ARIC Manuscript Proposal #2473

PC Reviewed: 12/9/14	**Status: A**	**Priority: 2**
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1.a. Full Title: Association between Dietary Xanthophyll Intake and Prevalent Early Age-Related Macular Degeneration

b. Abbreviated Title (Length 26 characters): Xanthophylls, HDL, and AMD

2. Writing Group:

Writing group members:

University at Buffalo: Henry Lin, BS (UB*) (paper lead), Amy Millen, PhD (UB), Michael LaMonte, PhD (UB), William Brady, PhD (UB), Michelle Sahli, MS (UB)

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All writing group members, with the exception of Dr. Brady (statistician) and Henry Lin, are co-investigators, consultants, programmers or research assistants on the R01 (ARIC Ancillary Study 2010.20) funding this project "Vitamin D Status and Retinal Diseases in Aging." Henry Lin is a master's student in the Department of Epidemiology and Environmental Health (advised by Dr. Millen) as well as an MD/PhD candidate at UB.

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

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3. Timeline: Analyses are planned to be completed between April and June 2015.

4. Rationale:

Age-related macular degeneration

Age-related macular degeneration (AMD) is the third leading cause of blindness worldwide, accounting for 5% of total blindness in 2010.[1] A recent meta-analysis estimated the global prevalence of AMD to be 8.7%, and projected that the burden of disease will rise exponentially over the next few decades given the current trends of population aging.[2] Moreover, in industrialized regions with better access to eye care[3,4] and the lowest proportions of blindness,[5] AMD remains the foremost cause of severe visual impairment in older adults,[6,7] and approximately 50% of blindness may be attributable to AMD.[5]

AMD is characterized by the formation of drusen in the subretinal space, between the retinal pigment epithelium (RPE) and Bruch's membrane. Drusen are insoluble extracellular aggregates partially composed of cellular remnants, lipoproteins, and immune complexes.[8] The presence of drusen is thought to incite autoimmune[9-11] and inflammatory responses[8,12-14] that damage the RPE as well as the overlying retina and photoreceptors, resulting in lesions with a depigmented, erosive appearance (geographic atrophy) on fundoscopic examination.[15] AMD severity is classified by the number and size of drusen, the extent of geographic atrophy, and the occurrence of aberrant choroidal neovascularization.[16] Early AMD is defined by the presence of medium-sized (63-124μm) and large drusen (>124 μm) with or without pigmentary abnormalities, while late or advanced AMD is defined by the presence of geographic atrophy or of choroidal neovascularization (neovascular AMD).[16] Neovascular AMD represents only 10-15% of prevalent late AMD, but contributes to >80% of legal blindness (i.e. visual acuity <20/200) in AMD patients.[17] In addition, while the clinical course of non-neovascular AMD tends to be insidious, neovascular AMD could result in rapid visual decline; proliferation of fragile, immature vessels increases the risk of hemorrhage or fluid accumulation, which in turn could lead to subretinal fibrosis or retinal detachment.[18-20] While intravitreal injection of vascular endothelial grow factor (VEGF) inhibitors[21,22] and laser photocoagulation[23] may slow or limit the progression of neovascular AMD, these treatments do not reverse most of the existing damage to the macula. *These findings, along with the absence of established therapies for geographic atrophy, highlight the importance of AMD prevention, particularly in an aging population.*[24]

Research suggests that that oxidative stress may be involved in AMD pathogenesis.[12,25-27] The RPE serves various supportive functions critical to the health of the retina, including phagocytosis of lipid-rich mature photoreceptor outer segments; uptake of glucose, carotenoids and lipoproteins; and maintenance of pH and fluid homeostasis.[28,29] However, the close proximity of RPE to phototransduction processes renders it highly susceptible to free radical injury. Specifically, light-induced formation of reactive oxygen species[30,31] and lipid peroxides[32-35] could directly damage RPE cells, resulting in the accumulation of metabolic waste. Together with free radicals, these compounds could activate the complement system[36] and cellular stress response pathways,[37] as well as recruit inflammatory mediators such as macrophages and T-cells.[27,38-40] Immune complex deposition then exacerbates structural injury and intensifies the inflammatory cascade, culminating in RPE dysfunction that promotes anomalous lipid deposition and angiogenesis, each distinctive characteristics of AMD progression.[41,42]

Dietary xanthophyll intake and age-related macular degeneration

Dietary intake of the xanthophyll pigments – lutein and zeaxanthin – may play an essential role in limiting oxidative stress in the retina and the RPE.[43,44] Xanthophylls are obtained from the diet or from supplements, and are concentrated in foods such as dark leafy greens, corn, squash, broccoli, peas and egg yolks.[45,46] They are the predominant carotenoids found in the macula,[47] and are concentrated in the outer plexiform layer overlying the photoreceptors.[48] Xanthophylls are strongly absorptive of blue light, thereby reducing the amount of high-energy radiation that reaches the posterior retina and the RPE.[49] Their molecular structure also allows them to interact with free radicals via non-photochemical reactions that dissipate the transferred energy as heat (physical quenching),[50] as well as to directly scavenge both singlet oxygen species[51] and lipid peroxides[52] via autoxidative processes (chemical quenching). Lastly, xanthophylls may have immunosuppressive and anti-inflammatory effects. Both *in vitro* studies using human cells[53,54] and *in vivo* studies using animal models[55-57] have demonstrated that lutein and zeaxanthin supplementation may influence the expression of inflammation-related genes associated with AMD, including complement factor H (CFH),[58-61] interleukin 8 (IL-8),[62-65] monocyte chemoattractant protein 1 (MCP-1),[65-67] and nuclear factor kappa-light-chain enhancer of B cells (NF-κB).[68] Lutein supplementation has been shown to decrease circulating levels of complement factors and inflammatory cytokines in humans.[69,70] Furthermore, a dietary intervention that increases plasma xanthophylls has been found to decrease lipid peroxidation in humans.[71]

Randomized trials of lutein and zeaxanthin supplementation have been shown to: 1) increase average xanthophyll retinal concentrations as measured by macular pigment optical density (MPOD),[72-74] 2) preserve visual acuity in early AMD,[74-76] and 3) decrease progression to advanced AMD when replacing beta carotene in individuals receiving a high-dose antioxidant regimen as well as in study participants who had low dietary intake at the start of the trial.[77] No clinical trial has investigated whether xanthophyll supplementation decreases risk of early AMD. Prospective cohorts have shown that xanthophyll intake is positively related to MPOD[78,79] and may be protective against neovascular AMD.[80,81] While only one study has found a relationship between xanthophyll intake and advanced AMD (both choroidal neovascularization and central geographic atrophy),[82] the pooled estimate from a meta-analysis of five previous studies suggest a significant negative association.[83] With the exception of the Blue Mountains Eye Study,[78] xanthophyll intake did not appear to influence the incidence of early AMD in various cohorts (i.e. Rotterdam Study, Beaver Dam Eye Study, Nurses' Health Study, and Health Professionals Study).[81,84-86] However, a cohort that initially found no association between xanthophyll intake and prevalence of early/intermediate AMD in postmenopausal women observed a significant inverse relationship after restricting the analyses to younger participants with stable dietary intake and without a history of chronic diseases (e.g. cardiovascular disease, diabetes and hypertension) that frequently lead to dietary changes.[87] In addition, there is evidence to suggest that xanthophyll intake may be associated with the development of retinal pigmentary abnormalities, a hallmark of early AMD, though the results have also been mixed.[84,88,89]

Genetic susceptibility as a potential effect modifier

Inconsistent results between xanthophyll intake and early AMD could reflect the presence of unmeasured effect modifiers. In particular, differential genetic susceptibility could modify the relationship between dietary xanthophyll intake and early AMD. Though the subject remains under vigorous debate, a randomized trial showed that the effects of antioxidant supplementation on AMD progression may vary by CFH and ARMS2 genotype.[90-92] Pooled analysis of the Blue Mountains Eye Study and Rotterdam Study further demonstrated that increased xanthophyll intake reduced incidence of early AMD only among individuals at higher genetic risk, as determined by the genotypes of the CFH rs1061170 and ARMS2 rs10490924 polymorphisms.[93] Interestingly, homozygosity at these two loci has

also been linked to lower MPOD, independent of serum xanthophyll levels.[94] Whether CFH and ARMS2 interact with xanthophyll intake to influence early AMD risk thus warrants further consideration.

High-density lipoprotein metabolism as a potential effect modifier

Perturbations in lipid metabolism have been implicated in AMD pathogenesis. Lipid deposits lining Bruch's membrane precede the formation of drusen,[95] and occupy a significant fraction (37-44%) of drusen volume.[96] Low-density lipoprotein (LDL) is responsible for the majority of cholesterol delivery to the retina.[97] However, high-density lipoprotein (HDL) also participates in cholesterol trafficking to the retina,[97] *and is the predominant carrier of circulating xanthophylls*.[114,115] Research further suggests that HDL has antioxidant and anti-inflammatory properties,[98,99] and may be involved in complement regulation.[100]

While some studies have found inverse associations between total HDL concentration (HDL-c) and AMD,[101-104] others have reported positive[105-112] or null[113-118] associations. In addition, though HDL-c has been positively associated with plasma xanthophyll levels,[119-124] most studies have found HDL-c to be unrelated to MPOD.[119-121,125] At the same time, some genetic polymorphisms in the HDL pathway may decrease AMD risk and/or increase plasma xanthophyll levels without influencing HDL-c.[126,127] Apolipoprotein A1 (apoA1) is the major protein component of HDL, and mediates reverse cholesterol transport from macrophage-derived foam cells in the periphery back to the liver.[100] Additionally, a recent *in vitro* study showed that ApoA1 may facilitate intestinal uptake of xanthophylls by HDL.[128] Measurement of serum ApoA1 is more reliable than that of HDL-c, as it is not influenced by concomitant triglyceride levels.[129] Serum ApoA1 concentrations have further been inversely related to cardiovascular disease,[130-132] diabetes,[133-136] and chronic kidney disease.[137,138] Interestingly, larger and lighter HDL particles (HDL2 subfraction) tend to carry higher concentrations of xanthophylls and apoAI[129] than smaller and denser HDL particles (HDL3 subfraction).[139] HDL2 concentration has further been inversely related to cardiovascular disease[140] and diabetes mellitus,[141] systemic diseases associated with higher risk for AMD.[117,142-144] Collectively, these findings indicate that serum HDL-c and other serum biomarkers of HDL metabolism may help define HDL metabolism, that systemic and intraretinal xanthophyll transport by HDL are related but distinct processes, or that HDL may influence AMD risk via non-lipid factors.

More work is needed to better understand the association between xanthophyll intake and early AMD. The interactive effects of CFH rs1061170, ARMS2 rs10490924, and dietary xanthophyll intake on AMD have not been thoroughly explored, and to our knowledge, previous studies have not examined the association between xanthophyll intake and early AMD by HDL-c or other serum biomarkers of HDL metabolism:

5. Main Hypothesis/Study Questions:

The aims of our study are two-fold:

Main Study Question 1:

Is there an association between dietary xanthophyll (lutein and zeaxanthin) intake, assessed at visit 1 (1987-1989) and prevalence of early AMD, assessed at visit 3 (1993-1995)?

Main Study Question Hypothesis:

We hypothesize that participants with higher compared to lower xanthophyll intake will have lower odds for early AMD.

Exploratory Study Question 1*:*
Is the association between dietary xanthophyll intake and early AMD modified by CFH rs1061170 and ARMS2 rs10490924?

Exploratory Study Question 1 Hypothesis:
We hypothesize that higher xanthophyll intake will be associated with lower odds of early AMD only among participants at high genetic risk (≥2 alleles of either CFH rs1061170 C or ARMS2 rs10490924 T).

Exploratory Study Question 2:
Is the association between dietary xanthophyll intake and AMD modified by measures of HDL cholesterol levels (HDL-c) and other serum biomarkers of HDL metabolism (HDL2 and apolA1)?

Exploratory Study Question 2 Hypothesis:
We hypothesize that higher xanthophyll intake will be associated with lower odds of early AMD only among participants with high HDL-c, HDL2 or apolipoprotein A1.

Additional Study Questions
We will evaluate whether the pattern of results varies by race.

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).

Disease endpoints
Prevalent AMD was determined via fundus photographs taken at visit 3 (1993-1995), using a non-mydriatic automatically focusing camera (Canon CR-45UAF). Patients were asked to sit in a darkened room for 5 minutes, after which the camera was centered on the region between the optic disc and the fovea, and a nonstereoscopic 45-degree retinal image was obtained of one eye without the use of pharmacologic dilation. Fundus photographs were evaluated by a masked grader at the University of Wisconsin Fundus Photograph Reading Center for the presence of soft drusen >63μm in diameter, RPE and retinal hypo-/hyperpigmentation, geographic atrophy, and neovascular AMD. Gradable fundus photographs were obtained from 11,532 of 12,887 eligible participants (89.5%). Of these, 596 (5.2%) exhibited signs of any AMD, 581 (5.0%) showed signs of early AMD, and 15 (0.13%) showed signs of advanced AMD.[145] Given the low prevalence of advanced AMD, the primary endpoint variable will be defined as the presence of early AMD.

Assessment of dietary xanthophyll intake
A 66-item food frequency questionnaire (FFQ) completed at visit 1 (1987-89) will be used to estimate dietary intake of lutein and zeaxanthin. This instrument was modified from a version developed by Willet *et al*, and its validity and reliability has been demonstrated.[146,147] Dietary xanthophyll intake will be adjusted for total energy intake. Participants with implausible total energy intake or with ≥10 (≥15%) missing values on the FFQ will be excluded.[148] Dietary supplements of these compounds were not available during the time of the study. Dietary xanthophyll intake will be operationalized as a categorical variable (e.g. greater or less than race-median combined lutein and zeaxanthin intake per the results of

previous National Health and Nutrition Examination Surveys,[88,149] and by quintiles). We will also examine associations between continuous concentrations of xanthophyll intake and prevalent early AMD. FFQ data gathered at visit 3 (1993-95) will also be used to explore associations between AMD and xanthophyll intake at visit 3, using the averaging intake from visits 1 and 3, and among those whose xanthophyll intake changed minimally from visits 1 and 3 (defined using change between quintiles at both time points).

Genetic data: Genotyping of single nucleotide polymorphisms (SNPs) in ARIC was completed using the Affymetrix Genome-Wide Human SNP Array 6.0.[150] Data are available on two high risk SNPs (*CFH* Y402H [rs1061170] and *ARMS2* A69S [rs10490924]) shown to be associated with increased risk of early AMD.[151] We will use this data to explore whether either variant confounds or modifies the association between xanthophyll intake and AMD.

Assessment of serum biomarkers of HDL-metabolism

Participants were asked to fast for $\geq$12 hours prior to the clinical examination. Blood was drawn from the antecubital vein into tubes containing EDTA, which were then fractionated via centrifugation at 3000g and 4°C for 10 minutes. Plasma samples were stored at -70°C until analysis at the ARIC Central Lipid Laboratory. Total cholesterol and triglycerides concentrations were assayed using the cholesterol oxidase-4-aminophenazone reaction scheme. HDL was then separated into subfractions and quantified using the Warnick dual-precipitation method. Apolipoprotein A1 concentration was determined via radioimmunoassay.[152] Measurements of HDL biomarkers from visit 1, converted to International System of Units values (mmol/L), will be considered for these analyses.

Proposed analysis

The distribution of participant characteristics and other risk factors according to dietary xanthophyll intake (quintiles), AMD status (none vs. early), and the presence of pathologic stigmata of early AMD (i.e. soft drusen, retinal pigmentary abnormalities) will be examined using chi-square test, t-test and analysis of variance. Bivariate relationships among these variables will also be explored using Pearson product-moment correlation, point-biserial correlation, or chi-square test. Tables summarizing these descriptive statistics will be presented.

Multivariate logistic regression will be used to evaluate the association between quintiles of dietary xanthophyll intake and AMD status. Crude, age-adjusted and multivariate-adjusted odds ratios, 95% confidence intervals, and p-values for trend analyses (using quintile medians) will be reported. Potential confounders will be identified using previous studies or the change-in-estimate method ($\geq$10% change in the OR). Identified confounders will be adjusted for in subsequent multivariate analyses. Effect modification by high risk genotype and HDL cholesterol levels (HDL-c) and other HDL-related biomarkers will be assessed via interpretation of the multiplicative interaction terms, synergy indices[153] and stratified analyses. Specifically, we will investigate interaction by adding multiplicative interaction terms (e.g., xanthophyll intake * HDL-related variable) to the regression model. A p-value for interaction of <0.10 will be considered statistically significant. All HDL-related biomarkers will be operationalized as continuous variables and as categorical variables based on existing guidelines or recommendations for prevention of atherogenesis.[154] To our knowledge, no threshold values have been established for HDL2.

Limitations and possible solutions

The proposed study has several limitations. First, the use of prevalent AMD as an outcome precludes inference of causality. It is impossible to determine whether maculopathy was already present at

baseline, and whether the reported dietary patterns reflect long-term intake. However, previous research using a subset of the ARIC cohort suggests that responses on the FFQ were reliable across the 3-year interval of interest.[145] Since secondary analyses of the AREDS2 randomized trial showed significant effects of xanthophyll supplementation after a median follow-up of 4.9 years,[77] it is plausible that differential xanthophyll intake during the ARIC study may have influenced AMD status. In this study, baseline/visit 1 (1987-1989) and visit 3 (1993-1995) FFQ responses will be used to assess changes in and stability of dietary behaviors. Change in xanthophyll intake will be tested as a potential confounder in multivariate models. All analyses will also be repeated after excluding participants reporting a significant change (e.g. >1 quintile) in dietary xanthophyll intake.

Second, in this sample, prevalence of advanced AMD was low (0.13%), even among persons over the age of 65 (0.4%). Thus, analyses may be limited to using early AMD or any AMD as the outcome of interest. Moreover, only 12,887 of the 26,427 participants (82% of the survivors) recruited at baseline (1987-1989) returned for Visit 3 (1993-1995). Of these individuals, 1,317 had ungradable fundus photographs, and may have been at greater risk of AMD (i.e. older, more likely to have diabetes mellitus, and more likely to have evidence of CVD on magnetic resonance imaging).[145] Taken together with the high rate of non-participation, conclusions drawn from this study may be susceptible to selection bias. Multivariate analyses will therefore be interpreted with and without adjustment for the propensity score, or the conditional probability of an outcome given a set of observed confounders.[155] The propensity score will be constructed using covariates that differed in distribution by fundus photograph status (gradable vs. ungradable).

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)?

The most related manuscript proposals would involve other work on age-related macular degeneration and would involve Drs. Ronald and Barbara Klein, both of whom are co-authors 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

__X__ A. primarily the result of an ancillary study (list number* 2010.20)

___ 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. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. Br J Ophthalmol 2012;96:614-8.
2. Wong WL, Su XY, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health 2014;2:E106-E16.
3. Freeman EE, Roy-Gagnon MH, Samson E, et al. The global burden of visual difficulty in low, middle, and high income countries. PLoS One 2013;8:e63315.
4. Vela C, Samson E, Zunzunegui MV, Haddad S, Aubin MJ, Freeman EE. Eye care utilization by older adults in low, middle, and high income countries. BMC Ophthalmol 2012;12:5.
5. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844-51.
6. Javitt JC, Zhou ZY, Maguire MG, Fine SL, Willke RJ. Incidence of exudative age-related macular degeneration among elderly Americans. Ophthalmology 2003;110:1534-9.
7. Augood CA, Vingerling JR, de Jong PT, et al. Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). Arch Ophthalmol 2006;124:529-35.
8. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol 2002;134:411-31.
9. Morohoshi K, Goodwin AM, Ohbayashi M, Ono SJ. Autoimmunity in retinal degeneration: autoimmune retinopathy and age-related macular degeneration. J Autoimmun 2009;33:247-54.
10. Iannaccone A, Neeli I, Krishnamurthy P, et al. Autoimmune biomarkers in age-related macular degeneration: a possible role player in disease development and progression. Adv Exp Med Biol 2012;723:11-6.

11. Camelo S. Potential Sources and Roles of Adaptive Immunity in Age-Related Macular Degeneration: Shall We Rename AMD into Autoimmune Macular Disease? Autoimmune Dis 2014;2014:532487.
12. Hollyfield JG, Bonilha VL, Rayborn ME, et al. Oxidative damage-induced inflammation initiates age-related macular degeneration. Nat Med 2008;14:194-8.
13. Parmeggiani F, Romano MR, Costagliola C, et al. Mechanism of inflammation in age-related macular degeneration. Mediators Inflamm 2012;2012:546786.
14. Parmeggiani F, Sorrentino FS, Romano MR, et al. Mechanism of inflammation in age-related macular degeneration: an up-to-date on genetic landmarks. Mediators Inflamm 2013;2013:435607.
15. Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. JAMA Ophthalmol 2014;133:338-45.
16. Davis MD, Gangnon RE, Lee LY, et al. The age-related eye disease study severity scale for age-related macular degeneration - AREDS report no. 17. Arch Ophthalmol 2005;123:1484-98.
17. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol 1984;102:1640-2.
18. Grossniklaus HE, Green WR. Choroidal neovascularization. Am J Ophthalmol 2004;137:496-503.
19. Coleman HR, Chan CC, Ferris FL, 3rd, Chew EY. Age-related macular degeneration. Lancet 2008;372:1835-45.
20. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. N Engl J Med 2008;358:2606-17.
21. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.
22. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 2009;116:57-65 e5.
23. Virgili G, Bini A. Laser photocoagulation for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2007:CD004763.
24. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. Ophthalmology 2014;121:1079-91.
25. Blasiak J, Petrovski G, Vereb Z, Facsko A, Kaarniranta K. Oxidative stress, hypoxia, and autophagy in the neovascular processes of age-related macular degeneration. Biomed Res Int 2014;2014:768026.
26. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 2000;45:115-34.
27. Klein R, Myers CE, Cruickshanks KJ, et al. Markers of inflammation, oxidative stress, and endothelial dysfunction and the 20-year cumulative incidence of early age-related macular degeneration: the Beaver Dam Eye Study. JAMA Ophthalmol 2014;132:446-55.
28. Boulton M, Dayhaw-Barker P. The role of the retinal pigment epithelium: topographical variation and ageing changes. Eye (Lond) 2001;15:384-9.
29. Strauss O. The retinal pigment epithelium in visual function. Physiol Rev 2005;85:845-81.
30. King A, Gottlieb E, Brooks DG, Murphy MP, Dunaief JL. Mitochondria-derived reactive oxygen species mediate blue light-induced death of retinal pigment epithelial cells. Photochem Photobiol 2004;79:470-5.
31. Rozanowska M, Jarvis-Evans J, Korytowski W, Boulton ME, Burke JM, Sarna T. Blue light-induced reactivity of retinal age pigment. In vitro generation of oxygen-reactive species. J Biol Chem 1995;270:18825-30.

32. Hoppe G, O'Neil J, Hoff HF, Sears J. Products of lipid peroxidation induce missorting of the principal lysosomal protease in retinal pigment epithelium. Biochim Biophys Acta 2004;1689:33-41.
33. Ethen CM, Reilly C, Feng X, Olsen TW, Ferrington DA. Age-related macular degeneration and retinal protein modification by 4-hydroxy-2-nonenal. Invest Ophthalmol Vis Sci 2007;48:3469-79.
34. Kopitz J, Holz FG, Kaemmerer E, Schutt F. Lipids and lipid peroxidation products in the pathogenesis of age-related macular degeneration. Biochimie 2004;86:825-31.
35. Njie-Mbye YF, Kulkarni-Chitnis M, Opere CA, Barrett A, Ohia SE. Lipid peroxidation: pathophysiological and pharmacological implications in the eye. Front Physiol 2013;4:366.
36. Khandhadia S, Cipriani V, Yates JR, Lotery AJ. Age-related macular degeneration and the complement system. Immunobiology 2012;217:127-46.
37. Athanasiou D, Aguila M, Bevilacqua D, Novoselov SS, Parfitt DA, Cheetham ME. The cell stress machinery and retinal degeneration. FEBS Lett 2013;587:2008-17.
38. Faber C, Singh A, Falk MK, Juel HB, Sorensen TL, Nissen MH. Age-related macular degeneration is associated with increased proportion of CD56D(+) T cells in peripheral blood. Ophthalmology 2013;120:2310-6.
39. Buschini E, Piras A, Nuzzi R, Vercelli A. Age related macular degeneration and drusen: neuroinflammation in the retina. Prog Neurobiol 2011;95:14-25.
40. Grunin M, Hagbi-Levi S, Chowers I. The role of monocytes and macrophages in age-related macular degeneration. Adv Exp Med Biol 2014;801:199-205.
41. Kinnunen K, Petrovski G, Moe MC, Berta A, Kaarniranta K. Molecular mechanisms of retinal pigment epithelium damage and development of age-related macular degeneration. Acta Ophthalmol 2012;90:299-309.
42. Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. Neuron 2012;75:26-39.
43. Kijlstra A, Tian Y, Kelly ER, Berendschot TT. Lutein: more than just a filter for blue light. Prog Retin Eye Res 2012;31:303-15.
44. Widomska J, Subczynski WK. Why has nature chosen lutein and zeaxanthin to protect the retina? J Clin Exp Ophthalmol 2014;5:326.
45. Handelman GJ, Nightingale ZD, Lichtenstein AH, Schaefer EJ, Blumberg JB. Lutein and zeaxanthin concentrations in plasma after dietary supplementation with egg yolk. Am J Clin Nutr 1999;70:247-51.
46. United States Department of Agriculture ARS. USDA National Nutrient Database for Standard Reference, Release 27.
47. Handelman GJ, Dratz EA, Reay CC, van Kuijk JG. Carotenoids in the human macula and whole retina. Invest Ophthalmol Vis Sci 1988;29:850-5.
48. Bone RA, Landrum JT. Macular pigment in Henle fiber membranes: a model for Haidinger's brushes. Vision Res 1984;24:103-8.
49. Junghans A, Sies H, Stahl W. Macular pigments lutein and zeaxanthin as blue light filters studied in liposomes. Arch Biochem Biophys 2001;391:160-4.
50. Kim SR, Nakanishi K, Itagaki Y, Sparrow JR. Photooxidation of A2-PE, a photoreceptor outer segment fluorophore, and protection by lutein and zeaxanthin. Exp Eye Res 2006;82:828-39.
51. Conn PF, Schalch W, Truscott TG. The Singlet Oxygen and Carotenoid Interaction. J Photoch Photobio B 1991;11:41-7.
52. Sujak A, Gabrielska J, Grudzinski W, Borc R, Mazurek P, Gruszecki WI. Lutein and zeaxanthin as protectors of lipid membranes against oxidative damage: The structural aspects. Arch Biochem Biophys 1999;371:301-7.
53. Bian Q, Gao S, Zhou J, et al. Lutein and zeaxanthin supplementation reduces photooxidative damage and modulates the expression of inflammation-related genes in retinal pigment epithelial cells. Free Radic Biol Med 2012;53:1298-307.

54. Li SY, Fu ZJ, Ma H, et al. Effect of lutein on retinal neurons and oxidative stress in a model of acute retinal ischemia/reperfusion. Invest Ophthalmol Vis Sci 2009;50:836-43.
55. Li SY, Fung FK, Fu ZJ, Wong D, Chan HH, Lo AC. Anti-inflammatory effects of lutein in retinal ischemic/hypoxic injury: in vivo and in vitro studies. Invest Ophthalmol Vis Sci 2012;53:5976-84.
56. 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. Nutr Res Pract 2012;6:113-9.
57. Izumi-Nagai K, Nagai N, Ohgami K, et al. Macular pigment lutein is antiinflammatory in preventing choroidal neovascularization. Arterioscler Thromb Vasc Biol 2007;27:2555-62.
58. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science 2005;308:419-21.
59. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. Science 2005;308:385-9.
60. Klein R, Myers CE, Meuer SM, et al. Risk alleles in CFH and ARMS2 and the long-term natural history of age-related macular degeneration: the Beaver Dam Eye Study. JAMA Ophthalmol 2013;131:383-92.
61. Edwards AO, Ritter R, 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science 2005;308:421-4.
62. Tsai YY, Lin JM, Wan L, et al. Interleukin gene polymorphisms in age-related macular degeneration. Invest Ophthalmol Vis Sci 2008;49:693-8.
63. Ricci F, Staurenghi G, Lepre T, et al. Haplotypes in IL-8 Gene Are Associated to Age-Related Macular Degeneration: A Case-Control Study. PLoS One 2013;8.
64. Miao H, Tao Y, Li XX. Inflammatory cytokines in aqueous humor of patients with choroidal neovascularization. Mol Vis 2012;18:574-80.
65. Jonas JB, Tao Y, Neumaier M, Findeisen P. Cytokine concentration in aqueous humour of eyes with exudative age-related macular degeneration. Acta Ophthalmol 2012;90:e381-8.
66. Kramer M, Hasanreisoglu M, Feldman A, et al. Monocyte chemoattractant protein-1 in the aqueous humour of patients with age-related macular degeneration. Clin Experiment Ophthalmol 2012;40:617-25.
67. Agawa T, Usui Y, Wakabayashi Y, et al. Profile of intraocular immune mediators in patients with age-related macular degeneration and the effect of intravitreal bevacizumab injection. Retina 2014.
68. Lukiw WJ, Surjyadipta B, Dua P, Alexandrov PN. Common micro RNAs (miRNAs) target complement factor H (CFH) regulation in Alzheimer's disease (AD) and in age-related macular degeneration (AMD). Int J Biochem Mol Biol 2012;3:105-16.
69. Xu XR, Zou ZY, Xiao X, Huang YM, Wang X, Lin XM. Effects of lutein supplement on serum inflammatory cytokines, ApoE and lipid profiles in early atherosclerosis population. J Atheroscler Thromb 2013;20:170-7.
70. Tian Y, Kijlstra A, van der Veen RL, Makridaki M, Murray IJ, Berendschot TT. The effect of lutein supplementation on blood plasma levels of complement factor D, C5a and C3d. PLoS One 2013;8:e73387.
71. Miller ER, 3rd, Appel LJ, Risby TH. Effect of dietary patterns on measures of lipid peroxidation: results from a randomized clinical trial. Circulation 1998;98:2390-5.
72. Huang YM, Dou HL, Huang FF, et al. Changes following supplementation with lutein and zeaxanthin in retinal function in eyes with early age-related macular degeneration: a randomised, double-blind, placebo-controlled trial. Br J Ophthalmol 2014.

73. Ma L, Dou HL, Huang YM, et al. Improvement of retinal function in early age-related macular degeneration after lutein and zeaxanthin supplementation: a randomized, double-masked, placebo-controlled trial. Am J Ophthalmol 2012;154:625-34.
74. Murray IJ, Makridaki M, van der Veen RLP, Carden D, Parry NRA, Berendschot TTJM. Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study. Invest Ophth Vis Sci 2013;54:1781-8.
75. Ma L, Yan SF, Huang YM, et al. Effect of lutein and zeaxanthin on macular pigment and visual function in patients with early age-related macular degeneration. Ophthalmology 2012;119:2290-7.
76. Beatty S, Chakravarthy U, Nolan JM, et al. Secondary outcomes in a clinical trial of carotenoids with coantioxidants versus placebo in early age-related macular degeneration. Ophthalmology 2013;120:600-6.
77. 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 Ophthalmol 2014;132:142-9.
78. Beatty S, Nolan J, Kavanagh H, O'Donovan O. Macular pigment optical density and its relationship with serum and dietary levels of lutein and zeaxanthin. Arch Biochem Biophys 2004;430:70-6.
79. Mares JA, LaRowe TL, Snodderly DM, et al. Predictors of optical density of lutein and zeaxanthin in retinas of older women in the Carotenoids in Age-Related Eye Disease Study, an ancillary study of the Women's Health Initiative. Am J Clin Nutr 2006;84:1107-22.
80. Tan JS, Wang JJ, Flood V, Rochtchina E, Smith W, Mitchell P. Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology 2008;115:334-41.
81. Cho E, Seddon JM, Rosner B, Willett WC, Hankinson SE. Prospective study of intake of fruits, vegetables, vitamins, and carotenoids and risk of age-related maculopathy. Arch Ophthalmol 2004;122:883-92.
82. Joachim N, Mitchell P, Rochtchina E, Tan AG, Wang JJ. Incidence and progression of reticular drusen in age-related macular degeneration: findings from an older Australian cohort. Ophthalmology 2014;121:917-25.
83. Ma L, Dou HL, Wu YQ, et al. Lutein and zeaxanthin intake and the risk of age-related macular degeneration: a systematic review and meta-analysis. Br J Nutr 2012;107:350-9.
84. VandenLangenberg GM, Mares-Perlman JA, Klein R, Klein BE, Brady WE, Palta M. Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol 1998;148:204-14.
85. van Leeuwen R, Boekhoorn S, Vingerling JR, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. JAMA 2005;294:3101-7.
86. Cho E, Hankinson SE, Rosner B, Willett WC, Colditz GA. Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration. Am J Clin Nutr 2008;87:1837-43.
87. Moeller SM, Parekh N, Tinker L, et al. Associations between intermediate age-related macular degeneration and lutein and zeaxanthin in the Carotenoids in Age-related Eye Disease Study (CAREDS): ancillary study of the Women's Health Initiative. Arch Ophthalmol 2006;124:1151-62.
88. Mares-Perlman JA, Fisher AI, Klein R, et al. Lutein and zeaxanthin in the diet and serum and their relation to age-related maculopathy in the third national health and nutrition examination survey. Am J Epidemiol 2001;153:424-32.
89. Morris MS, Jacques PF, Chylack LT, et al. Intake of zinc and antioxidant micronutrients and early age-related maculopathy lesions. Ophthalmic Epidemiol 2007;14:288-98.

90. Chew EY, Klein ML, Clemons TE, et al. No clinically significant association between CFH and ARMS2 genotypes and response to nutritional supplements: AREDS report number 38. Ophthalmology 2014;121:2173-80.
91. Awh CC, Lane AM, Hawken S, Zanke B, Kim IK. CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. Ophthalmology 2013;120:2317-23.
92. Klein ML, Francis PJ, Rosner B, et al. CFH and LOC387715/ARMS2 genotypes and treatment with antioxidants and zinc for age-related macular degeneration. Ophthalmology 2008;115:1019-25.
93. Wang JJ, Buitendijk GH, Rochtchina E, et al. Genetic susceptibility, dietary antioxidants, and long-term incidence of age-related macular degeneration in two populations. Ophthalmology 2014;121:667-75.
94. Loane E, Nolan JM, McKay GJ, Beatty S. The association between macular pigment optical density and CFH, ARMS2, C2/BF, and C3 genotype. Exp Eye Res 2011;93:592-8.
95. Ruberti JW, Curcio CA, Millican CL, Menco BP, Huang JD, Johnson M. Quick-freeze/deep-etch visualization of age-related lipid accumulation in Bruch's membrane. Invest Ophthalmol Vis Sci 2003;44:1753-9.
96. Wang L, Clark ME, Crossman DK, et al. Abundant lipid and protein components of drusen. PLoS One 2010;5:e10329.
97. Tserentsoodol N, Sztein J, Campos M, et al. Uptake of cholesterol by the retina occurs primarily via a low density lipoprotein receptor-mediated process. Mol Vis 2006;12:1306-18.
98. Nofer JR, Kehrel B, Fobker M, Levkau B, Assmann G, von Eckardstein A. HDL and arteriosclerosis: beyond reverse cholesterol transport. Atherosclerosis 2002;161:1-16.
99. Zhu X, Parks JS. New roles of HDL in inflammation and hematopoiesis. Annu Rev Nutr 2012;32:161-82.
100. Rosenson RS, Brewer HB, Jr., Davidson WS, et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. Circulation 2012;125:1905-19.
101. Klein R, Cruickshanks KJ, Nash SD, et al. The prevalence of age-related macular degeneration and associated risk factors. Arch Ophthalmol 2010;128:750-8.
102. Nowak M, Swietochowska E, Marek B, et al. Changes in lipid metabolism in women with age-related macular degeneration. Clin Exp Med 2005;4:183-7.
103. Tan JS, Mitchell P, Smith W, Wang JJ. Cardiovascular risk factors and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology 2007;114:1143-50.
104. Huang FF, Lin XM. [Comparison of daily intake of lutein+zeaxanthin, serum concentration of lutein/zeaxanthin and lipids profile between age-related macular degeneration patients and controls]. Beijing Da Xue Xue Bao 2014;46:237-41.
105. Butt AL, Lee ET, Klein R, et al. Prevalence and risks factors of age-related macular degeneration in Oklahoma Indians: the Vision Keepers Study. Ophthalmology 2011;118:1380-5.
106. Delcourt C, Michel F, Colvez A, et al. Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. Ophthalmic Epidemiol 2001;8:237-49.
107. Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration. Age-Related Macular Degeneration Risk Factors Study Group. Arch Ophthalmol 2000;118:351-8.
108. Klein R, Klein BE, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1993;100:406-14.
109. Klein R, Klein BE, Jensen SC. The relation of cardiovascular disease and its risk factors to the 5-year incidence of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 1997;104:1804-12.

110. Klein R, Klein BE, Tomany SC, Cruickshanks KJ. The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 2003;110:1273-80.
111. van Leeuwen R, Klaver CC, Vingerling JR, et al. Cholesterol and age-related macular degeneration: is there a link? Am J Ophthalmol 2004;137:750-2.
112. Cougnard-Gregoire A, Delyfer MN, Korobelnik JF, et al. Elevated high-density lipoprotein cholesterol and age-related macular degeneration: the Alienor study. PLoS One 2014;9.
113. Cackett P, Wong TY, Aung T, et al. Smoking, cardiovascular risk factors, and age-related macular degeneration in Asians: the Singapore Malay Eye Study. Am J Ophthalmol 2008;146:960-7 e1.
114. Chakravarthy U, Wong TY, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC ophthalmology 2010;10:31.
115. Smith W, Mitchell P, Leeder SR, Wang JJ. Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye Study. Arch Ophthalmol 1998;116:583-7.
116. Tomany SC, Wang JJ, Van Leeuwen R, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. Ophthalmology 2004;111:1280-7.
117. Yang K, Wang FH, Liang YB, et al. Associations between cardiovascular risk factors and early age-related macular degeneration in a rural Chinese adult population. Retina 2014.
118. Klein R, Myers CE, Buitendijk GH, et al. Lipids, lipid genes, and incident age-related macular degeneration: the three continent age-related macular degeneration consortium. Am J Ophthalmol 2014.
119. Renzi LM, Hammond BR, Dengler M, Roberts R. The relation between serum lipids and lutein and zeaxanthin in the serum and retina: results from cross-sectional, case-control and case study designs. Lipids Health Dis 2012;11.
120. Loane E, Nolan JM, Beatty S. The respective relationships between lipoprotein profile, macular pigment optical density, and serum concentrations of lutein and zeaxanthin. Invest Ophthalmol Vis Sci 2010;51:5897-905.
121. Broekmans WM, Berendschot TT, Klopping-Ketelaars IA, et al. Macular pigment density in relation to serum and adipose tissue concentrations of lutein and serum concentrations of zeaxanthin. Am J Clin Nutr 2002;76:595-603.
122. Wang Y, Chung SJ, McCullough ML, et al. Dietary carotenoids are associated with cardiovascular disease risk biomarkers mediated by serum carotenoid concentrations. J Nutr 2014;144:1067-74.
123. Karppi J, Laukkanen JA, Kurl S. Plasma lutein and zeaxanthin and the risk of age-related nuclear cataract among the elderly Finnish population. Br J Nutr 2012;108:148-54.
124. Lidebjer C, Leanderson P, Ernerudh J, Jonasson L. Low plasma levels of oxygenated carotenoids in patients with coronary artery disease. Nutr Metab Cardiovasc Dis 2007;17:448-56.
125. Lima VC, Rosen RB, Maia M, et al. Macular pigment optical density measured by dual-wavelength autofluorescence imaging in diabetic and nondiabetic patients: a comparative study. Invest Ophth Vis Sci 2010;51:5840-5.
126. Merle BM, Maubaret C, Korobelnik JF, et al. Association of HDL-related loci with age-related macular degeneration and plasma lutein and zeaxanthin: the Alienor study. PLoS One 2013;8:e79848.
127. Neale BM, Fagerness J, Reynolds R, et al. Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC). Proc Natl Acad Sci U S A 2010;107:7395-400.
128. Niesor EJ, Chaput E, Mary JL, et al. Effect of compounds affecting ABCA1 expression and CETP activity on the HDL pathway involved in intestinal absorption of lutein and zeaxanthin. Lipids 2014;49:1233-43.
129. Marcovina S, Packard CJ. Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. J Intern Med 2006;259:437-46.

130. Maciejko JJ, Holmes DR, Kottke BA, Zinsmeister AR, Dinh DM, Mao SJ. Apolipoprotein A-I as a marker of angiographically assessed coronary-artery disease. N Engl J Med 1983;309:385-9.
131. Buring JE, O'Connor GT, Goldhaber SZ, et al. Decreased HDL2 and HDL3 cholesterol, Apo A-I and Apo A-II, and increased risk of myocardial infarction. Circulation 1992;85:22-9.
132. Luc G, Bard JM, Ferrieres J, et al. Value of HDL cholesterol, apolipoprotein A-I, lipoprotein A-I, and lipoprotein A-I/A-II in prediction of coronary heart disease: the PRIME Study. Prospective Epidemiological Study of Myocardial Infarction. Arterioscler Thromb Vasc Biol 2002;22:1155-61.
133. Siegel RD, Cupples A, Schaefer EJ, Wilson PWF. Lipoproteins, apolipoproteins, and low-density lipoprotein size among diabetics in the Framingham offspring study. Metabolism 1996;45:1267-72.
134. Russo GT, Giandalia A, Romeo EL, et al. Markers of Systemic Inflammation and Apo-AI Containing HDL Subpopulations in Women with and without Diabetes. Int J Endocrinol 2014;2014:607924.
135. Ye Z, Haycock PC, Gurdasani D, et al. The Association Between Circulating Lipoprotein(a) and Type 2 Diabetes: Is It Causal? Diabetes 2014;63:332-42.
136. Mora S, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM. Lipoprotein(a) and risk of type 2 diabetes. Clin Chem 2010;56:1252-60.
137. Goek ON, Kottgen A, Hoogeveen RC, Ballantyne CM, Coresh J, Astor BC. Association of apolipoprotein A1 and B with kidney function and chronic kidney disease in two multiethnic population samples. Nephrol Dial Transplant 2012;27:2839-47.
138. Lamprea-Montealegre JA, Sharrett AR, Matsushita K, Selvin E, Szklo M, Astor BC. Chronic kidney disease, lipids and apolipoproteins, and coronary heart disease: the ARIC study. Atherosclerosis 2014;234:42-6.
139. Goulinet S, Chapman MJ. Plasma LDL and HDL subspecies are heterogenous in particle content of tocopherols and oxygenated and hydrocarbon carotenoids. Relevance to oxidative resistance and atherogenesis. Arterioscler Thromb Vasc Biol 1997;17:786-96.
140. Salonen JT, Salonen R, Seppanen K, Rauramaa R, Tuomilehto J. HDL, HDL2, and HDL3 subfractions, and the risk of acute myocardial infarction. A prospective population study in eastern Finnish men. Circulation 1991;84:129-39.
141. Xian X, Ma Y, Yang DD, et al. Reduced high-density lipoprotein 2b in non-obese type 2 diabetic patients analysed by a microfluidic chip method in a case-control study. Biomarkers 2009;14:619-23.
142. Topouzis F, Anastasopoulos E, Augood C, et al. Association of diabetes with age-related macular degeneration in the EUREYE study. Br J Ophthalmol 2009;93:1037-41.
143. Choi JK, Lym YL, Moon JW, Shin HJ, Cho B. Diabetes mellitus and early age-related macular degeneration. Arch Ophthalmol 2011;129:196-9.
144. Wu J, Uchino M, Sastry SM, Schaumberg DA. Age-related macular degeneration and the incidence of cardiovascular disease: a systematic review and meta-analysis. PLoS One 2014;9:e89600.
145. Klein R, Clegg L, Cooper LS, et al. Prevalence of age-related maculopathy in the Atherosclerosis Risk in Communities Study. Arch Ophthalmol 1999;117:1203-10.
146. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51-65.
147. Stevens J, Metcalf PA, Dennis BH, Tell GS, Shimakawa T, Folsom AR. Reliability of a food frequency questionnaire by ethnicity, gender, age and education. Nutr Res 1996;16:735-45.
148. Shahar E, Folsom AR, Wu KK, et al. Associations of fish intake and dietary n-3 polyunsaturated fatty acids with a hypocoagulable profile. The Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb 1993;13:1205-12.
149. Johnson EJ, Maras JE, Rasmussen HM, Tucker KL. Intake of lutein and zeaxanthin differ with age, sex, and ethnicity. J Am Diet Assoc 2010;110:1357-62.

150. Psaty BM, O'Donnell CJ, Gudnason V, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. Circ Cardiovasc Genet 2009;2:73-80.
151. Holliday EG, Smith AV, Cornes BK, et al. Insights into the genetic architecture of early stage age-related macular degeneration: a genome-wide association study meta-analysis. PLoS One 2013;8:e53830.
152. Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond MG, Davis CE. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb 1994;14:1098-104.
153. Rothman KJ. The estimation of synergy or antagonism. Am J Epidemiol 1976;103:506-11.
154. Millan J, Pinto X, Munoz A, et al. Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention. Vascular Health and Risk Management 2009;5:757-65.
155. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-81.