

ARIC Manuscript Proposal # 1893

PC Reviewed: 1/10/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

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

2. Writing Group: Pamela L. Lutsey, Aaron R. Folsom, Alvaro Alonso, Laura Loehr, Brad Astor, Joe Coresh. Other interested investigators welcome.

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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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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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 women¹. 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^{2,3}. Epidemiologically, low serum magnesium has been linked to both increased CVD risk factors⁴⁻⁹ and events^{3, 10-13}.

High phosphorous levels have also been associated with elevated risk of CVD¹⁴⁻¹⁷ and poorer outcomes among chronic kidney disease patients¹⁸ in epidemiologic studies. Although the mechanisms are not entirely clear, elevated serum phosphorous is thought to influence CVD risk through vascular calcification¹⁹, myocardial fibrosis²⁰, and development of left ventricular hypertrophy²¹.

Results of epidemiological investigations exploring relations of serum calcium to CVD have been mixed^{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^{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 albumin¹⁵, 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 ≥ 90 , 60-89, and 15-59 ml/min/1.73 m²) 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
 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

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)?

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

#483: Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The atherosclerosis risk in communities (aric) study. *Am Heart J.* 1998;136:480-490

#1196: Peacock JM, Ohira T, Post W, Sotoodehnia N, Rosamond W, Folsom AR. Serum magnesium and risk of sudden cardiac death in the atherosclerosis risk in communities (aric) study. *American Heart Journal.* 2010;160:464-470

#1268: Ohira T, Peacock JM, Iso H, Chambless LE, Rosamond WD, Folsom AR. Serum and dietary magnesium and risk of ischemic stroke. *American Journal of Epidemiology.* 2009;169:1437-1444

N/A?: Onufrak SJ, Bellasi A, Shaw LJ, Herzog CA, Cardarelli F, Wilson PW, Vaccarino V, Raggi P. Phosphorus levels are associated with subclinical atherosclerosis in the general population. *Atherosclerosis.* 2008;199:424-431

N/A?: Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: The atherosclerosis risk in communities (aric) study. *American Heart Journal.* 2008;156:556-563

NOT YET PUBLISHED

#1845: Faye L. Lopez... Alvaro Alonso. Serum phosphorus levels and the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities study

8. Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in type 2 diabetes: A meta-analysis of randomized double-blind controlled trials. *Diabetic Medicine*. 2006;23:1050-1056
9. Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care*. 2004;27:59-65
10. Ohira T, Peacock JM, Iso H, Chambless LE, Rosamond WD, Folsom AR. Serum and dietary magnesium and risk of ischemic stroke. *American Journal of Epidemiology*. 2009;169:1437-1444
11. Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The atherosclerosis risk in communities (aric) study. *Am Heart J*. 1998;136:480-490
12. Chakraborti S, Chakraborti T, Mandal M, Mandal A, Das S, Ghosh S. Protective role of magnesium in cardiovascular diseases: A review. *Molecular and Cellular Biochemistry*. 2002;238:163-179
13. Eisenberg MJ. Magnesium deficiency and sudden death. *American Heart Journal*. 1992;124:544-549
14. Dhingra R, Sullivan LM, Fox CS, Wang TJ, D'Agostino RB, Sr., Gaziano JM, Vasan RS. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med*. 2007;167:879-885
15. Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: The atherosclerosis risk in communities (aric) study. *American Heart Journal*. 2008;156:556-563
16. Onufrak SJ, Bellasi A, Shaw LJ, Herzog CA, Cardarelli F, Wilson PW, Vaccarino V, Raggi P. Phosphorus levels are associated with subclinical atherosclerosis in the general population. *Atherosclerosis*. 2008;199:424-431
17. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation*. 2005;112:2627-2633
18. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, Strippoli GFM. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease. *JAMA: The Journal of the American Medical Association*. 2011;305:1119-1127
19. Foley RN, Collins AJ, Herzog CA, Ishani A, Kalra PA. Serum phosphorus levels associate with coronary atherosclerosis in young adults. *Journal of the American Society of Nephrology*. 2009;20:397-404
20. Amann K, Tornig J, Kugel B, Gross M-L, Tyralla K, El-Shakmak A, Szabo A, Ritz E. Hyperphosphatemia aggravates cardiac fibrosis and microvascular disease in experimental uremia. *Kidney Int*. 2003;63:1296-1301
21. Foley RN, Collins AJ, Herzog CA, Ishani A, Kalra PA. Serum phosphate and left ventricular hypertrophy in young adults: The coronary artery risk development in young adults study. *Kidney Blood Press Res*. 2009;32:37-44