheet.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice 2010;87(1):4-14.
3. Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. Diabetes Care 2012;35(3):556-564.
4. Zheng YF, He MG, Congdon N. The worldwide epidemic of diabetic retinopathy. Indian Journal of Ophthalmology 2012;60(5):428-431.
5. Ciulla TA. Epidemiology and impact of diabetic retinopathy. Advanced Studies in Medicine 2004;4:694-701.
6. Ola MS, Nawaz MI, Siddiquei MM, Al-Amro S, Abu El-Asrar AM. Recent advances in understanding the biochemical and molecular mechanism of diabetic retinopathy. Journal of Diabetes and Its Complications 2012;26(1):56-64.
7. 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):115-134.
8. Kowluru RA, Chan PS. Oxidative Stress and Diabetic Retinopathy. Experimental Diabetes Research 2007.
9. Anonymous. Immune Response. In: U.S. Department of Health and Human Services National Institutes of Health, editor. A.D.A.M. Medical Encyclopedia [Internet] -. Atlanta (GA): : A.D.A.M., Inc.; 2013.
10. Calle MC, Fernandez ML. Inflammation and type 2 diabetes. Diabetes & Metabolism 2012;38(3):183-191.
11. Chibber R, Ben-Mahmud BM, Chibber S, Kohner EM. Leukocytes in diabetic retinopathy. Curr Diabetes Rev 2007;3(1):3-14.
12. Krinsky NI, Landrum JT, Bone RA. Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. Annual Review of Nutrition 2003;23:171-201.
13. Kim JE, Clark RM, Park Y, Lee J, Fernandez ML. Lutein decreases oxidative stress and inflammation in liver and eyes of guinea pigs fed a hypercholesterolemic diet. Nutrition Research and Practice 2012;6(2):113-119.
14. Shanmugasundaram R, Selvaraj RK. Lutein supplementation alters inflammatory cytokine production and antioxidant status in F-line turkeys. Poultry Science 2011;90(5):971-976.
15. Hozawa A, Jacobs DR, Steffes MW, Gross MD, Steffen LM, Lee DH. 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. Clinical Chemistry 2007;53(3):447-455.
16. Hu BJ, Hu YN, Lin S, Ma WJ, Li XR. Application of Lutein and Zeaxanthin nonproliferative diabetic retinopathy. International Journal of Ophthalmology 2011;4(3):303-306.

17. Kowluru RA, Menon B, Gierhart DL. Beneficial effect of zeaxanthin on retinal metabolic abnormalities in diabetic rats. Investigative Ophthalmology & Visual Science 2008;49(4):1645-1651.
18. Brazionis L, Rowley K, Itsiopoulos C, O'Dea K. Plasma carotenoids and diabetic retinopathy. British Journal of Nutrition 2009;101(2):270-277.
19. Garcia-Medina JJ, Pinazo-Duran MD, Garcia-Medina M, Zanon-Moreno V, Pons-Vazquez S. A 5-year follow-up of antioxidant supplementation in type 2 diabetic retinopathy. European Journal of Ophthalmology 2011;21(5):637-643.
20. Goebel W, Kretzchmar-Gross T. Retinal thickness in diabetic retinopathy - A study using optical coherence tomography (OCT). Retina-the Journal of Retinal and Vitreous Diseases 2002;22(6):759-767.
21. Atherosclerosis Risk in Communities (ARIC) Study Research Group. Exam 3 Derived Variable Dictionary Version 37. In: Atherosclerosis Risk in Communities (ARIC) Study Research Group.; 2010.
22. Klein R, Clegg L, Cooper LS, Hubbard LD, Klein BE, King WN, et al. Prevalence of age-related maculopathy in the Atherosclerosis Risk in Communities Study. Arch Ophthalmol 1999;117(9):1203-10.
23. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98(5 Suppl):786-806.
24. Atherosclerosis Risk in Communities (ARIC) Study Research Group. Manual 2 - Cohort Component Procedures Version 2.0. In. Chapell Hill, NC: The ARIC Coordinating Center; 1988.
25. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. American Journal of Epidemiology 1985;122(1):51-65.
26. Albandar JM. Global risk factors and risk indicators for periodontal diseases. Periodontology 2000 2002;29:177-206.
27. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires - The eating at America's table study. American Journal of Epidemiology 2001;154(12):1089-1099.