PC Reviewed: 8/11/15   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Incidence of Dementia and its relationship to midlife vascular risk factors in ARIC

 b. Abbreviated Title (Length 26 characters): **Dementia Incidence**

2.   Writing Group: Rebecca Gottesman (first author), David Knopman (senior author), Tom Mosley, Marilyn Albert, Lisa Wruck, A. Richey Sharrett, Andrea Schneider, Josef Coresh, Ola Selnes, Laura Coker, Guy McKhann, Gwen Windham, Others Welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __RG__ **[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: within 6 months of approval

4.   Rationale: Although ARIC-NCS will allow evaluation of mild cognitive impairment (MCI) and dementia prevalence, the dementia surveillance methods being employed will allow evaluation of dementia incidence, otherwise not available in many other epidemiologic studies. Using these incident cases (and dates of estimated onset), we will

have the ability to evaluate hazard of dementia in association with the primary cardiovascular risk factors, to include hypertension and diabetes. We have previously described associations between each of these primary risk factors with cognitive decline,[1,2], but the public health impact of these results is limited given the lack of interpretability of cognitive change as an outcome. With the increasing focus on dementia (specifically, Alzheimer's Disease) and an emphasis on dedicated funds to support research on dementia, using "hard" outcomes such as dementia will allow better estimates of the effect of vascular risk—and therefore reductions in vascular risk—on dementia incidence rates.

The use of CMS data will allow evaluation of incident cases, by relying on dementia codes in the CMS database and then the ongoing ARIC dementia surveillance methods. Although dementia, and particularly Alzheimer's disease diagnoses from Medicare claims data has limitations,[3] we will have the ability to specifically address concerns about the quality of/ misclassification using Medicare claims data in those persons who have dementia codes and also had a more detailed dementia surveillance evaluation (via the TICS, informant interview, or a full neurocognitive evaluation).

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

1. Midlife (ARIC visit 1) diabetes, hypertension, hyperlipidemia, BMI, and smoking history, are related to risk of incident dementia (all types).
2. These associations (#1) will be independent of apoE genotype but may also be modified by apoE genotype, with stronger associations in those participants who are apoE E4 carriers.
3. These associations (#1) will remain in participants without history of stroke up through ARIC visit 5.
4. We do not anticipate interactions by sex or race in the above associations (#1).

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).

This analysis will rely on dementia as the primary outcome (without information about reviewer classification of dementia etiology). Dementia will be defined using information from the full visit 5 examination with expert committee diagnosis, from the TICS instrument administered after visit 5, and from ARIC's dementia surveillance (using coder from hospitalizations and death certificates, validated when possible from informant interviews (DRL/DRD). Supplementary analyses will use CMS data. This information will be used as follows, to determine "onset"/ timing of dementia diagnoses (see Table):

Visit 5/TICS Dx	Informant Call Dx	Dementia Discharge or Death Code	Timing of Event/Censoring
Dementia		Yes	Earliest discharge
Dementia		No	Assessment
Not dementia		Yes/No	Censor at assessment
	Dementia	Yes	Earliest discharge or death
	Dementia	No	Assessment
	Not dementia	Yes/No	Censor at assessment
		Yes	Earliest discharge or death
		No	Censor at earliest of end of Visit 5, death or loss to follow-up

The following covariates will be used in models: race (self-reported, from visit 1); gender; age (calculated from birthdate, defined at start of visit 5), education level, and apoE status (0,1, or 2 E4 alleles). The primary exposures of interest will also be defined from ARIC visit 1: history of hypertension (per ARIC definition, to include use of antihypertensives), history of diabetes/ diabetes medications, hyperlipidemia, BMI, and smoking status. Adjudicated data on stroke events will be used to conduct sensitivity analyses with exclusion of persons with history of stroke up to visit 5.

The primary analysis plan is a Discrete Time Analysis, which will be helpful given the clustering of persons with a dementia diagnosis at visit 5, as well as long intervals with censoring. This also allows for non-proportional hazards. We plan to use DTA with complementary log-log link; we will consider three models to define time: one, with linear year, centered at 2005; two, quadratic year, centered at 2005; and three, log interval for durations of time (pre-1995, 1996, etc). We will also consider analysis using Cox proportional hazards methods by adjusting timing of dementia diagnoses.

We will also plan to describe the sensitivity, specificity, and positive and negative predictive values of CMS dementia discharge and death codes for those participants with a code within 1 year of the ARIC visit 5 evaluation.

A sensitivity analysis will exclude dementias ascertained only from hospitalizations for CHD, stroke or heart failure, to evaluate the possibly non-conservative bias which might result from ascertaining these cases through the occurrence of major vascular outcomes.

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

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

   ___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)?
   MP 2120. Knopman

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* 2008.06)
   ___   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.
Understood.

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __X__ Yes ____ No.

Bibliography and References Cited

1. Rawlings AM, Sharrett AR, Schneider AL, Coresh J, Albert M, Couper D, Griswold M, Gottesman RF, Wagenknecht LE, Windham BG, Selvin E. Diabetes in midlife and cognitive change over 20 years: a cohort study. *Ann Intern Med.* 2014;161(11):785-793.
2. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, Coresh J, Knopman D, Power MC, Rawlings A, Sharrett AR, Wruck LM, Mosley TH. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol.* 2014;71(10):1218-1227.
3. Newcomer R, Clay T, Luxenberg JS, Miller RH. Misclassification and selection bias when identifying Alzheimer's disease solely from Medicare claims records. *J Am Geriatr Soc.* 1999;47(2):215-219.