ARIC Manuscript Proposal #2224

PC Reviewed: 9/10/13 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: 25-hydroxyvitamin D and risk of incident heart failure: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Vitamin D & incident heart failure

2. Writing Group: Pamela L Lutsey, Erin D. Michos, Jim Pankow, Linda Kao, Laura Loehr, Myron Gross, John Eckfeldt, Aaron R. Folsom, Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _X_

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3. Timeline: Data analyses will begin immediately. Goal completion is Dec 2013.

4. Rationale:

Vitamin D is a fat-soluble vitamin obtained through cutaneous synthesis resulting from sun exposure, and through oral intake from food and supplement sources[1]. Insufficient vitamin D, as assessed by low circulating 25-hydroxyvitamin D [25(OH)D], has recently drawn attention as a potential CVD risk factor. Suboptimal vitamin D is thought to influence CVD risk predominantly by acting on established CVD risk factors, namely hypertension[2-8], diabetes[9-13], and inflammation[37, 38].

Low vitamin D levels have been prospectively associated with greater risk of heart failure (or heart failure mortality) among members of the Intermountain Healthcare System[14] and in a population of Germans referred for coronary angiography[15]. Additionally, low 25(OH)D has also been linked to heart failure in cross-sectional data from NHANES[16] and in a number of small clinical studies[17-20].

It is presently unclear whether the association between vitamin D and heart failure varies by race/ethnicity. Relative to whites, it is well-known that African Americans have low vitamin D levels but paradoxically high bone density and low fracture risk[21]. Additionally, there is some suggestion that associations of low vitamin D with risk of diabetes[22], peripheral artery disease[23], stroke[24], and coronary heart disease[25] are stronger in whites then blacks. However, these studies were limited in that they were cross-sectional and/or had limited power for race/ethnicity-stratified analyses. Racial differences in vitamin D metabolism are suspected to underlie the racial/ethnic interaction: black individuals have higher circulating concentrations of $1,25(OH)_2D$ at a given level of 25(OH)D[26], and vitamin D receptor gene affinity and polymorphism frequencies vary by race[27]. Additionally, it is presently unknown whether there is racial variation in vitamin D binding protein levels, and/or the ratio of free (bioavailable) 25(OH)D to total 25(OH)D.

5. Main Hypothesis:

1. Serum vitamin D will be inversely associated with risk of incident heart failure, but this association will be partly mediated with adjustment for traditional CVD risk factors and kidney function.
2. The association between vitamin D and heart failure will be stronger among Caucasians then among African Americans.
3. Among African Americans, the association between vitamin D and incident heart failure will be stronger among those with a greater proportion of European ancestry, relative to those with a lesser proportion of European ancestry.

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 from visit 2 through the most recent follow-up data available.

Inclusion/Exclusion

Participants with prevalent heart failure at visit 2 will be excluded, as will those who are neither African American nor white, and African Americans from the MN and MD centers. For admixture analyses, which will be restricted to African Americans, we will also exclude those who did not consent to genetic research.

Variables

Exposures:

Primary: Serum 25(OH)D (measured in visit 2 serum; sum of $25(OH)D_2$ + $25(OH)D_3$). Since serum vitamin D levels vary greatly by sun exposure, which is seasonal, we will account for seasonal variation by computing the residuals from a linear regression model with vitamin D as the dependent variable and month of blood draw as the independent variable. By definition, these residuals will be uncorrelated with month of blood draw. The grand mean will be added to the vitamin D residuals obtained from this model. This new variable "vitamin D adjusted for month of blood draw" will be used as the main exposure variable for all analyses.

Secondary: We will also look, separately, at associations of the vitamin D epimer [3-epi-25(OH)D3], vitamin D2 [25(OH)D2] and vitamin D3 [25(OH)D3] with risk of incident heart failure.

Outcome: Incident heart failure hospitalization.

Main covariates: Age, race, center, sex, education, physical activity, smoking status, BMI, diabetes, LDL-C, HDL-C, triglycerides, antihyperlipidemic medication use, CRP, mean systolic blood pressure, antihypertensive medication, eGFR (modeled as $\geq$90, 60-89, and 15-59 ml/min/1.73 m^2). eGFR will be calculated using both creatinine and cystatin-C[28].

Potential effect modifiers: Age, race, sex, eGFR, serum magnesium, genetic admixture (in African Americans only).

Data analysis

Visit 2 will serve as baseline for the current analysis. Visit 2 participant characteristics will be described using means and proportions stratified by levels of vitamin D. We will also evaluate whether vitamin D serum level is correlated with genetic ancestry.

Cox proportional hazards regression will be used to explore associations between vitamin D and risk of incident heart failure. We will use restricted cubic splines to characterize the continuous association, and aid in selecting the most appropriate exposure representation. Our first model will adjust for age, sex, and race-center. Model 2 will additionally adjust for education, physical activity, smoking status and BMI. Model 3 will further adjust for prevalent diabetes, prevalent CHD, systolic BP, hypertension medication use, lipid medication use, LDL-C, HDL-C, and CRP. Additional models will, separately, adjust for factors which may clearly be mediators of any association between vitamin D and heart failure: eGFR, PTH, FGF23, and incident CHD as a time-varying covariate. Mediation will be considered present if beta coefficients are altered by 10% or more upon inclusion of potential mediators in the statistical models.

Cross-product terms will be used to evaluate whether age, race, sex, and/or eGFR modify associations between vitamin D and risk of incident heart failure. Given inherent interest, we will report race-stratified results, regardless of whether a significant race-interaction is present. In African Americans only, we will also evaluate whether genetic admixture modifies the relation between vitamin D and heart failure. The genetic

ancestry variable is highly skewed with very few African Americans with >50% European ancestry. Therefore we will likely restrict this analysis to people with between 0% and 50% European ancestry.

In sensitivity analyses, we will restrict our analysis to participants with normal kidney function, and separately, those whose self-reported health was good, very good, or excellent at visit 2. The rationale for restriction based on self-reported health is that participants who are ill may be less likely to go outside and be exposed to sunlight, and thus have lower vitamin D levels. Restricting based on health status will hopefully help control for confounding by comorbid conditions. Additional sensitivity analyses may be conducted excluding participants with a myriad of prevalent conditions at visit 2, and also those with high CRP. Sensitivity analyses will also censor participants upon incident CHD, stroke, and CKD.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X_ 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 ICTDER 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

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)?

#1893: Serum magnesium, phosphorus, calcium and risk of incident heart failure: The Atherosclerosis Risk in Communities Study. *Pamela L. Lutsey, Aaron R. Folsom, Alvaro Alonso, Laura Loehr, Brad Astor, Joe Coresh.*

#2108: Fibroblast growth factor-23 and incident coronary heart disease, heart failure, and total mortality: The Atherosclerosis Risk in Communities Study (ARIC). *Pamela L Lutsey, Jim Pankow, Alvaro Alonso, Joe Coresh, Elizabeth Selvin, Erin Michos, Sunil Agarwal, Laura Loehr, John Eckfeldt.*

#2019: 25-hydroxyvitamin D levels and incident stroke: Twenty-year followup in a biethnic cohort. *Erin D Michos, Pamela Lutsey, Tom Mosley, Richey Sharrett, Kathryn Carson, Wendy Post, Rebecca Gottesman, Aaron Folsom, Jim Pankow*

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

2009.17 (Lutsey PI)
- "Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort"

2009.16 (Selvin PI)
- "Short-term markers of glycemia and long-term outcomes"
- Numerous biomarkers which may be confounders and/or effect modifiers in the present analysis were measured as part of this grant (e.g. CysC, CRP, BNP and TNT).

2005.02 (Kao PI)
- "Genome-wide association analysis of type 2 diabetes using mapping by admixture linkage disequilibrium (MALD) (AADMMALD)"
- Percent ancestry was calculated as part of this ancillary study.

___ 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.

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