1.a. Full Title: Serum and Dietary Magnesium and Risk of Ischemic Stroke. The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Magnesium & Stroke Incidence

2. Writing Group:
Writing group members: Tetsuya Ohira, MD; Aaron R. Folsom, MD; James Peacock, PhD; Wayne D. Rosamond, PhD; Lloyd E. Chambless, PhD.

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

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3. Timeline: We expect to complete the manuscript by September 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, type 2 diabetes mellitus, and the metabolic syndrome. Therefore, low magnesium intake could increase risk of stroke, especially ischemic stroke, but few prospective studies have reported the association of magnesium intake with incidence of ischemic stroke. The Nurses’ Health Study reported that women in the highest quintile of dietary magnesium intake had a 21% lower risk of incidence of ischemic stroke compared with those in the lowest quintile, but the association did not reach statistical significance. Since serum magnesium levels are modified by intake of other dietary minerals, such as calcium and potassium, alcohol intake, and physical exercise, not only dietary magnesium but also serum magnesium levels must be used in analyses of the association of magnesium with incidence of stroke. No study, however, has reported this association.

In a previous ARIC study, serum magnesium levels were inversely associated with incidence of hypertension, but dietary magnesium levels were not associated with incidence of hypertension. Further, another ARIC study demonstrated that serum magnesium levels were inversely associated with incidence of coronary heart disease, but not dietary magnesium. Therefore, the associations between serum magnesium and incidence of ischemic stroke may be stronger than those between dietary magnesium and incidence of ischemic stroke.

5. Main Hypothesis/Study Questions:

1) Age-, sex, and race-field center-adjusted serum and dietary magnesium is inversely associated with ischemic stroke.
2) Associations (hazard ratios) of serum and dietary magnesium with ischemic stroke incidence attenuate after adjustment for confounding factors and blood pressure (which may be on the intermediate path).
3) Associations (hazard ratios) of serum magnesium with stroke incidence are stronger than those of dietary magnesium.

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).

Design: Prospective observational study

Analysis: Dependent variables: ischemic and hemorrhagic stroke incidence (up to 2002)

Independent variables: serum and dietary magnesium

Model 1: Adjustment for age, gender, and race-field center. Model 2: Adjustment for age, gender, race-field center, smoking, LDL & HDL cholesterol, fibrinogen, von Willebrand
factor, and education level. Model 3a: Model 2 + systolic blood pressure and hypertensive medication. Model 3b: Model 2 + diabetes mellitus. Model 3c: Model 2 + systolic blood pressure, hypertensive medication, and diabetes mellitus. Model 4: Model 3c + dietary potassium and calcium. Dietary magnesium will be adjusted for total energy intake in all models.

Exclusion: history of stroke, no baseline magnesium measured.

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

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.csec.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)?

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.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