

ARIC Manuscript Proposal # 1478

PC Reviewed: 3/17/09
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Dietary phosphorus and incidence of hypertension: the MESA and ARIC studies

b. Abbreviated Title (Length 26 characters): Phosphorus and blood pressure

2. Writing Group:

Writing group members:

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

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3. Timeline:

Analysis: 6 months after manuscript approval

Writing of manuscript: 6 months.

4. Rationale:

Hypertension is a major public health problem, responsible for 7.6 million premature deaths worldwide in 2001.¹ Along with other lifestyles, diet has a major role in the development of hypertension. Intake of minerals, specifically, seems to be extremely relevant: a high intake of potassium and a decreased intake of sodium are associated with lower levels of blood pressure (BP) in the general population.² Calcium and magnesium have been also linked to lower levels of BP, but the supporting evidence is less consistent.³ The association between dietary phosphorus and BP has been seldom studied in epidemiologic studies.

A recent report from the International Study of Macro- and Micro-Nutrients and Blood Pressure (INTERMAP), a cross-sectional study in 4680 individuals from 4 countries (Japan, China, US, United Kingdom), suggested that dietary phosphorus could be inversely associated with the levels of systolic and diastolic BP independently of other nutrients.⁴ Similarly, in NHANES, phosphorus intake was inversely, but not significantly, associated with systolic and diastolic BP.⁵ This potential association, however, has not been tested prospectively. Determining the relationship between dietary phosphorus and the risk of incident hypertension is particularly important, since phosphorus in the diet could affect levels of serum phosphorus, as shown in some studies⁶⁻⁸ (but not in others).⁹ Elevated serum phosphorus levels, in turn, could increase the risk of cardiovascular events.^{10, 11} Additionally, the intake of phosphorus in the US population has increased considerably in the last decades, particularly due the important amount of phosphorus in processed foods.¹² This makes the assessment of cardiovascular effects of dietary phosphorus a crucial public health need. Although there is not a clear mechanism to explain how dietary phosphorus could affect BP, further longitudinal studies are required to improve our understanding of the effect of this nutrient on cardiovascular health.

The MESA and ARIC studies, with their population-based approach and multi-ethnic representation, constitute an excellent setting to address this research question. Additionally, having been conducted in different period of time (ARIC late 80s and 90s, MESA in the last 6 years), this analysis could provide an unique opportunity to determine whether changes in diet in the last 20 years (increased consumption of processed foods) have an impact in the associations of interest.

5. Main Hypothesis/Study Questions:

We hypothesize that a higher phosphate intake will be associated with:

- (1) lower levels of BP at baseline, and
- (2) decreased risk of hypertension during follow-up

in MESA and ARIC participants, independently of other dietary and non-dietary determinants of BP.

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).

We will analyze the cross-sectional association between dietary phosphorus and systolic and diastolic BP at visit 1, and subsequent risk of developing hypertension among non hypertensive individuals at baseline.

Inclusion / exclusion criteria

MESA and ARIC participants with measured systolic and diastolic BP not taking antihypertensive medication will be included in the cross-sectional analysis. Individuals with prevalent cardiovascular disease or diabetes, or with incomplete dietary information will be excluded. Additionally, for the longitudinal analysis, individuals with systolic BP \geq 140 mmHg or diastolic BP \geq 90 mmHg at baseline will be excluded. Individuals with diabetes will be excluded because diabetics usually change their diets and this could lead to issues of reverse causation.

Dietary information

Nutrient intakes will be adjusted for total energy intake using the residual method and categorized in sex-specific quintiles. The main exposure variable will be the intake of dietary phosphorus. Other dietary variables that will be considered are: calcium, potassium, magnesium, sodium, vitamin D (only in ARIC), fiber, total fat intake, alcohol, daily servings of fruits and vegetables, and daily serving of whole grains. Reasons to include these dietary components is their potential relation with phosphorus intake and/or their defined role as potential dietary determinants of hypertension.

Other covariates

Variables that will be considered as potential confounders, in addition to the dietary factors mentioned before, include age, race, sex, study center, socioeconomic status (education, income), eGFR, physical activity, body mass index, and waist circumference.

Endpoint

In the cross-sectional analysis, the main outcome variable will be systolic and diastolic BP. In the longitudinal analysis, the main outcome variable will be incidence of hypertension, defined as systolic BP \geq 140 or diastolic BP \geq 90 or use of antihypertensive medication,¹³ in any of the ARIC and MESA follow-up visits.

Brief Analysis Plan and Methods

Because of differences in study design, dietary assessment and study period, analyses will be separate for cohort. If there is no evidence of between-cohort heterogeneity, we will pool results weighting them by the inverse of their variance.

For the cross-sectional analysis, we will run multiple linear regression models with quintiles of dietary phosphorus as the main independent variable and systolic or diastolic BP as the dependent variables. Additional analyses will consider exposure as a continuous variable. A first model will include age, sex, race, and study center. A second model will include known non-dietary risk factors for hypertension (socioeconomic status, body mass index, physical activity, eGFR). Finally, a third model will include other dietary factors.

To estimate the association between dietary phosphorus and risk of hypertension, we will use Cox proportional hazards models, with time to diagnosis of hypertension or censoring as the main outcome. Different models will be constructed following the same process as for the cross-sectional analysis.

We will test the robustness of our results with several sensitivity analyses. To avoid including undiagnosed prevalent hypertension in the longitudinal analysis, we will conduct an analysis including only individuals with BP lower than 130/80 at baseline.

Similarly, to avoid misclassification bias in the outcome caused by differential use of antihypertensive medication, we will conduct an additional analysis not considering use of antihypertensive medication in the outcome.

We will also estimate associations between different sources of dietary phosphorus (meat, dairy, fish and seafood, cereals, other) and the incidence of hypertension. Interactions between phosphorus intake and age, sex, and race/ethnicity will be done using the likelihood ratio test comparing models with and without interaction terms.

Statistical power

The minimum detectable systolic/diastolic BP difference between extreme quintiles, assuming $\alpha=0.05$, $\beta=0.10$, equal variances, standard deviation=13.3 mmHg for systolic and 9.0 for diastolic BP will be 1.5/1.0 in ARIC (1666 individuals in each quintile) and 2.6/1.8 in MESA (553 individuals in each quintile).^{14, 15} The statistical power will be even higher to detect a linear trend in the association, if this exists.

For the longitudinal analysis, we expect to observe at least 550 cases of hypertension in MESA¹⁵ and 1486 in ARIC.¹⁴ We will have more than 90% statistical power to detect a hazard ratio higher than 1.5 (or lower than 0.67) in MESA and higher than 1.25 (or lower than 0.8) in ARIC.

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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____ 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 overlap

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)?

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* _____)**

_____ **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.unc.edu/aric/forms/>

12. 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.

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