ARIC Manuscript Proposal #3984

PC Reviewed: 12/14/21   **Status: _____**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Magnesium-Rich Foods are Associated with Incident Cardiovascular Disease: The Atherosclerosis in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Magnesium-Rich Foods and CVD

2.   Writing Group:
        Writing group members: Lyn Steffen, Casey Rebholz, Pamela Lutsey, So Yun Yi, Mary Rooney

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __KC___ **[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:
        1. December 2021-Mar 2022, Literature search
        2. January 2022-April 2022, Conduct data analysis
        3. February 2022-June 2022, Prepare manuscript
        4. June 2022-August 2022, coauthor review, revisions, submit to P&P committee for Review

4.   Rationale:

Numerous studies have shown inverse associations between serum magnesium levels and risk of cardiovascular disease (CVD) and adverse CVD risk factors. In healthy individuals, serum magnesium is regulated by the kidneys, intestines, and bone with normal serum mg concentrations ranging between 0.7mM and 1.1mM. In addition, serum mg may be influenced by aging, medication use, and dietary intake. Because serum mg is regulated, about 40-60% of dietary magnesium is usually absorbed; but when magnesium is low, as much as 80% can be absorbed. While women and men consume 271mg and 343mg of magnesium per day, respectively, the Recommended Daily Allowance for women is 310-320mg and 400-420mg in men. As many as 75% of adults in the United States do not meet the RDA for dietary magnesium intake.

Excellent food sources of magnesium include whole grains, nuts, fruits and vegetables, coffee, and tea. Whole grain intake has been shown to be inversely associated with CVD, CHD, CAD, and type 2 diabetes. Intake of more nuts and of nuts in the context of a healthy diet pattern, such as the Mediterranean diet, decrease the risk of CVD and adverse cardiovascular events. Similarly, fruit and vegetable consumption has been observed to be protective of CVD and CVD risk factors, although study results are inconsistent. Specifically, apples, pears, citrus fruits, green leafy vegetables, and cruciferous vegetables showed the strongest inverse association with cardiovascular disease. Other studies have found no significant relationship with fruits and vegetables. Studies about coffee consumption show null associations with risk of CVD, even among hypertensive individuals; although moderate coffee consumption may be beneficial for CVD.

When separated from the usual diet pattern, individual foods may or may not be associated with the CVD, suggesting a synergy between the foods in the diet pattern. To date, no studies have examined the association of a diet pattern rich in magnesium with risk of CVD. Therefore, we will examine the association between a diet pattern rich in mg and risk of developing CVD. We hypothesize that this diet pattern will be inversely associated with incident CVD, including CHD and ischemic stroke.

5.   Main Hypothesis/Study Questions:

We hypothesize that a magnesium-rich diet pattern will be inversely associated with incident CVD.

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 and population

The Atherosclerosis Risk in Communities (ARIC) Study is a population-based prospective study to examine cardiac health etiology and outcomes for middle-aged and older adults. Study participants were adults aged 45-64 years living in Forsyth County, NC, Jackson, MS, selected suburbs of Minneapolis, MN, and Washington County, MD, enrolling 15,792 participants. Data for these analyses include visits 1 and 3, and follow up for incident CVD events.

Exclusions:
- Prevalent CVD at baseline (n=xx)
- Missing diet information from visit 1 (n=xx)
    - if missing from visit 3 we will use ppt visit 1 only
- Participants with implausible dietary intake (n=xx)
    - For women, less than 500 or more than 3500 kcals/day
    - For men, less than 700 or more than 4500 kcals/day
- Self-identify as neither white nor African American (n=xx)
- African Americans from Maryland and Minnesota field centers (n=xx)

Our final sample included xxx participants.

Statistical Analysis
Exposure variables
Food groups (sv/day) obtained at visit 1 and visit 3 FFQ.

Magnesium-rich diet score: A score will be created by summing the number of daily servings consumed of magnesium-rich foods (whole grains, fortified breakfast cereals, nuts, seeds, cocoa, leafy green vegetables, coffee and tea, beans, and fruits and vegetables).

Outcome variable
Incident CVD by 2019, including incident CHD and incident stroke.

Covariates
Age, sex, race, field center, education, energy intake, smoking, alcohol, physical activity, diet, medication use, eGFR, type 2 diabetes, BMI, hypertension, lipids.
Remaining food intake score will be derived by principal components analysis (PCA; servings of the remaining food intake will be included in a PCA model)

Models proposed for the analysis:
- Model 1 is adjusted for age, sex, race, education, field center, energy intake.
- Model 2 is adjusted for model 1 + lifestyle factors (smoking, alcohol, physical activity, remaining food intake score).
- Model 3 is adjusted for model 2 + medications (anti-hypertensives, diuretics, lipid-lowering medications, proton pump inhibitors, eGFR).
- Model 4 is adjusted for model 3 + factors in the causal pathway (type 2 diabetes, BMI, hypertension, dyslipidemia).

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ 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 __X__ 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

    __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)?

Rooney MR, Bell EJ, Alonso A, Pankow JS, Demmer RT, Rudser KD, Chen LY, Lutsey PL. Proton Pump Inhibitor Use, Hypomagnesemia and Risk of Cardiovascular Diseases: The Atherosclerosis Risk in Communities (ARIC) Study. J Clin Gastroenterol. 2021 Sep 1;55(8):677-683. doi: 10.1097/MCG.0000000000001420. PMID: 33471493; PMCID: PMC7921206.

Rooney MR, Alonso A, Folsom AR, Michos ED, Rebholz CM, Misialek JR, Chen LY, Dudley S, Lutsey PL. Serum magnesium and the incidence of coronary artery disease over a median 27 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study and a meta-analysis. Am J Clin Nutr. 2020 Jan 1;111(1):52-60. doi: 10.1093/ajcn/nqz256. PMID: 31622458; PMCID: PMC7307183.

Lutsey PL, Alonso A, Michos ED, Loehr LR, Astor BC, Coresh J, Folsom AR. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr. 2014 Sep;100(3):756-64. doi: 10.3945/ajcn.114.085167. Epub 2014 Jul 16. PMID: 25030784; PMCID: PMC4135486.

Misialek JR, Lopez FL, Lutsey PL, Huxley RR, Peacock JM, Chen LY, Soliman EZ, Agarwal SK, Alonso A. Serum and dietary magnesium and incidence of atrial fibrillation in whites and in

African Americans--Atherosclerosis Risk in Communities (ARIC) study. Circ J. 2013;77(2):323-9. doi: 10.1253/circj.cj-12-0886. Epub 2012 Oct 6. PMID: 23047297; PMCID: PMC4228988.

Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. J Clin Epidemiol. 1995 Jul;48(7):927-40. doi: 10.1016/0895-4356(94)00200-a. PMID: 7782801.

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 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.