ARIC Manuscript Proposal #4085

PC Reviewed: 8/9/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Dietary phosphorus intake at middle age and coronary artery and extra-coronary calcification at older ages: The ARIC Study

b. Abbreviated Title (Length 26 characters): Diet phosphorus and CAC/ECC

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. Y.N.S. **[please confirm with your initials electronically or in writing]**

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3. Timeline:
These analyses will use existing ARIC data; thus, manuscript preparation will be conducted over the next 6 months.

4. Rationale:
Phosphorus is essential for our body, by providing mechanical strength to bones,[1] being a part of cell membranes as phospholipids, and maintaining cellular functions, for example, as adenosine triphosphate.[1-3] Approximately 700-800 g of phosphorus is in the human adult body,[1-3] with 85% in bones and teeth, 14% in intracellular and soft tissues, and only 1% in extracellular

fluid.[1-3] Despite this relatively small amount of phosphorus in sera, a few previous studies have shown that higher levels of serum phosphorus are associated with an elevated risk of cardiovascular disease (CVD) events in individuals with chronic kidney disease (CKD) and in the general population.[4,5] However, data regarding the association between dietary phosphorus intake and adverse outcomes including CVD are limited, and a few relevant studies showed conflicting results.[6-9]

Given vascular calcification as a major mechanism linking phosphorus to elevated CVD risk,[10-12] a few studies have explored the association of phosphorus intake with coronary artery calcification (CAC), one of the strongest predictors of CVD,[13,14] but observed inconsistent results. For example, a cross-sectional study enrolling individuals with CKD reported a positive association between dietary phosphorus intake and CAC,[15] whereas a large Korean cross-sectional study with over 23,000 participants did not observe an association between dietary phosphorus intake with higher CAC.[16] These inconsistent results may reflect the relatively smaller contribution of phosphorus intake as a determinant of serum phosphorus levels compared to kidney function.[1,2] In fact, unless kidney function is severely reduced, serum phosphorus levels remain controlled by parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). [1,2 17,18] The difficulty of accurately measuring phosphorus intake may also play a role in these inconsistent findings.[19,20] Additionally, the contributions of vascular risk factors have been shown to be different across different vascular beds (e.g., smoking impacting more leg arteries than coronary arteries[21]), although to our knowledge no studies have examined the associations of phosphorus intake with extra-coronary calcification (ECC).

To address these caveats in the previous literature, using data from the Atherosclerosis Risk in Communities (ARIC) Study, we will evaluate whether phosphorus intake assessed using a validated food frequency questionnaire at two-time points over six years at middle age is associated with CAC and ECC (i.e., aortic valve, aortic ring, ascending and descending aorta, and mitral valve) at the age of ~75 years or older.

5. Main Hypothesis/Study Questions:

1. Dietary phosphorus intake at middle age will be independently associated with CAC at older ages in community-dwelling adults.
2. Dietary phosphorus intake at middle age will be independently associated with extra-coronary calcification at older ages in community-dwelling adults.

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

Inclusion Criteria

- All ARIC participants who underwent chest CT scan at visit 7. CT scan was not performed among participants with coronary heart disease prior to December 31, 2015 (reflecting a lag time to ascertain coronary disease in ARIC).

Exclusion Criteria

• Prevalent coronary heart disease (by the design of the ARIC CAC ancillary study)
• Missing CAC or ECC data
• Missing dietary data at visit 1 or visit 3
• Missing data on covariates of interest

Exposure variables

• Main exposure: Dietary phosphorus intake
  -We will use the average dietary phosphorus intake between visit 1 and visit 3 for the primary analysis.
  -Diet data were assessed using a 66-item food frequency.[22]
  -Dietary phosphorus intake will be adjusted for total energy intake. [23]
• Secondary exposures: Dietary calcium intake
  Since the metabolism of calcium and phosphorus is interrelated, we will secondarily explore dietary calcium intake as well. For example, excessive calcium intake decreases PTH levels, which regulate serum phosphorus levels.[24] Also, a study using data from the Multi-Ethnic Study of Atherosclerosis (MESA) has reported that high calcium intake was inversely associated with a high CAC score.[25]

Outcome variables

• CAC and ECC were recorded as Agatston score.[26]
• ECC will include 5 sites: ascending aorta, descending aorta, aortic ring (aortic root or annulus at the level of the aortic ring), aortic valve, and mitral valve.
• CAC and ECC will be modeled as continuous variables after log-transformation (i.e., ln [CAC+1] or ln [ECC+1]).
• CAC and ECC will be also categorized using clinical thresholds (e.g., ≥ vs. <100 and ≥ vs. <75th percentiles).[27]

Covariates

- Sociodemographic: age, sex, race, center, education level, and income level
- Anthropometric: body mass index, systolic and diastolic blood pressure, and heart rate
- Lifestyle: alcohol intake, smoking status, physical activity,
- Comorbidities: prevalent diabetes mellitus
- Medications: Use of antihypertensive medicine, cholesterol-lowering medicine vitamin D, and calcium supplement.
- Laboratory examinations: total cholesterol, high-density lipoprotein (HDL) cholesterol, and estimated glomerular filtration rate (eGFR) (we will use 2021 CKD-EPI creatinine-based equation).[28]

Data analysis plan

A) Baseline characteristics will be compared across quartiles of dietary phosphorus intake and summarized as mean (SD) for continuous variables (median and interquartile interval if skewed distribution), and number (proportion) for categorical variables. Continuous variables will be compared across quartiles using ANOVA, whereas categorical variables will be compared using χ^2 test.

B) Subsequently, we will run linear regression models to evaluate the association of dietary phosphorus intake (as independent, continuous variables) with ln [CAC+1] or ln [ECC+1] (as dependent, continuous variables). We will explore a few models to assess potential confounders:

-Model 1; total dietary energy intake

-Model 2; Model 1 + age, sex, race, center, alcohol intake, smoking status, physical activity, body mass index, education level, and income level.

-Model 3; Model 2+ systolic blood pressure, total cholesterol level, HDL-cholesterol level, eGFR, use of antihypertensive medicine, cholesterol-lowering medicine, prevalent diabetes mellitus.

-Model 4; Model 3+ dietary calcium intake, use of vitamin D, and calcium supplement.

C) We will also run logistic regression models with CAC and ECC as dichotomous dependent variables (e.g., ≥ vs. <100 and ≥ vs. <75th percentiles).[27] We will explore the same models with the covariates listed above.

D) We will repeat the analysis with dietary calcium intake as an exposure.

Sensitivity analysis

- We will conduct subgroup analysis according to demographics (age, sex, and race) and clinical conditions (e.g., diabetes and kidney function).
- We will conduct analyses with dietary data at visit 1 and visit 3 separately.
- We will conduct analyses with dietary phosphorus by above vs. below recommended daily phosphate intake in the guideline (700 mg/day).[29]

<u>Limitations</u>

- Although it is described that FFQ is a useful tool for the measurement of most nutrients,[30,31] there may be potential measurement errors in the assessment of dietary data, especially the possibility of underestimating phosphorus intake.[19,20]
- The results will not be generalizable to races other than Whites and Blacks.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __✗__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 __✗__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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/aricproposals/dtSearch.html __✗__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)?

The followings are proposals focused on dietary phosphorus.

#1478: Dietary phosphorus and incidence of hypertension: the MESA and ARIC studies.

#2206: Serum fibroblast growth factor 23, phosphorus, and risk of incident hypertension: The Atherosclerosis Risk in Communities Study.

The followings are proposals on coronary artery calcification.

#3628: Estimated glomerular filtration and albuminuria and calcification of coronary arteries, aorta, and cardiac valves in older adults

#3570: Psychosocial factors and calcification of coronary arteries, aorta, and cardiac valves at older age.

#3724: Physical activity and calcification of coronary arteries, aorta, and cardiac valves: The Atherosclerosis Risk in Communities (ARIC) Study.

No ARIC proposal has ever looked at the relationship between dietary phosphorus intake and CAC or ECC.

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* __2016.06_____)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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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