1.a. Full Title: Serum magnesium, phosphorous, calcium and risk of incident heart failure: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Serum Mg, P, Ca & Heart Failure


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

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3. Timeline: Data analysis to being immediately, anticipated draft completion Summer/Fall 2012

4. Rationale:
   Heart failure (HF) is a common cause of morbidity and mortality in the developed world. At 40 years of age, the lifetime risk for developing HF is 20% for both men and women\(^1\). Although some risk factors for heart failure are firmly established (e.g.
increasing age, hypertension, diabetes, antecedent myocardial infarction), given the high societal burden of heart failure there is interest in identifying new characteristics which may be associated with heart failure development.

Magnesium, phosphorous and calcium are micronutrients traditionally viewed in relation to bone health or chronic kidney disease (CKD). Recent work has suggested they may also be related to risk of cardiovascular disease (CVD). Magnesium is believed to be linked to CVD risk through a broad range of physiological roles. Low levels have been associated with impaired glucose homeostasis and insulin action, elevated blood pressure, chronic inflammation, impaired vasomotor tone and peripheral blood flow, and electrocardiogram abnormalities\textsuperscript{2, 3}. Epidemiologically, low serum magnesium has been linked to both increased CVD risk factors\textsuperscript{4-9} and events\textsuperscript{3, 10-13}.

High phosphorous levels have also been associated with elevated risk of CVD\textsuperscript{14-17} and poorer outcomes among chronic kidney disease patients\textsuperscript{18} in epidemiologic studies. Although the mechanisms are not entirely clear, elevated serum phosphorous is thought to influence CVD risk through vascular calcification\textsuperscript{19}, myocardial fibrosis\textsuperscript{20}, and development of left ventricular hypertrophy\textsuperscript{21}.

Results of epidemiological investigations exploring relations of serum calcium to CVD have been mixed\textsuperscript{14, 15}. Mechanisms linking calcium levels to risk of CVD are similar to those proposed for elevated phosphorous.

Although prior studies have explored the relation of magnesium, phosphorous, and calcium to risk of CVD risk factors and other CVD phenotypes, relatively little is known about the relation of these micronutrients to risk of heart failure\textsuperscript{14, 17}. As such, we propose to explore these relations in the ARIC cohort. Given the nature of the micronutrients being explored as well as of heart failure, special attention will be paid to racial/ethnic differences in associations, and whether or not the incident heart failure was preceded by hypertension, CKD, diabetes and/or myocardial infarction.

5. **Main Hypothesis:**
   - Low serum magnesium will be associated with greater risk of incident heart failure.
   - High serum phosphorous will be associated with greater risk of incident heart failure.
   - Serum calcium will not be associated with risk of incident heart failure.

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 baseline to most recent follow-up.

**Inclusion/Exclusion**
Participants with prevalent heart failure at baseline will be excluded, as will those who are neither African American nor white, and African Americans from the MN and MD centers. For analyses where magnesium is the exposure of interest we will also conduct sensitivity analyses to evaluate whether or not it is prudent to exclude participants taking diuretics.
Variables

Exposures: Serum magnesium, phosphorous, calcium, calcium corrected for albumin\(^{15}\), and calcium*phosphorous.

*Note*: In instances where the exposures were measured at both visits 1 and 2, we will explore simply averaging the measures, or using a cumulative average approach, in addition to looking at the baseline values.

Outcome: Incident heart failure based on hospital ICD codes

Potential effect modifiers and/or mediators: Race, sex, hypertension, diabetes, eGFR (modeled as \(\geq 90, 60-89,\) and \(15-59\) ml/min/1.73 m\(^2\)) and myocardial infarction.

Other confounders: Age, sex, ARIC field center, education, physical activity, smoking status, BMI, diabetes, LDL-C, HDL-C, triglycerides, and antihyperlipidemic medication use. When evaluated as a confounder, we may use SBP and antihypertensive medication use in lieu of prevalent hypertension. Serum potassium will also be evaluated to determine whether it is a confounder.

Data analysis

Baseline characteristics of participants will be described using means and proportions stratified by levels of the exposures (some may be in supplemental tables due to space limitations). Cox proportional hazards regression will be used to explore relations between serum magnesium, phosphorous, calcium and risk of incident heart failure. The micronutrients will be modeled both as quintiles, and also according to clinically relevant cut-points, where present. Cubic splines may also be used to visually depict the associations, and aid in selecting the most appropriate representation.

Our first model will adjust for age, sex, and race*ARIC field center. Model 2 will additionally adjust for education, physical activity, smoking status and BMI. Model 3 will further adjust for prevalent hypertension, diabetes, eGFR and CHD as well as LDL-C, HDL-C, triglycerides, antihyperlipidemic medication use, and possibly serum potassium. Sensitivity analyses will explore the impact of modeling hypertension, diabetes, eGFR and myocardial infarction as time-dependent covariates. Updated information on these variables will come from study visits, as well as annual follow-up phone calls (i.e. HTN, DM) and events surveillance (i.e. MI).

Cross-product terms will be used to evaluate whether race, sex, hypertension, diabetes, kidney function, and/or myocardial infarction modify the relations of serum magnesium, phosphorous and calcium to risk of incident heart failure. Stratified results will be presented, as appropriate. Mediation will be considered present if beta coefficients are altered by 10% or more upon inclusion of diabetes, hypertension, eGFR, or myocardial infarction in the statistical models.

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 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  ___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.csc.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)?

PUBLISHED (Please note that heart failure was not included in as an outcome in any of these prior ARIC manuscripts)


NOT YET PUBLISHED

#1845: Faye L. Lopez… Alvaro Alonso. Serum phosphorus levels and the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities study
#1819: Jeffrey R. Misialek… Alvaro Alonso. Serum and dietary magnesium and the incidence of atrial fibrillation in whites and African Americans: the ARIC study

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

11.b. If yes, is the proposal
   ___ A. primarily the result of an ancillary study (list number* __________)
   ___ 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.csc.c.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.c.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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