ARIC Manuscript Proposal #3637

PC Reviewed: 6/9/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1.a. Full Title: Associations of serum magnesium with cognitive function and dementia: The Atherosclerotic Risk in Communities Study

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

2. Writing Group: Writing group members: Aniqa B. Alam, Pamela L. Lutsey, Rebecca Gottesman, Adrienne Tin, Alvaro Alonso, 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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3. Timeline:
Analysis is to begin immediately. Expected manuscript to be drafted over the next 6 months.

4. Rationale:

Cognitive impairment and dementia (CID) are public health issues that will increase in importance as the population of the United States ages. Prevalence estimates suggest that 22% of persons over age 70 have some form of non-dementia cognitive impairment and 13% over the age of 70 have a form of dementia.[1]

N-methyl-D-aspartate (NMDA) receptors play critical roles in learning processes and the formation of memories.[2] Through the glutamatergic excitation of NMDA receptors, calcium ions flow into cells and trigger other signaling pathways important in dementia and cognitive decline pathology.[3] Over-excitation of NDMA receptors, however, may impair synaptic activity and lead to neuronal necrosis.[4]

Minerals and the roles they may play in cognition have been attracting attention in dementia and cognitive decline research. Magnesium (Mg), for example, serves multiple functions in the body.[5-7] Within the context of cognition, Mg is able to block NMDA-induced excitotoxicity by inhibiting NMDA receptors and subsequent cellular cascades.[8,9]

While Mg's potentially protective effect against cognitive decline has been demonstrated in several animal models,[10-12] human studies are limited with conflicting results, and mainly focus on dietary intake of Mg,[13,14] which has only a low correlation with serum Mg (ARIC r = 0.03).[15] The only study to date to examine serum Mg within a cohort setting found a U-shaped – rather than linear – trend of baseline serum Mg with cognitive decline over a 10-year period (i.e.: high and low baseline serum Mg were associated with increased risk of dementia).[16]

Evidence of race- or sex-based effect modification of the effect of magnesium levels is scarce. African Americans in the NHANES cohort had lower intake of Mg than their white counterparts,[17] though how this might manifest in a risk differential for dementia is unclear. There is also evidence to suggest associations of higher plasma magnesium with Alzheimer's disease may be applicable to men, but not necessarily to women.[18]

5. Main Hypothesis/Study:

1. Compared to those with serum magnesium levels within normal range, the lowest and highest levels of serum magnesium will be associated with an increased risk of incident dementia from visit 2 through visit 7 (if/when V7 is available).
2. The lowest and highest levels of serum magnesium will be associated with faster cognitive decline in at least one cognitive domain among participants with baseline cognitive assessment at visit 2.
3. The lowest and highest levels of serum magnesium will be associated with increased risk of dementia and faster cognitive decline in men, but not women.
4. These associations will not differ between whites and blacks.

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).

Exclusion Criteria:

We intend to include all ARIC study participants who attended visit 2, excluding on:

- Refused consent to use data for genetic research

- Prevalent dementia (based on incident dementia between baseline and visit 2)

Variables:

Main variable of interest:

- Serum magnesium (V2, V5)

Covariates (baseline = V2, except for Period 2 cognitive decline analysis where baseline will be V5 – described in statistical analysis)

- Age at baseline
- Sex
- Site-Race (white/Forsyth, white/Minneapolis, white/Washington County, black/Forsyth, black/Jackson)
- Education (11 years or less, 12-16 years, 17 years or greater)
- History of coronary artery disease (CAD), stroke, and heart failure
- Systolic and diastolic blood pressure
- Antihypertensive medication (including diuretics)
- Estimated globular filtration rate (eGFR)
- LDL Cholesterol
- HDL Cholesterol
- Serum Sodium
- Serum Calcium
- Serum Potassium
- Diabetes mellitus
- Smoking status
- Alcohol consumption
- Waist-to-hip ratio
- APOE e4 genotype (apoe4 allele/no apoe4 allele)
- High sensitivity C-reactive protein as a marker of inflammation
- Prudent/western diet scores

Outcomes:

- Incident dementia and dementia hospitalization through 2019 (if/when available) in individuals who attended visit 2 (defined by level 3 diagnosis of dementia by the ARIC-NCS neurocognitive committee)
- Difference in cognitive functioning within three time periods: from V2 to V7, V2 to V5, and V5 to V7 based on z-scores from the delayed word recall test (DWRT), digit symbol substitution test (DSST), word fluency test (WFT), and overall global cognition based on a composite of the three tests.

Statistical Analysis:

Incident Dementia:

We will study the association between serum magnesium and incident dementia and dementia hospitalizations using Cox proportional hazards models and assess the proportional hazards assumption by testing time covariates in the assessment of incident dementia.

Cognitive Decline:
We will assess overall cognitive decline from V2 to V7 across serum Mg measured in V2. In an additional analysis, we will rerun this model updating serum Mg using V5 data. We will also assess the impact of fluctuating serum Mg levels by assessing decline within two periods:

- **Period 1**: cognitive decline from V2 to V5, using V2 Mg as the variable of interest.
- **Period 2**: cognitive decline from V5 to V7, using V5 Mg as the variable of interest.
    - Period 2 analysis will be adjusted for the change in serum Mg since Period 1 by including the difference of V5 Mg and V2 Mg in the model.

We will use multivariable linear models fitted with generalized estimating equations (GEE) with an unstructured correlation matrix to estimate changes in cognitive functioning across serum Mg levels. We will conduct sensitivity analyses to evaluate the impact of losses to follow-up on the estimates of cognitive change. Because attrition is highly correlated with cognitive decline in an aging cohort,[19,20] we will implement multiple imputation by chained equations (MICE) to handle missing data. ARIC guides for cognitive decline analyses from V2 through V7 are actively being developed. Therefore, we will consider amendments to our methods based on workgroup recommendations as they are made.

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

Table I: Baseline Characteristics of study population

Table II: Hazard ratios (cox proportional hazards model) of incident dementia by serum magnesium quintiles.

Model 1: Cox proportional hazards model adjusted for age, gender, education, and site-race.

Model 2: Cox proportional hazards model adjusted for age, gender, site-race, education level (three categories), ever smoking (dichotomous), drinking status (dichotomous), systolic blood pressure (continuous), waist to hip ratio (continuous), total and HDL cholesterol (both continuous), sodium (continuous), calcium (continuous), potassium (continuous), history of CAD, stroke, and heart failure (dichotomous), diabetes mellitus (dichotomous), APOE e4 genotype (dichotomous), eGFR (continuous), antihypertensive medication use (three categories), diuretic use (dichotomous), inflammation markers (continuous), prudent/western diet scores (continuous).

Table III: For each cognitive test: Differences in cognitive function by serum magnesium quintiles.

Model 1: GEE model adjusted for age, gender, site-race, time, and interactions of covariates with time.

Model 2: GEE model adjusted for age, gender, site-race, education level (three categories), ever smoking (dichotomous), drinking status (dichotomous), systolic blood pressure (continuous), waist to hip ratio (continuous), total and HDL cholesterol (both

continuous), sodium (continuous), calcium (continuous), potassium (continuous), (continuous), history of CAD, stroke, and heart failure (dichotomous), diabetes mellitus (dichotomous), APOE e4 genotype (dichotomous), eGFR (continuous), antihypertensive medication use (dichotomous), diuretic use (dichotomous), inflammation markers (continuous), prudent/western diet scores (continuous), time, and interactions of covariates with time.

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

Limitations:
We will not differentiate between the types of dementia.

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.

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