ARIC Manuscript Proposal #3841

PC Reviewed: 5/11/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1.a. Full Title: Associations of serum magnesium with markers of cerebrovascular disease: The Atherosclerosis Risk In Communities Study (ARIC MRI study)

b. Abbreviated Title (Length 26 characters): Magnesium and Cerebrovascular Disease

2. Writing Group: Writing group members: Aniqa Alam, Alvaro Alonso, Pam Lutsey, Srishti Shrestha, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _ABA_ [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:
Analysis is to begin immediately. Expected manuscript to be drafted over the next 6 months.

4. Rationale:

Magnesium serves multiple functions in the body, including involvement in cognition. The mineral has been associated with lower risk of dementia[1,2] and may be protective against the progression of dementia,[3,4] but the exact mechanisms in which magnesium acts upon these systems to prevent neurological insults remain unclear.

Magnesium deficiency has been linked with increased risk of hypertension,[5] cardiovascular diseases,[6] and thrombosis.[7] Magnesium promotes the synthesis of nitric oxide, which itself is protective against thrombosis and hypertension due its anti-platelet properties and ability to induce vasodilation.[8] Magnesium is also a natural antagonist to calcium, which has been known to encourage the over-excitation – and subsequent death – of neurons[9], making it important within the context of dementia. Elevated serum magnesium is associated with a lower risk of cardioembolic stroke[10] and a lower risk of death in patients with acute ischemic stroke.[11] Conversely, lower magnesium can predict ischemic stroke events and the need for carotid revascularization in patients with severe atherosclerosis.[12]

Evaluating the association of circulation magnesium with brain imaging markers of neurodegeneration and cerebrovascular disease may offer a clearer picture on the underlying mechanisms linking magnesium and dementia.

5. Main Hypothesis/Study:

1. Lower levels of serum magnesium will be associated with lower volumes in the frontal lobe, temporal lobe, occipital lobe, parietal lobe, and deep grey matter, along with total brain volume.
2. Lower levels of serum magnesium will be associated with higher odds of cortical, subcortical and lacunar infarcts and higher volume of white matter hyperintensities.

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 intend to include all ARIC study participants who attended visit 5, have available serum magnesium at visit 5 and participated in the MRI study, excluding on:

- Prevalent stroke by visit 5

Variables

Variable of interest:

- Serum magnesium (V5)

Covariates (baseline = V5):

- Age at baseline
- Sex
- Site-Race (white/Forsyth, white/Minneapolis, white/Washington County, black/Forsyth, black/Jackson)

- Education (did not complete HS, HS graduate and/or vocational school, at least some college)
- History of coronary heart disease (CHD) and heart failure
- Diabetes mellitus
- Systolic and diastolic blood pressure
- Antihypertensive medication (antihypertensive diuretics, non-diuretic antihypertensives, no antihypertensives)
- Body-mass index
- Smoking (ever smoked/never smoked)
- Sodium
- Calcium
- Potassium
- estimated globular filtration rate (eGFR)
- LDL Cholesterol
- HDL Cholesterol
- High sensitivity C-reactive protein as a marker of inflammation
- APOE genotype

Outcomes:
Markers of brain disease, including:

- Differences in brain volume across serum magnesium: total brain volume, frontal lobe, temporal lobe, occipital lobe, parietal lobe, deep grey matter. Volumes will be modeled in standard deviation units to facilitate comparisons across different regions.
- Subclinical cerebrovascular disease: cortical, subcortical and lacunar infarcts, and white matter hyperintensity volume

Statistical Analysis:
We will study the association between serum magnesium and markers of cerebrovascular disease using multiple linear regression to assess differences in brain volume, including white matter hyperintensities across serum magnesium measured at visit 5 (categorized into quintiles) and then logistic regression to assess the association of magnesium with the occurrence of cortical, subcortical and lacunar infarcts measured in participants who underwent a brain MRI while in ARIC's Neurocognitive study.

Below, we provide a summary of the tables to be included in the manuscript:

Table I: Baseline Characteristics of study population

Table II: Association of serum magnesium with brain volumes, as measured through multiple linear regression.

Model 1: Multiple linear regression model adjusted for age, sex, education, site-race, and total intracranial volume

Model 2: Multiple linear regression adjusted for age, sex, site-race, intracranial volume, education level (three levels), history of CHD and heart failure (dichotomous), diabetes mellitus (dichotomous), systolic and diastolic blood pressure (continuous), antihypertensive medication use (three categories: antihypertensive diuretics, non-diuretic antihypertensives, no antihypertensives), body-mass index (continuous), ever smoking (dichotomous), sodium (continuous), calcium (continuous), potassium (continuous), eGFR (continuous), total and HDL cholesterol (both continuous), inflammation markers (continuous), APOE genotype..

Table III: Association of serum magnesium with subclinical cerebrovascular disease, as measured through logistic regression.

Model 1: Logistic regression model adjusted for age, sex, education and site-race.
Model 2: Logistic regression model adjusted for age, sex, site-race, education level (three levels), history of CHD and heart failure (dichotomous), diabetes mellitus (dichotomous), systolic and diastolic blood pressure (continuous), antihypertensive medication use (three categories: antihypertensive diuretics, non-diuretic antihypertensives, no antihypertensives), body-mass index (continuous), ever smoking (dichotomous), sodium (continuous), calcium (continuous), potassium (continuous), eGFR (continuous), total and HDL cholesterol (both continuous), inflammation markers (continuous), APOE genotype.

For each table, we will stratify on race and gender to assess interaction.

Limitations:

- Cross-sectional study
- Limited sample size for subgroup analysis

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 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? __X__ 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"? __X__ Yes ____ No

10. 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/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)?

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

11.b. If yes, is the proposal:

X_ A. primarily the result of an ancillary study (list number* _ARIC-NCS_)

___ 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.cscc.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.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.

References:

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