ARIC Manuscript Proposal # 3137

PC Reviewed: 2/20/18  Status: _____  Priority: 2
SC Reviewed: _________ Status: _____  Priority: ____

1.a. **Full title:** Serum albumin as a risk factor for short-term hospitalization and death in older adults: the Atherosclerosis Risk in Communities (ARIC) Study

1.b **Abbreviated title (Length 26 characters):** Albumin in older adults

2. **Writing group:**

   Writing group members:
   Colleen Shannon, BA
   Amy Saenger, PhD, DABCC
   Shoshana Ballew, PhD
   Josef Coresh, MD, PhD, MHS
   Elizabeth Selvin, PhD, MPH
   Morgan Grams, MD, MHS, PhD
   *Others welcome*

I, the first author, confirm that each of the coauthors have given his or her approval for this manuscript proposal. CMS

**First author:** Mrs. Colleen Shannon  
**Address:** Johns Hopkins Bloomberg School of Public Health  
615 N. Wolfe St.  
Baltimore, MD 21218

**Phone:** 610-505-5396  
**E-mail:** colleen.shannon@jhu.edu  

**ARIC author:** Dr. Morgan Grams  
**Address:** 2024 E. Monument Street  
Room 2-638  
Baltimore, MD 21287

**Phone:** 443-287-1827  
**E-mail:** mgrams2@jhmi.edu

3. **Timeline:**

Analysis will be completed by 4/30/2018. A manuscript draft will be ready for co-author review by 6/30/2018.
4. **Rationale:**

Prior studies have reported associations between low serum albumin and adverse health outcomes. In 1989, Phillips et al. observed an inverse association between serum albumin level and mortality that persisted even after adjustment for potential confounders. In 1992, Klonoff-Cohen et al. confirmed the inverse association between serum albumin concentration and mortality. These early findings have been supported by a number of later studies. Since that time, lower serum albumin has been associated with a variety of adverse outcomes, including—but not limited to—cardiovascular disease, kidney disease, and diabetes. It has further been found to have prognostic value in hospitalized, older adults.

Serum albumin is an acute-phase reactant that decreases in the setting of inflammation. It may also serve as a marker for nutritional status. As such, there is reason to believe that lower serum albumin may be associated with risk of both hospitalization and death among community-dwelling, older adults. If the strengths of these associations are greater than those of some traditional risk factors, serum albumin may improve prediction accuracy for the outcomes of interest.

5. **Main hypothesis/study questions:**

We hypothesize that low serum albumin will be associated with increased short-term risk of both all-cause hospitalization and death in community-dwelling, older adults. We anticipate that serum albumin concentration will improve short-term prediction of hospitalization risk and mortality over and above prevalent health status. We hypothesize that these associations will be similar by frailty status.

6. **Design and analysis:**

*Study Design:* We will conduct a prospective cohort analysis using visit 5 (2011-2013) as baseline and subsequent follow-up data for hospitalizations and deaths. We will exclude participants with missing serum albumin or covariates.

*Exposure:* Serum albumin, as measured in g/dL, during visit 5. Both albumin and glycated albumin were measured in serum using a method developed by Asahi Kasei Pharma and adapted to the Roche Mod P800 chemistry analyzer manufactured by Roche Diagnostics in Indianapolis, IN. The assay requires two separate measurements. First, total albumin was measured using the bromocresol purple method. Second, glycated albumin was measured using an enzymatic method that relies on ketoamine oxidase and an albumin-specific protease.

Glycated albumin is expressed as a percentage of total albumin using the following formula:

\[ \frac{(\text{glycated albumin concentration (g/dL)} / \text{serum albumin concentration (g/dL)})}{1.14} + 2.9 \]. For albumin, the lower and upper limits of detection are: (1 g/dL, 16 g/dL). For glycated albumin, the lower and upper limits of detection are: (1 g/dL, 12 g/dL). For albumin,
coefficients of variation were 1.9% at a concentration of 4.48 g/dL and 4.0% at a concentration of 2.5 g/dL. Serum albumin will be analyzed both as a continuous variable, using linear splines as needed for non-linear associations, and as a categorical variable using quartiles.

**Outcomes:**
1) Number of hospitalizations, as determined through self-report during semi-annual telephone follow-up and active surveillance of local hospitals.
2) Death, as ascertained through linkage to the National Death Index.

**Covariates:**
1) Age
2) Sex
3) Race-center
4) Body mass index (BMI)
5) Smoking status
6) Presence of inflammatory state, as measured by C-reactive protein (mg/L)
7) Hypertension status, with hypertension defined as:
   a. Systolic blood pressure > 140 mm Hg,
   b. Diastolic blood pressure > 90 mm Hg, or
   c. Hypertensive medications taken within the last 4 weeks
   *Alternate definitions (such as the new guideline definition) will be explored using sensitivity analyses
8) Diabetes status, with diabetes defined as:
   a. HbA1c ≥ 6.5%,
   b. Fasting plasma glucose ≥ 126 mg/dL, or non-fasting glucose ≥200 mg/dL
   c. Diabetes medications taken within the last 4 weeks
9) Kidney function, measured using
   a. eGFR (mL/minute/1.73 m²), as measured using creatinine
   b. Urine albumin (mcg/L) to creatinine (mg/L) ratio
   *Alternate definitions (such as eGFR assessed with cystatin C and both cystatin C and creatinine) will also be explored in sensitivity analysis
10) Cardiovascular disease status, with cardiovascular disease present if:
    a. Self-reported heart failure,
    b. Self-reported coronary heart disease,
    c. Self-reported history of myocardial infarction, or
    d. Self-reported history of stroke
11) Chronic obstructive pulmonary disease (COPD) status, with COPD present if self-reported COPD
12) Cancer status, with cancer present if self-reported current cancer at any site
    *Alternate definitions (such as those identified by cancer registry linkage) will also be explored in sensitivity analysis
13) Frailty, with frailty defined using the Cardiovascular Health Study criteria
    *Alternate definitions (such as those using variables of physical function) will also be explored in sensitivity analysis

**Main Analyses:**
1) Characterize the distribution of serum albumin among community-dwelling, older adults.
2) Estimate the relative risk of hospitalization per g/dL increase in serum albumin using Poisson regression or—if the outcome is over-dispersed—negative binomial regression.
   a. Model 1: Unadjusted
   b. Model 2: Adjusted for age, sex, and race-center
   c. Model 3: Model 2 + adjusted for BMI, smoking, CRP, hypertension, diabetes, chronic kidney disease, cardiovascular disease, chronic obstructive pulmonary disease, cancer, and frailty
3) Estimate the hazard ratio for death per unit change in serum albumin level using Cox regression models.
   a. Model 1: Unadjusted
   b. Model 2: Adjusted for age, sex, and race-center
   c. Model 3: Model 2 + adjusted for BMI, smoking, CRP, hypertension, diabetes, chronic kidney disease, cardiovascular disease, chronic obstructive pulmonary disease, cancer, and frailty
4) Determine the contribution of serum albumin to prediction of mortality using Harrell’s C-statistic, comparing model 3 without serum albumin to model 3 with serum albumin.
5) Assess for effect modification by age, sex, CKD, diabetes, and frailty status

Limitations:
The results may not be generalizable to institutionalized older adults, including those receiving hospital or residential care. We will have limited power to examine important demographic subgroups. Also, serum albumin was quantified using a bromocresol purple method (Lucica GAL Glycated Albumin assay, Asahi Kasai Pharma Corp) rather than a bromocresol green method. The UMN laboratory conducted a validation study of the two methods (n=20 serum samples), which demonstrated an R^2 of 0.9455. These results will be described in more detail and included in an appendix to the manuscript.

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?
   _____ 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”?

___ 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)?
   Albumin levels and atherosclerosis (MS 198)
   Levels of albumin, creatinine, and incident coronary heart disease (MS172)
   Association of serum albumin and incident stroke—the ARIC study (MS 441)
   Associations of serum albumin with lower extremity arterial disease and carotid artery plaque in participants without symptomatic cardiovascular disease at baseline (MS 380)

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

___ A. primarily the result of an ancillary study
 ___ x B. primarily based on ARIC data, with ancillary data from study number 2009.16 playing a minor role

*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


