

**ARIC Manuscript Proposal #2357**

**PC Reviewed:** 5/13/14  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
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**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** Vitamin D, Vitamin D Binding Protein Genetic Polymorphisms, C-3 epimer Vitamin D3 and Cognitive Change Over 20-years: the Atherosclerosis Risk in Communities (ARIC) Study

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

**2. Writing Group:** Writing group members:

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

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### **3. Timeline:**

Vitamin D lab assays from ARIC visit 2 have been completed. We plan to work on this proposal immediately pending approval. We realize that for some sensitivity analyses, we will need to wait until the adjudicated dementia data are available.

### **4. Rationale:**

Low serum 25-hydroxyvitamin D [25(OH)D] levels are associated with an elevated risk of cardiovascular disease and its risk factors such as hypertension and diabetes<sup>1</sup>. Emerging data suggest that vitamin D may be important for cognitive functioning and may be protective against neurovascular injury<sup>2</sup>. Vitamin D receptors are located in the human cortex and hippocampus are important for cognitive functioning, and vitamin D receptors down regulation in these key areas has been associated with Alzheimer's disease<sup>2</sup>.

The literature regarding the cross-sectional association of 25(OH)D levels and performance on neurocognitive testing has been conflicting. Most, but not all, cross-sectional studies have found an association of 25(OH)D levels with at least one marker of cognitive function<sup>3-11</sup>. These studies were limited by their cross-sectional design and direction of association cannot be determined. There have only been a few published prospective studies of vitamin D and cognitive decline<sup>12-15</sup>. These studies were largely limited to only older white populations, but have tended to find protective effects of high vitamin D levels, raising the possibility that vitamin D supplementation may be useful for the prevention of cognitive decline and dementia. However, among the longitudinal studies published, mean follow-up time was between 5 and 10 years. Given that sun exposure and subsequent skin synthesis is a major source of vitamin D, and people with cognitive impairment spend less time outdoors, exploring the association between vitamin D and cognitive function cross-sectionally or in studies with short follow-up is potentially problematic due to the possibility of reverse causation, whereby those with prevalent cognitive impairment/dementia may be less likely to spend time outdoors and therefore would have lower levels of vitamin D.

We previously analyzed the association of 25(OH)D levels measured during the ARIC visit 3 (1993-1995) with cognition among 852 whites and 800 blacks participants of the ARIC Brain MRI ancillary study from the Jackson and Forsythe County sites (ARIC MSP #2021, paper accepted to *European Journal of Neurology*). We found that lower 25(OH)D was not associated with 3 cognitive measures (DWRT, DSST, WFT) cross-sectionally at visit 3, nor with greater DWRT, DSST, or WFT decline for both short term follow-up (visit 3 to visit 4) and ~10-year follow-up (visit 3 to the 2004-2006 ARIC Brain MRI visit) ( $p > 0.05$  for all associations). Over a median of 16.6 years, there were 145 incident hospitalized dementia cases. Though not statistically significant, lower levels of 25(OH)D were suggestive of an association with increased dementia risk (HR lowest versus highest race-specific tertile: whites 1.32 [95% CI: 0.69, 2.55]; blacks 1.53 [95% CI: 0.84, 2.79]). We concluded that in contrast to prior studies performed in older white populations, our study did not find significant associations between lower levels of 25(OH)D measured in late-middle age black or white participants with lower cognitive test scores at baseline, change in scores over time, or dementia risk.

Since our original paper proposal, vitamin D levels have been newly measured at ARIC visit 2 (years 1990-1992) in the full cohort (~14,000), a much larger sample size than our previous analyses. Therefore, to further evaluate this question regarding vitamin D and cognition, we propose to expand on our prior work from the previous proposal by looking at the association of 25(OH)D measured at ARIC visit 2 with cognitive testing through ARIC-NCS (visit 5), a much longer follow-up of approximately 20 years.

Additionally, recent work has shown that blacks and whites have similar concentrations of estimated bioavailable 25(OH)D, secondary to blacks having lower levels of both total 25(OH)D and vitamin D binding protein compared to whites<sup>16</sup>. There are two common single nucleotide polymorphisms (SNPs), rs7041 and rs4588, that are associated with the vitamin D binding protein gene<sup>16</sup>. Blacks have been shown to be more likely than whites to have a T allele at rs7041 and to have a C allele at rs4588<sup>16</sup>. The rs7041 G versus T allele and the rs4588 A versus C allele have been shown to genetically predispose individuals to higher vitamin D binding protein levels and thus lower levels of bioavailable vitamin D for a given total 25(OH)D concentration. Additionally, newer 25(OH)D assays using mass spectroscopy have allowed for measurement of C-3 vitamin D3 epimer [3-epi-25(OH)D3], but the clinical significance of 3-epi-25(OH)D3 is not known<sup>17</sup>. Therefore, we propose to investigate the association of 25(OH)D and 3-epi-25(OH)D3 measured at ARIC visit 2 with cognitive change measured over 20-years. We propose to investigate possible effect modification in these associations by race and by vitamin D binding protein SNP status.

## 5. Main Hypothesis/Study Questions:

1. To determine whether 25(OH)D levels (measured in mid-life) are independently associated with cognitive change (assessed by the Delayed Word Recall Test [DWRT], the Digit Symbol Substitution Test [DSST], the Word Fluency Test [WFT], and a composite global z-score) over 20 years of follow-up.

Hypothesis: Low 25(OH)D levels will be significantly associated with global cognitive decline, cognitive decline on DSST and WFT (reflective primarily of vascular disease pathology) and on DWRT (test of memory, more reflective of Alzheimer's disease pathology) over 20-years of follow-up.

2. To determine whether the association of 25(OH)D with cognitive change differs by race.

Hypothesis: Associations of low vitamin D with cognitive change over 20-years of follow-up will be similar by race.

3. To determine whether the association of 25(OH)D with cognitive change differs by vitamin D binding protein polymorphism status (SNPs rs7041 and rs4588).

Hypothesis: The association of 25(OH)D with cognitive change will differ by vitamin D binding protein polymorphism status. Low vitamin D among individuals with genotypes associated with higher vitamin D binding protein levels (G allele of rs7041 and A allele

of rs4588) and thus lower levels of bioavailable vitamin D for a given 25(OH)D level, will be more strongly associated with cognitive decline over 20-years of follow-up.

4. To determine whether 3-epi-25(OH)D3 levels are independently associated with cognitive change (assessed by the Delayed Word Recall Test [DWRT], the Digit Symbol Substitution Test [DSST], the Word Fluency Test [WFT], and a composite global z-score) over 20 years of follow-up.

Hypothesis: Due to the unknown clinical significance of 3-epi-25(OH)D3, we do not have any a priori hypothesis about the association of 3-epi-25(OH)D3 with cognitive change. This analysis is purely hypothesis generating and exploratory in nature.

## **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: Prospective cohort study (baseline ARIC visit 2: 1990-1992 through ARIC visit 5 (2011-2013)).

Participants: All white and black (excluding blacks from Minnesota/Maryland) ARIC participants with cognitive test data and 25(OH)D measured at ARIC visit 2 who are not missing genetic data (vitamin D binding protein SNPs: rs7041 and rs4588) and not missing covariates included in statistical models.

We additionally will exclude data from individual study visits (not participants) when the individual reports taking CNS altering medications that may affect cognitive test performance. We will also consider excluding data from individual study visits (not participants) that occur after a stroke.

Vitamin D variables: This proposal makes use of the newly measured 25(OH)D2, 25(OH)D3, and C-3 Epi-25(OH)D3 levels measured from serum samples and stored at -70°C until analyzed using liquid chromatography-tandem high-sensitivity mass spectrometry (Waters Alliance e2795, Milford, Massachusetts) in 2012-2013. The inter-assay coefficient of variations (CVs) for 25(OH)D2 is 10.9%, for 25(OH)D3 is 6.2%, and for 3-epi-25(OH)D3 is 9.2%. 25(OH)D2 and 25(OH)D3 were added together for total 25(OH)D concentration. This proposal also considers vitamin D binding protein polymorphism status (rs7041 and rs4588).

*Seasonally adjusted 25(OH)D:* 25(OH)D concentrations vary by season. Therefore will we adjust 25(OH)D for seasonal change by computing the residuals from a linear regression model with 25(OH)D as the dependent variable and month of visit as the independent variable. The residuals will be added back to the grand mean to determine an estimated annual 25(OH)D value. We will perform this adjustment separately for whites and for blacks, as 25(OH)D concentrations also vary by race. This vitamin D adjusted for month of visit will be used in all analyses. For the primary analysis, 25(OH)D will be categorized into quintiles based on the overall cohort, as the association of vitamin D with cognitive decline/dementia is not expected to be linear. We will

assess for any threshold effects and condense categories as appropriate (e.g. top 4 quintiles versus lowest quintiles).

*C-3 Epi-25(OH)D3*: 3-epi-25(OH)D3 will be categorized as undetectable, <limit of quantification,  $\geq$ limit of quantification. 3-epi-25(OH)D3 concentration varies with 25(OH)D concentration, but does not vary as much by season, so we will not create a seasonally adjusted 3-epi-25(OH)D3 variable. We will adjust for season (January-March; April-June; July-September; October-December) in all 3-epi-25(OH)D3 analyses.

*Vitamin D binding protein SNPs (rs7041 and rs4588)*: We will categorize rs7041 as TT (reference) versus TG/GG and rs4588 as CC (reference) versus AC/AA.

Covariates: Demographic factors: age (continuous, centered), age<sup>2</sup> (continuous, centered), sex (male; female), and race/center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks).

Socioeconomic and lifestyle factors: education (<high school; high school, GED, vocational school; college, graduate or professional school), smoking (never; former; current), alcohol consumption (never; former; current), physical activity (continuous, centered), and vitamin D supplementation use (yes; no; more as a surrogate for health seeking behavior). Vitamin D supplementation use was not well characterized at visit 2, but we could consider using visit 3 data for this variable.

Cardiovascular disease related factors: body mass index (<25 kg/m<sup>2</sup>; 25-<30 kg/m<sup>2</sup>,  $\geq$ 30 kg/m<sup>2</sup>), hypertension (yes; no; defined as diastolic blood pressure  $\geq$ 90 mmHg or systolic blood pressure  $\geq$ 140 mmHg or hypertension medication use), diabetes (yes; no; defined as fasting glucose  $\geq$ 126 mg/dl or non-fasting glucose  $\geq$ 200 mg/dl or self-reported physician diagnosis or diabetes medication use), prevalent stroke (yes; no; defined by standardized criteria and physician adjudication), and prevalent coronary heart disease (yes; no; defined by standardized criteria and physician adjudication).

We will also include two spline terms for time in our models (time <6 years and time >6 years; split at median of visit 4 dates, per NCS analysis guidelines), as well as interactions between each of our covariates and both time spline terms.

Possible Effect Modifiers: Race and vitamin D binding protein SNPs (rs7041 and rs4588).

Outcome Ascertainments (Cognitive Tests): Cognitive testing measured by DWRT, DSST, and WFT was performed at ARIC visit 2 (1990-1992), visit 4 (1996-1998), and visit 5 (2011-2013).

The DWRT<sup>18</sup> is a test of verbal learning and recent memory. Participants were given 10 common nouns that they were asked to learn by using each word in one or two sentences. After a five-minute delay, participants were given 60 seconds to recall the 10 words. The score is the number of words correctly recalled.

The DSST<sup>19</sup> is a test of executive function and processing speed. Participants were asked to translate numbers to symbols using a key. The score (range 0-93) is the total number of numbers correctly translated to symbols within 90-seconds.

The WFT<sup>20</sup> is a test of executive function and language, and tests the ability to spontaneously generate words beginning with a particular letter, excluding proper names or places. Participants were given 60 seconds for each of the letters “F”, “A”, and “S”. The score is the total number of words generated across the three trials.

We will perform analyses using the raw cognitive test scores and using z-scores that were generated by the ARIC coordinating center for each cognitive test (at visits 2, 4, and 5), standardized using the visit 2 mean and standard deviation. We will also perform analyses using a global z-score. The coordinating center also averaged test z-scores to create global z-scores, which were then standardized using the visit 2 global z mean and standard deviation.

Data Analysis: All analyses will be performed in accordance with the ARIC-NCS analysis working group recommendations (details can be found in the ARIC-NCS analysis plan).

Briefly, we will use Generalized Estimating Equations (GEE) linear regression models with an unstructured correlation matrix (to account for within-person repeated cognitive test data) and robust variance to estimate the association between vitamin D and cognitive change over 20-years of follow-up. Time on study will be modeled using a linear spline with a knot at 6 years (approximately the time of visit 4). We will explore if more than one spline knot is needed by examining lowess and scatter plots of residuals versus time. Our primary coefficients of interest will be the interaction of vitamin D category with time spline terms.

Models will be adjusted for age, age<sup>2</sup>, sex, race/center, education, smoking, alcohol consumption, physical activity, vitamin D supplementation use, body mass index, hypertension, diabetes, prevalent stroke, and prevalent coronary heart disease. We will also consider further adjustment for biomarkers associated with 25(OH)D, including parathyroid hormone, calcium, and phosphate.

We will formally test for interaction by race and by vitamin D binding protein polymorphism genotype (rs7041 and rs4588). If there is any evidence for interaction by race or by polymorphism status, results will be presented stratified.

In accordance with the ARIC-NCS analysis working group recommendations, we will also perform sensitivity analyses to account for the significant attrition (dropout/death) in the cohort over the 20-year follow-up period. One method that we will use is inverse probability of attrition weighting (IPAW). IPAW will be performed using GEE linear regression with an unstructured correlation matrix (to account for within-person repeated cognitive test data) and robust variance. Another method is “expanded measurement,” whereby we estimate cognitive test scores for those participants that developed dementia (until the adjudicated dementia data is available we will be using ICD-9 codes for dementia hospitalization). We will use linear mixed models with an unstructured correlation matrix (to account for within-person repeated cognitive test data) and robust variance when performing these “expanded measurement” analyses.

Limitations/Challenges:

One challenge in this analysis is attrition. However, we propose two methods to account for attrition in this proposal (IPAW and expanded measurement). Using these attrition-adjustment methods will likely provide more accurate estimates of the effect of vitamin D on cognition, but it remains possible that our method of adjustment does not fully account for the effects of dropout and death. Other limitations of our study include only one test comprising each cognitive domain at each visit and a single measurement of vitamin D at baseline in the full cohort. Additionally, as in all observational studies, there remains the possibility of residual confounding.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**     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?**

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     No

Yes – we will look at vitamin D binding protein polymorphisms rs7041 and rs4588.

**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”?**     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.csc.unc.edu/ARIC/search.php>**

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)?**

This proposal most closely overlaps with our previous proposal #2021 (Michos; Schneider), regarding vitamin D (measured at visit 3 in a subset ~1600) and cognitive decline through 2004-2006 (~10 year follow-up). This new proposal expands on our previous work by testing this association in nearly the whole cohort at visit 2 (N~13,000), a much larger sample, and updating cognitive decline through ARIC-NCS, a longer follow-up period (~20 year follow-up). Most of

the writing committee (and analyst, Dr. Schneider) is the same to ensure consistency of methods used.

This proposal also is similar to other proposals that investigate associations between mid-life risk factors (i.e., measured at ARIC visit 2) and cognitive change between ARIC visits 2 and 5 (see below). We include some of the authors of in the author group for this proposal. We will work in accordance with the NCS analysis working group policies (i.e., before submission, we will circulate the manuscript to all listed on the “back-page” acknowledgments section). All analyses will be conducted in accordance with the recommendations set forth by the NCS working group (the analyst, Dr. Schneider, is familiar with these methods and performed the analyses for MS #2175 previously).

#2160 - Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study (Rawlings)

#2175 - Midlife blood pressure and 20-year cognitive change: The ARIC-Neurocognitive Study (Gottesman)

#2284 - Lifetime socioeconomic position and cognitive decline: the ARIC-NCS study (Patel)

#2135 - Abnormal sleep characteristics and cognitive change: The Atherosclerosis Risk in Communities Study (Lutsey)

#2327 - Hearing impairment and cognitive performance in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS): cross-sectional and longitudinal results (Deal)

#1982 - Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS (Gottesman)

#2179 - Ischemic stroke risk score at baseline and 20-year cognitive decline: The Atherosclerosis Risk in Communities Study (Wruck)

#2245 - Lower extremity arterial disease and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (Palta)

#2201r - Lipids, stains, and 20-year cognitive change: The ARIC-Neurocognitive Study (Power)

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

**11.b. If yes, is the proposal**

**A. primarily the result of an ancillary study (list number\* 2009.17)**

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

Lutsey ARIC Ancillary Study number 2009.17

Michos ARIC Ancillary Study number 2010.01

Selvin ARIC Ancillary Study number 2009.16

\*ancillary studies are listed by number at <http://www.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

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