ARIC Manuscript Proposal # 3133

PC Reviewed: 3/20/2018	**Status: ____**	**Priority: 2**
SC Reviewed: _____	**Status: ____**	**Priority: ___**

1a. Full Title: Diet Patterns and the Incidence and Progression of Age-Related Macular Degeneration: the Atherosclerosis Risk In Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): Diet Patterns and the risk of Incident AMD.

2. Writing Group:

Writing group members:

Shruti Dighe (first author), Dr Amy Millen (senior author)
Dr. Jiwei Zhao (University at Buffalo)
Dr. Julie Mares (University of Wisconsin)
Stacy Meuer (University of Wisconsin)
Dr. Ronald Klein and Dr. Barbara E.K. Klein (University of Wisconsin)
Dr. Lyn Steffen (University of Minnesota) - sposoring ARIC PI

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

First author: **Shruti Dighe MPH, Amy E. Millen PhD**
Address: University at Buffalo
Department of Epidemiology and Environmental Health
Farber Hall, Room, 3435 Main Street (South Campus)
Buffalo, NY 14214-8001
Phone: 716-829-5377 Fax: 716-8292979
E-mail: aemillen@buffalo.edu (senior author email for correspondence)

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Ronald Klein, MD
Address: Room 450, 610 Walnut St.
Madison, WI 53705
Phone: 608-263-0280 Fax: 608-263-0279
E-mail: kleinr@epi.ophth.wisc.edu

3. Timeline: Analyses to be completed 01/05/2018 to 04/01/2018

4. Rationale:

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among the elderly [1]. Nearly 2.1 million Americans age 50 and older have late AMD whereas approximately 9.1 million Americans have early AMD [2, 3]. It is also predicted that one in ten Americans over 80 has late AMD, more in women than men [4].Poor vision poses a challenge to one's physical, mental and social well-being leading to increased falls, fractures and a higher prevalence of depression [5-7].

The only treatments are in the form of intraocular injections and lasers [4]; which are invasive, expensive and available only for the late stage of AMD [4, 8]. In addition, the pathogenesis of AMD is complex and poorly understood [9]. Thus, it becomes important to focus attention on the identification of modifiable risk factors such as diet, to preserve vision and autonomy by preventing the development and progression of conditions such as AMD.

Clinical trials have demonstrated the protective role of antioxidants and supplements such as Vitamin C, E, zinc [10], carotenoids such as lutein and zeaxanthin [11] and omega 3 fatty acids [11]. Some observational studies have shown protective effect of some lesser established dietary components like higher Vitamin D [12-14] and foods with lower glycemic indices [15]. However, foods or nutrients are not consumed in isolation but as a combination of several items constituting a meal/diet. Intakes of several nutrients are highly correlated owing to common food sources. Thus, using an integrated approach to investigate the impact of overall diet on chronic diseases (such as AMD) where dietary patterns are assessed, instead of individual foods or nutrients, may be more informative and a better predictor of disease risk [16].

The body of literature to date suggests that consumption of a healthy diet pattern is associated with a reduced odds of prevalent late/advanced/neovascular AMD [17-21]. All but one study [22], examined the association between overall diet and AMD using prevalent cases of disease, the study design being either cross-sectional or case control. Temporality cannot be established in such study designs. We cannot decipher at what point in time a participant developed AMD, and how one's diet would influence that risk. Furthermore, the one prospective study assessed the risk of advanced/late AMD, but not early AMD [22]. Also, this study assessed adherence to a Mediterranean diet pattern only [22].

We propose to test the association between consumption of an overall healthy diet in the past, and the 18-year incidence of early and late AMD using data from the Atherosclerosis Risk in Communities (ARIC) Study. This study will add to the literature by providing another prospective analysis of diet and incident AMD as well as provide evidence as to the association between diet and development of early AMD. The Atherosclerosis Risk in Communities (ARIC) Study is a well-characterized epidemiologic cohort that has graded retinal fundus photographs for AMD at visit 3 (1993-1995) (n=11,863) and in a subset of participants at visit 5 (2011-2013)n=1891), allowing for assessment of AMD incidence (early and late) at Visit 5 and progression over ~18 years. Diet was assessed using a food frequency questionnaire (FFQ) at Visit 1 and 3.

5. Main Hypothesis/Study Questions:

Question 1: Is there an association between diet in the past, (assessed using a-posteriori data driven method of dietary pattern analyses) using average of Visit 1 and Visit 3, with the incidence and progression of AMD from visit 3 (1993-1995) to visit 5 (2011-2013)?

Hypothesis Q1:

We hypothesize that ARIC participants who consumed a healthy diet in the past (average of diet at visit 1 and visit 3) have a lower incidence of AMD as compared to those who consumed an unhealthy diet.

Additional questions/Exploratory Analyses:

- *Is there an association between overall diet in the past using diet data from one time point (Visit 3) and the risk of incident AMD using dietary pattern analysis?*
- *Do polymorphism in high risk genes, such as ARMS2 and CFH, act as effect modifiers of the association between dietary patterns and any incident AMD.*
- *Are the participants who returned for Visit 5 different from those who did not? Does loss to follow up bias the study findings?*

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).

Study Design:

These analyses will be conducted among participants who answered FFQ's at Visit 1 and/or Visit 3 and subsequently had gradable retinal photographs taken at Visit 3 (1993-1995) and Visit 5(2011-2013).

Of the 12,091 eligible participants attending visit 3 (796 were excluded from the 12,887 due to non-consent), 11,863 had nonmydriatic retinal photographs taken of one randomly chosen eye with film using a photo centered between the disc and fovea. Digital photographs without mydriatics were used to obtain retinal photographs (fields 1 and 2) of both eyes of participants at visit 5 follow-up. Previous research has demonstrated film and digital photo grading of AMD to be comparable [23]. Thus, incidence of early and late AMD at Visit 5 and progression of disease can be assessed by comparing the retinal photographs taken at Visit 3 with film and Visit 5 with a digital camera.

There were 1,891 participants who had retinal photos at both Visit 3 and Visit 5. Of these 565 participants were excluded due to ungradeable photos either at Visit 3 or/and Visit 5 and 1 who had late AMD at Visit 3 (ineligible for incidence/progression). Further, 47 participants were

outliers for energy consumption and were excluded, providing an analytic sample of 1,278 participants.

At study visits 1-3, participants answered questionnaires on their lifestyle habits and medical history [24]. They also had a physical exam and a blood draw [25]. Prior to the visit, participants were asked to fast for twelve hours and to bring with them any medications or supplements they were taking or had taken within the past two weeks [24].

Outcome/Disease endpoints

Our primary outcomes is any incident AMD, including both incident early and incident late AMD cases which developed between Visit 3 and 5. Among our final study sample of 1,278, who had appropriate diet data, eye photos taken at both visits and were graded using the Wisconsin Age-Related Maculopathy Grading System [26]. Graders were masked to results from earlier visit. Then a side-by-side grading was conducted on those eyes that had change across visits (either progression or regression). Between Visit 3 and Visit 5, 117 participants developed incident early AMD, 20 participants developed incident late AMD, and 7 progressed from early to late AMD. Whereas, 1,119 participants remained without disease and 15 remained with early AMD between the visits.

Exposure

For dietary assessment, a modification of Harvard's Willet 61-Item semi-quantitative FFQ was utilized. The FFQ was administered by interviewers at the baseline Visit 1 and 6 years later at Visit 3 [27]. The FFQ assessed usual dietary intake over the past year. For each food item, participants were asked to report their frequency of consumption in 9 different categories which ranged from never to ≥6 times a day; standard portion sizes were assumed (serving units). For the purpose of this study in addition to looking at diet at one visit only we will be averaging FFQ data from Visit 1 and Visit 3. This mean/average should better represent an individual's long-term dietary window of exposure from 1987-1995. Previous studies in this cohort used this approach as it was thought to improve precision of dietary data [28, 29].

The 66 line items on the ARIC FFQ will be collapsed into 29 food groups. A Principal Component Analysis (PCA) (PROC FACTOR) will be used to derive dietary patterns and determine factor loadings for each of the 29 food groups. Factors will be rotated to maintain uncorrelated factors only. Based on previous literature, we will retain dietary patterns with eigen values above 2 for our analyses [28, 30]. Dietary patterns will be named according to the nature of the food groups loading highest for each of the factors. The PCA will provide us with linear models for each dietary pattern with every one of the 29 food groups having a beta-coefficient, or loading. The more a food contributes to the dietary pattern, the more heavily weighted (or greater) the beta-coefficient. For every participant we will estimate an overall dietary pattern by entering the servings consumed of each of the 29 food groups into the linear equations for each diet pattern. The scores of the major diet patterns that emerge will be arranged in ascending order and then

categorized into increasing tertiles. These tertiles of the major dietary pattern(s) scores will be the final exposure of interest.

Other pertinent covariates

We will investigate the following covariates as potential confounders, age, race, gender, education, smoking status, body mass index (BMI), cholesterol level, alcohol intake, energy intake, physical activity, hormonal intake status. Hypertension and diabetes status will be examined as pathway variables.

Genetic data

Genetic data are available in ARIC on high risk AMD genes like the *CFH* and *ARMS2.* Genotyping of single nucleotide polymorphisms (SNPs) in ARIC was completed using the Affymetrix Genome-Wide Human SNP Array 6.0 [31]. 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 [32]. We will use this data to explore whether either variant acts as a confounder or whether it modifies the association between diet in the past and AMD.

Proposed analysis

Logistic regression models will be used to estimate odds ratios (ORs) and respective 95% confidence intervals (CIs) for the odds of developing any AMD, incident early AMD and incident late (includes the progressed from early to late cases) AMD at Visit 5 by increasing tertiles of dietary pattern scores. A crude model followed by a multivariable adjusted model will be constructed to test the association between increasing tertiles of dietary pattern scores, and the outcomes of interest, parameterized as dichotomous variables. Tertile 1 will be used as referent group. P for trend will be reported for increasing tertiles of diet pattern scores and a $p<0.05$ will be considered a significant difference in odds (either higher/lower) of developing any/early/late incident AMD by increasing tertiles of exposure. The above mentioned covariates will be tested as confounders. A step-wise approach will be utilized to test the potential risk factors as confounders in our study. Each variable will be added to the age-adjusted model one at a time. If the beta-estimate demonstrates a change by more than 10%, it will be considered as a confounder and the strongest covariate (one that changes the beta-estimate to the greatest extent) will be adjusted for first. At minimum we plan to adjust for age, sex and total energy intake. Our will also investigate the influence of further adjustment for hypertension and diabetes as pathway variables. As an exploratory analysis we will repeat the models using Visit 3 diet data only instead of the average. In addition, we also intend to test for potential effect modification by presence of the high risk genetic alleles from *ARMS2* and *CFH.* This will be achieved by calculating ORs and 95% CIs for incident AMD by tertiles of dietary pattern scores stratified by genetic risk alleles. Addition of an interaction term diet pattern tertile*genotype will be considered statistically significant if the p for interaction is <0.10. An important limitation to this study that could bias results is loss to follow up of participants with retinal photos between Visits 3 and Visit 5. To determine the magnitude of this potential bias, we will compare

participants in the final sample with those that were lost to follow up between visits 3 and 5. Our participants are from the ARIC Visit 5, stage 2/3, those recruited for retinal photography. We will conduct a sensitivity analysis by applying inverse probability weights, specifically S2SAMWT51 from the derived dataset for Visit 5, to account for this loss to follow up from non-participation or death. This weight represents the product of the base weights (S2BASEWT51), "the inverse of the empirical sampling fractions" and the weights accounting for the "probability of selection" (S2SAMWT51) [33]. This method has been previously conducted in ARIC [34]. ***We would greatly appreciate ARIC review and <u>confirmation</u> of the use of the correct sampling weights for this analysis.***

Limitations and solution

At Visit 3, retinal photographs were available only from one eye. There may be misclassification of endpoints ascertained at Visit 3. However, since the eye photographed was chosen at random, we expect the misclassification to be non-differential in nature which would bias our risk estimate towards the null. Another potential but significant limitation is the loss to follow up of participants with retinal photographs from Visit 3 to Visit 5. We will conduct a sensitivity analysis to investigate potential bias owing to loss to follow up (as described above). Using only FFQ as measure of dietary intake has its limitations such as measurement error and recall bias. Averaging dietary intake at two time points addresses this to some extent. It is also possible that due to the long gap between visits participants could have changed their diet.

7a. Will the data be used for non-CVD analysis in this manuscript? __ <u>X</u>__ 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? __<u>X</u>__ Yes ___ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

We have excluded participants who have not given consent to have their data used in non-CVD related analyses.

8.a. Will the DNA data be used in this manuscript? __x__ Yes _____ 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"? __<u>X</u>__ Yes ___ No

We have received our DNA data from the CC.

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 are those involving Dr Lyn Steffen's work involving dietary pattern analysis and the outcomes of peripheral arterial disease and metabolic syndrome. Other relevant proposals include the work of Dr Amy Millen and Dr Ronald Klein. All 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* AS 2010.20**)**

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

*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.

References

1. Jager, R.D., W.F. Mieler, and J.W. Miller, *Age-related macular degeneration.* N Engl J Med, 2008. **358**(24): p. 2606-17.
2. *Eye Health Statistics, American Academy of Ophthalmology* 2017; Available from: https://www.aao.org/newsroom/eye-health-statistics#_edn3.
3. Rein, D.B., et al., *Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments.* Arch Ophthalmol, 2009. **127**(4): p. 533-40.
4. Knight, O.J., et al., *Effect of race, age, and axial length on optic nerve head parameters and retinal nerve fiber layer thickness measured by Cirrus HD-OCT.* Arch Ophthalmol, 2012. **130**(3): p. 312-8.
5. Rovner, B.W., et al., *Low vision depression prevention trial in age-related macular degeneration: a randomized clinical trial.* Ophthalmology, 2014. **121**(11): p. 2204-11.
6. Wood, J.M., et al., *Risk of falls, injurious falls, and other injuries resulting from visual impairment among older adults with age-related macular degeneration.* Invest Ophthalmol Vis Sci, 2011. **52**(8): p. 5088-92.
7. Desai, M. and L. Pratt, *Trends in Vision and Hearing Among Older Americans*, in *Aging trends*. 2001, CDC, NCHS.
8. Brown, M.M., et al., *Age-related macular degeneration: economic burden and value-based medicine analysis.* Can J Ophthalmol, 2005. **40**(3): p. 277-87.
9. Nowak, J.Z., *Age-related macular degeneration (AMD): pathogenesis and therapy.* Pharmacol Rep, 2006. **58**(3): p. 353-63.
10. *A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8.* Arch Ophthalmol, 2001. **119**(10): p. 1417-36.
11. The Age-Related Eye Disease Study 2 Research, G., *Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The age-related eye disease study 2 (areds2) randomized clinical trial.* JAMA, 2013. **309**(19): p. 2005-2015.
12. Parekh, N., et al., *Association between vitamin d and age-related macular degeneration in the third national health and nutrition examination survey, 1988 through 1994.* Archives of Ophthalmology, 2007. **125**(5): p. 661-669.
13. Lee, V., et al., *Vitamin D rejuvenates aging eyes by reducing inflammation, clearing amyloid beta and improving visual function.* Neurobiology of Aging. **33**(10): p. 2382-2389.
14. Millen, A.E., et al., *Vitamin d status and early age-related macular degeneration in postmenopausal women.* Archives of Ophthalmology, 2011. **129**(4): p. 481-489.
15. Chiu, C.J., et al., *Dietary compound score and risk of age-related macular degeneration in the age-related eye disease study.* Ophthalmology, 2009. **116**(5): p. 939-46.
16. Hu, F.B., *Dietary pattern analysis: a new direction in nutritional epidemiology.* Curr Opin Lipidol, 2002. **13**(1): p. 3-9.
17. Amirul Islam, F.M., et al., *Dietary patterns and their associations with age-related macular degeneration: the Melbourne collaborative cohort study.* Ophthalmology, 2014. **121**(7): p. 1428-1434.e2.
18. Mares, J.A., et al., *Healthy lifestyles related to subsequent prevalence of age-related macular degeneration.* Arch Ophthalmol, 2011. **129**(4): p. 470-80.
19. Hogg, R.E., et al., *Mediterranean Diet Score and Its Association with Age-Related Macular Degeneration: The European Eye Study.* Ophthalmology, 2017. **124**(1): p. 82-89.

20. Montgomery, M.P., et al., *Overall Diet Quality and Age-Related Macular Degeneration.* Ophthalmic Epidemiology, 2010. **17**(1): p. 58-65.
21. Chiu, C.J., et al., *The relationship of major American dietary patterns to age-related macular degeneration.* Am J Ophthalmol, 2014. **158**(1): p. 118-127.e1.
22. Merle, B.M., et al., *Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: a prospective cohort study.* Am J Clin Nutr, 2015. **102**(5): p. 1196-206.
23. Klein, R., et al., *Detection of age-related macular degeneration using a nonmydriaticdigital camera and a standard film fundus camera.* Archives of Ophthalmology, 2004. **122**(11): p. 1642-1646.
24. *The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators.* Am J Epidemiol, 1989. **129**(4): p. 687-702.
25. *ARIC study Research Group. Manual 7 Blood Collection.* 1988: p. 10-15, 16-24.
26. Klein, R., et al., *The Wisconsin age-related maculopathy grading system.* Ophthalmology, 1991. **98**(7): p. 1128-34.
27. Willett, W.C., et al., *Reproducibility and validity of a semiquantitative food frequency questionnaire.* Am J Epidemiol, 1985. **122**(1): p. 51-65.
28. Lutsey, P.L., L.M. Steffen, and J. Stevens, *Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study.* Circulation, 2008. **117**(6): p. 754-61.
29. Hu, F.B., 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): p. 531-40.
30. Ogilvie, R.P., et al., *Dietary intake and peripheral arterial disease incidence in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study.* Am J Clin Nutr, 2017. **105**(3): p. 651-659.
31. Psaty, B.M., 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**(1): p. 73-80.
32. Holliday, E.G., 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**(1): p. e53830.
33. *ARIC Visit 5/NCS Analysis Manual. pages. 14-15.*
34. Gottesman, R.F., et al., *Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC neurocognitive study.* Am J Epidemiol, 2014. **179**(8): p. 956-66.