ARIC Manuscript Proposal #2457

PC Reviewed: 11/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Vitamin D Status and Prevalent Age-Related Macular Degeneration (AMD) in a Population-based, Biracial Cohort

b. Abbreviated Title (Length 26 characters): **Vitamin D and AMD**

2. Writing Group:

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

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3. Timeline:

Analyses are planned to be completed between 11/1/14 and 3/31/15

4. Rationale:

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss (1), affecting ~6.5% of Americans 40 years and older (2). AMD affects the macula, which is the part of the retina needed for central vision and discerning fine detail (1). Vision impacts several aspects of an individual's quality of life and functional independence, including ability to read, drive, exercise and prepare food. Currently, treatment exists for vision-threatening, advanced, neovascular AMD and involves invasive injection of anti-angiogenic agents into the vitreous (1). No effective treatment exists for geographic atrophy, the other form of advanced AMD (3). Advancement of effective modalities for preventing and controlling AMD may depend on discovering novel, modifiable risk factors related to disease development or progression. Inadequate vitamin D status has been hypothesized to be such a novel risk factor (4) and is relatively understudied with respect to AMD particularly in populations of racial-ethnic diversity.

Inflammation is implicated in the pathogenesis of AMD (5-7), and vitamin D is hypothesized to prevent development of AMD, at least in part, through its anti-inflammatory and immune modulating properties (8-10). Results of epidemiologic (11) and animal studies (12, 13) suggest vitamin D favorably influences the renin-angiotensin system to reduce blood pressure. Hypertension is a risk factor for AMD and it is possible that vitamin D could affect AMD through its known benefit on arterial blood pressure (14).

Data from a nationally representative sample (15) showed the percentage of vitamin D deficient (25(OH)D <30 nmol/L) individuals in the US population increased from 5.2% in 1988-94 to 9.9% in 2001-2006 (16). Deficiency status was defined by the Institute of Medicine's (IOM) 2011 report on Dietary Reference Intakes (16) and pertains to bone health. The IOM noted that there was not enough scientific evidence to make conclusions on vitamin D adequacy/deficiency regarding other health outcomes, such as AMD, and that more research is needed to clarify and expand understanding of the health benefits and risks associated with vitamin D status.

Previous epidemiologic research on the role of vitamin D in AMD is minimal. A study using data from using data from the Third National Health and Nutrition Examination (NHANES III) and an ancillary study in the Women's Health Initiative (WHI) observed decreased odds of early AMD with high compared to low serum 25(OH)D concentrations (4, 17). Results in NHANES III were similar when the data were stratified by race-ethnicity (non-Hispanic white, non-Hispanic black and Mexican American), although only statistically significant among non-Hispanic whites. Data from WHI were limited to Caucasian postmenopausal women. A study of Caucasian, male, monozygotic twins (primarily 70+ years) with discordant AMD, showed a lower grade of AMD and smaller drusen size in twins with greater dietary intake of vitamin D (18). This study is limited by using dietary vitamin D intake instead of serum 25(OH)D which reflects vitamin D from foods, supplements and sunlight. In a different study of 133 sibling pairs discordant for AMD (19) lower odds of neovascular AMD were observed with higher compared to lower estimated yearly annual ultraviolet light exposure. In a subset analysis, mean serum 25(OH)D concentrations were slightly lower in affected siblings compared to unaffected siblings, but this difference was not statistically significant. This study also observed that variants in the *CYP24A1* gene (which metabolizes the active hormone $1,25[OH]_2D$) was associated with a lower odds of AMD.

Results from two clinical studies suggest an association between vitamin D status and AMD. Thirty-one cases of AMD drawn from a database of a Geriatric Mobile Team showed a greater prevalence of having serum 25(OH)D concentrations < 50 nmol/L (71%) when compared with 34 matched controls (44.1%) (20). A 20 month study of 178 patients with AMD observed no difference between 25(OH)D concentrations across stages of AMD, but did observe lower 25(OH)D concentrations in patients with, compared to without, subretinal fibrosis, a clinical indication of late stage AMD (21). A retrospective cohort of Medicare beneficiaries (22) observed no association between Medicare claims for vitamin D deficiency and incident AMD diagnosis, even after stratification by race (white vs. black). Similar null results were observed in a cross-sectional analysis of members of a health maintenance organization (23). Medical diagnosis codes for AMD status were used to investigate associations with vitamin D status

determined as part of a clinical exam. In both studies, it is possible that misclassification of both AMD status and vitamin D status biased study findings to the null.

The current body of literature needs large studies involving well-defined cohorts where AMD cases are based on retinal photographs graded using reliable, standardized protocols, and vitamin D status is assessed using serum 25(OH)D concentrations with documented quality control measures to ensure minimal laboratory variation across batches of samples sent for analysis. These methods will help to minimize measurement error in both the exposure and outcome to enhance valid of study results. The Atherosclerosis Risk in Communities (ARIC) Study is a well-characterized epidemiologic cohort that has graded retinal fundus photographs for AMD and serum 25(OH)D measures assessed using LC-MS/MS with implemented quality control measures. ARIC data will allow us to investigate the association between vitamin D status and AMD in both whites and blacks, which has only been previously investigated in two studies (4, 23). Additionally, available data on genotypes of high risk AMD genes allows us the opportunity to investigate how genetic factors confound or modify the observed association of vitamin D status and AMD. Only one study (Millen et al., 2014 unpublished paper), conducted in primarily Caucasian, post-menopausal women, has investigated effect modification of the vitamin D and AMD association by high risk AMD genotype.

5. Main Hypotheses/Study Questions:

Main Study Questions

Note: We intend to analyze and interpret the data as though it were cross-sectional, even though the primary exposure and outcome measurements took place 3 years apart.

Question 1: Is there an association between serum 25(OH)D concentrations assessed at visit 2 (1990-1992), and the presence of early AMD assessed at visit 3 (1993-1995) among participants with retinal photographs at visit 3?

Hypothesis Q1: *We hypothesize that ARIC participants with adequate vitamin D status (25(OH)D >50 nmol/L) at visit 2 compared to those with deficient or inadequate vitamin D status (25(OH)D ≤ 50 nmol/L) will have lower odds for early AMD at visit 3.*

Question 2: Is this association between serum 25(OH)D and early AMD confounded or modified by variants in two high risk AMD genes [the Y402H polymorphism (rs1061170) in the complement factor H (*CFH)* gene and the A69S polymorphism (rs10490924) in the age-related maculopathy susceptibility protein 2 (*ARMS2)* gene]?

Hypothesis Q2: *We hypothesize that the protective association between vitamin D status and AMD will be strongest among individuals who have two high risk AMD alleles as compared to individuals with one or no high risk alleles.*

Question 3: Are there associations between proxy measures of vitamin D status (dietary vitamin D intake and physical activity assessed at visit 1 [1987-1989]; these measures were not available at visit 2 when serum 25(OH)D was assessed) and the presence of early AMD assessed at visit 3 (1993-1995) among participants with retinal photographs at visit 3?

Hypothesis Q3: *We hypothesize that ARIC participants with high compared to low dietary vitamin D intake and high compared to low physical activity will have lower odds for early AMD.*

Additional Study Questions

- Does age, race or gender modify the association between vitamin D status and early AMD?
- Is vitamin D status associated with the odds of late AMD? There are very few late AMD cases, but we will look at these data.

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 with gradable retinal fundus photographs taken at visit 3 (1993-1995) and available serum 25(OH)D concentrations at visit 2 (1990-1992). Of the 12,887 participants at visit 3, 12,091 gave permission for their data to be used for non-cardiovascular disease related studies. Of these, participants will be excluded if they are not of black or white race (n=34), do not have retinal photographs (n=228), or have ungradable retinal photographs for AMD (n=1,022). Of the remaining 10,807 participants, 1,017 do not have serum 25(OH)D measures at visit 2. This creates an analytic sample of 9,790 participants (7,815 white and 1,975 black). For analyses involving genetic data (Question 2), data for Y402H and A69S are available from imputation in 6,595 of the white participants. Imputed data have recently been completed in blacks to determine Y402H and A69S genotype and we are in the process of requesting this data from the ARIC Coordinating Center.

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).

Disease endpoints: Our disease endpoint is age-related macular degeneration (AMD) at visit 3. Among the 9,790 participants, there are 524 (5%) AMD cases. Of these 442 (5.7%) cases are in whites and 82 (4.2%) in blacks. Of the total cases, 13 are late AMD cases. Analyses will be conducted examining the odds of early and late AMD separately.

Serum 25-hydroxyvitamin D: Serum obtained at ARIC Visit 2 (1990-92) was used to assess 25(OH)D with liquid chromatography/tandem mass spectrometry (26) at the University of Minnesota, under the direction of Myron Gross (Minneapolis, MN). To adjust for season of blood draw, serum 25(OH)D concentrations we will be regressed (using a local polynomial smoother) on day of the year. Residuals from this regression will be added back to the sample 25(OH)D concentration mean. This regression will be done separately in whites and blacks and the residual-adjusted 25(OH)D concentrations will be used in all subsequent analyses.

Other Proxy Measures of Vitamin D Status:

Dietary and supplemental vitamin D data: An estimate of dietary vitamin D intake from foods is available from the Willett 66-item semi-quantitative food frequency questionnaire (FFQ) (27) administered at Visits 1 and 3. This FFQ has been previously validated (27) and shown to be reliable over a 3 year period in the ARIC cohort (28). Reported use of vitamin D and cod liver oil supplements (yes/no) was also ascertained at Visit 3.

Physical activity data as a proxy measure of sunlight exposure: Data was collected at Visits 1 and 3 on physical activity and will be used as a proxy measure of sunlight exposure. Vitamin D can be produced dermally upon exposure to UVB light. We have previously shown that time spent in recreational activity predicts serum 25(OH)D concentrations (29) and that recreational physical activity is a good proxy measure for sun exposure (30). A modified version of the Baecke questionnaire (31) was used to assess physical activity over the previous year while *at work*, when *engaged in sports*, and *during leisure time*; and has been previously tested for its validity and reliability (31-33). For each component of physical activity, a score ranging from 1 (low activity) to 5 (high activity) was created using algorithms for questionnaire responses (34). Scores for each type of physical activity will be combined to create an overall physical activity index score. The overall physical activity index score will also be assessed as a potential confounder of the association between serum 25(OH)D and AMD.

Genetic data: Genetic data are available in ARIC on a number of high risk AMD genes including *CFH* and *ARMS2*. Genotyping of single nucleotide polymorphisms (SNPs) in ARIC was completed using the Affymetrix Genome-Wide Human SNP Array 6.0 (35). 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 (36). We will use this data to explore whether either variant confounds or modifies the association between vitamin D and AMD.

Other pertinent covariates: We will investigate the following covariates as potential confounders: age, race, gender, field center, education, income, health insurance, smoking status, drinking status, ethanol intake, blood glucose level, weight, waist circumference, waist to hip ratio, body mass index (BMI), measures of serum total cholesterol, serum high density lipoprotein, serum triglycerides, and use of hormone therapy (in females), statins or aspirin. Diastolic and systolic blood pressure as well as hypertension status will be examined as pathway variables.

Proposed Analysis

Logistic regression models will be used to estimate the association between the log odds for early AMD in participants with adequate (≥50 nmol/L) compared to deficient or inadequate (<50 nmol/L) 25(OH)D concentrations. Odds ratios (OR) and 95% confidence intervals (95% CIs) will be reported. 25(OH)D will also be modeled as a continuous variable and in clinically defined 25(OH)D cutpoints based on adequate, inadequate and deficient levels defined by the Institute of Medicine (IOM) (16): <30 (deficient), 30 to <50 (inadequate), 50 to <75 (adequate) and ≥75 (adequate) nmol/L. If needed, cubic splines will be utilized to help us determine the most appropriate representation of the dose-response between 25(OH)D concentrations and AMD. Exploratory analyses will investigate results for subgroups of early AMD (drusen and pigmentary abnormalities) as well as for the odds of late AMD (minimal cases for this outcome exist).

We will investigate confounding by adding potential confounders to our model in a step-wise fashion. Potential confounders will be added to the model if they change the OR 10% or more. After development of the multivariate model for AMD we will explore the effect of addition of blood pressure and hypertension as a pathway variable to the multivariate model. We will also further adjust the multivariable model for high risk AMD genes.

We will explore effect modification of the vitamin D and AMD associations by age, gender and race and by variants in high risk AMD genes. We will test for interaction by adding interaction terms to our logistic regression models. A p-value <0.10 for the interaction term will be considered statistically significant. If significant interactions are present, stratified results will be reported, though interpretation will be guided by the cell sizes and precision of effect estimates. We acknowledge that power to evaluate effect modification is reduced compared to the power to investigate the main effects and therefore these are exploratory analyses.

Proxy Measures of Vitamin D Status: We will estimate the odds of early AMD by quintile of dietary vitamin D at visit 1, as visit 1 data precedes assessment of eye photos. A p for trend using continuous vitamin D intake will be estimated. If the associations between vitamin D intake and the log odds of early AMD appear linear, we will also estimate the odds of early AMD per 100 IU of dietary vitamin D intake. Further, we will examine the odds of early AMD by servings of vitamin D rich foods (milk and fish). The odds of early AMD will also be assessed by overall physical activity index score assessed at visit 1 using the score as an ordinal variable. We will also explore these associations using dietary vitamin D intake and physical activity measures from visit 3; and also by averaging the visit 1 and 3 data.

Limitations and possible solutions: A limitation of our data is the availability of retinal photographs in only one eye at Visit 3 for classification of retinal eye disease. Therefore, there may be misclassification of endpoints ascertained at Visit 3. As the eye photographed at Visit 3 was chosen randomly, we would expect non-differential misclassification of our endpoint which would bias our observed risk estimates toward the null. We also realize a limitation of these analyses is our inability to as determine causality, as we only have prevalent outcome data.

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? __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"? __X__ Yes ____ No

As we requested the genetic data from the ARIC Coordinating Center in 2014, we assume they have removed these individuals.

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 be those involving Pam Lutsey's work on vitamin D and cardiovascular disease. Other relevant proposals are those that focus on diabetic retinopathy and would involve Dr. Ronald Klein. Both Drs. Lutsey and Klein 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)*

*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

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