ARIC Manuscript Proposal # 1196r

PC Reviewed: __12_/_19__/06____ **Status:** _A___ **Priority:** _2__
SC Reviewed: _____ **Status:** _____ **Priority:** ____

1.a. Full Title: Serum and Dietary Magnesium and Risk of Sudden Cardiac Death

b. Abbreviated Title (Length 26 characters): Magnesium & Sudden Death

2. Writing Group:

Writing group members: James M. Peacock, PhD, Aaron Folsom, MD, Tetsuya Ohira, MD, Wayne Rosamond, PhD, Nona Sotoodehnia, MD, Wendy Post,MD, Christina Wassel-Fyr, MS

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

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3. Timeline: First draft expected in January 2007.

4. Rationale:

Magnesium is a natural calcium antagonist and modulates vasomotor tone, blood pressure, and peripheral blood flow. Previous epidemiological studies have reported that magnesium intake is inversely associated with cardiovascular risk factors such as hypertension, [1, 2] type 2 diabetes mellitus, [3] the metabolic syndrome, [4] and coronary heart disease. [5, 6] Additional evidence from ecologic, clinical, and autopsy studies has shown increased Mg to potentially offer a protective role in sudden death, [7, 8] but no prospective studies have reported the association of magnesium levels with incidence of sudden death. In addition to its role in the regulation of blood pressure and maintenance of vascular smooth muscle tone, Mg deficiencies are known to cause ECG changes, leading to both atrial and ventricular arrhythmias, the most common precursors to sudden cardiac death. [7] The outcome of sudden cardiac death has only recently been defined in ARIC, allowing us to target an outcome whose primary precursor is known to be associated with magnesium deficiency. Since serum magnesium levels are modified by intake of other dietary minerals, such as calcium, potassium, and magnesium, alcohol intake, and physical exercise, [9, 10], these potential confounders will also be considered for adjustment.

Previous ARIC studies have shown that serum magnesium levels were associated inversely with incidence of hypertension [4] and coronary heart disease. [5, 6] In two of these studies [4, 5], there was no association between dietary magnesium as measured from a food frequency questionnaire and either outcome. Given the unreliability associated with dietary data collected from food frequency questionnaires, it is likely any observed associations of serum magnesium with sudden death will be attenuated when looking at dietary magnesium as the predictor.

5. **Main Hypothesis/Study Questions**:

1) Age-, sex, and race-field center-adjusted serum and dietary magnesium is inversely associated with incidence of sudden death.

2) These associations may be attenuated after adjustment for potential confounders

(Emphasis will be on serum magnesium, but analyses of dietary magnesium as the predictor will be conducted as well, if only to satisfy potential questions from reviewers).

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).

Dependent variables: Incidence of Sudden Cardiac Death

To identify cases of sudden cardiac death (SCD) in the ARIC study, all cases of fatal CHD (definite fatal MI, definite fatal CHD, or possible fatal CHD, in- and out-of-hospital deaths) were reviewed and adjudicated by a committee of physicians, funded through the Johns Hopkins University Donald W. Reynolds Cardiovascular Research Center

(ancillary study proposals #54 and #69). SCD was defined as a sudden pulseless condition from a cardiac origin in a previously stable individual. After review of data available from death certificates, informant interviews, physician questionnaires, coroner reports, and hospital discharge summaries the reviewers completed the Reynolds Sudden Death Event Classification Form. From this form a classification of Definite sudden arrhythmic death, Possible sudden arrhythmic death, Not sudden arrhythmic death, or unclassifiable was obtained. Cases were identified as either in or out of hospital deaths.

The cutoff dates for adjudication for SCD was 5/31/01 date. Fatal CHD deaths occurring after that date will be censored since they were not evaluated for SCD.

Independent variables: baseline serum and dietary magnesium (adjusted for total energy intake)

Model 1: Adjustment for age, gender, and race-field center

Model 2: Add adjustment for smoking, LDL & HDL cholesterol, triglycerides, education, physical activity, ETOH intake

Model 3: Add adjustment for diabetes, systolic blood pressure and/or hypertensive status, diuretic use

(For dietary Mg analysis)
Model 4: Add sodium, potassium, calcium, dietary fiber, caffeine, polyunsaturated/saturated fat ratio, protein

Exclusions: missing magnesium measurements, diet (calorie) outlier

**Perform two analyses: 1) including individuals with prevalent (at baseline) and incident (during follow-up, before death) CHD (adjust for CHD medication use), and 2) exclude prevalent CHD cases and censor incident CHD cases at time of event.

Proportional hazards (Cox) regression will be used to examine both the univariate and multivariable-adjusted associations between independent variables and time to incidence of sudden cardiac death.

In the ARIC Study, Mg has a reliability coefficient (0.69) in the middle range for a dozen important chemistry analytes.[11] The within-person variability was comparable to that from other published reports, but its magnitude makes it more difficult to detect associations between serum Mg and any outcome of interest. Despite this, previous studies within ARIC have demonstrated significant associations between serum Mg and various cardiovascular disease outcomes. [2,3,5,6]

7.a. Will the data be used for non-CVD analysis in this manuscript?
____ Yes __×__ No

b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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 file ICTDER02 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/ARIC/search.php

___×___ 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)?

Manuscript ARIC #424: Magnesium & Hypertension; ARIC #438: Serum magnesium: A risk factor for CHD?; In review: Magnesium & Stroke Incidence

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
_x__ A. primarily the result of an ancillary study (list number* _54 and 69)
___ B. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)
Ancillary study numbers 54 (Prineas/Rosamond) and 69 (Chakravarti/Post) are funded through the Johns Hopkins University Donald W. Reynolds Cardiovascular Research Center. The SCD variable that is the main outcome of this current proposal was adjudicated through this mechanism.

*ancillary studies are listed by number at http://www.cscc.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.

References

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