ARIC Manuscript Proposal #1871

PC Reviewed: 12/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Type 2 diabetes and cognitive decline over 14 years, accounting for mortality

b. Abbreviated Title (Length 26 characters): T2DM, cognition, and mortality

2. Writing Group:

Writing group members: Elizabeth Rose Mayeda, MPH (Doctoral Student, UCSF), Mary N. Haan, MPH, DrPH (Professor of Epidemiology, UCSF), John Neuhaus, PhD (Professor of Biostatistics, UCSF), Kristine Yaffe, MD (Professor of Psychiatry, UCSF), David S. Knopman, MD (Professor of Neurology, Mayo Clinic, ARIC), Thomas Mosley (University of Mississippi Medical Center)

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

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3. Timeline:

Data analysis and manuscript preparation: June 2012-December 2012

4. Rationale:

In most longitudinal population based studies of older adults, death is a highly prevalent event, contributing to substantial attrition over time. In standard statistical analysis, death is usually treated as a form of non-informative censoring. However, many risk factors and health

outcomes, including cognitive decline, are associated with death[1,2] which results in competing risk or differential selective survival by exposure. This influences the estimate of effect observed between an exposure and an outcome. For example, those with higher exposures may die earlier and in greater numbers, leaving less vulnerable subpopulations in the cohort. Type 2 diabetes has been associated with dementia and cognitive decline in older populations in many studies[3-19].

The goal of this analysis is to evaluate the effect of type 2 diabetes (T2DM) on cognitive decline in a middle-aged population (ARIC) with the expectation that selective survival will have less effect on risk factor associations with cognitive decline than in older populations. Additionally, we expect race to modify these associations. Many people with T2DM may not survive to an age where they experience significant cognitive decline. Due to exposure-related death at earlier ages in disadvantaged groups, the effect and timing of mortality on the association between T2DM and cognitive function may differ by race/ethnicity.

To accomplish this we will examine how the effect estimates differ when standard regression techniques are applied compared with techniques that account for the dependence between cognitive decline and death. When the dependence between cognitive decline and death is not taken into account, the estimated association between T2DM and cognitive decline may be biased. Statistical methods that account for the dependence between cognitive decline and death may provide more valid effect estimates.

5. Main Hypothesis/Study Questions:

The aims of this paper are to (1) evaluate the effect of T2DM on cognitive decline in a bi-racial cohort of middle-aged adults over 14 years, (2) examine whether the association between T2DM and cognitive decline is modified by race/ethnicity, (3) examine how these effect estimates differ when standard regression techniques are applied vs. techniques that account for the dependency between cognitive decline and death, (4) examine how the effect of adjustment for death differs by race/ethnicity, (5) assuming that T2DM is associated with cognitive decline, examine to what extent the association is partially mediated by higher fasting blood glucose levels, higher fasting blood insulin levels, vascular disease, and hypertension.

Hypothesis 1: Those with T2DM experience faster cognitive decline compared to those without T2DM.

Hypothesis 2: The association between T2DM and cognitive decline will be modified by race/ethnicity such that among those with T2DM, African Americans will experience more rapid cognitive decline and at earlier ages than whites.

Hypothesis 3: Compared to results from models that account for the dependency between cognitive decline and death, association between T2DM and cognitive decline in the joint models will be reduced compared to traditional models that do not account for death.

Hypothesis 4: Assuming African Americans experience higher premature mortality than whites, when the dependency between cognitive decline and death is accounted for, the reduction in the association between T2DM and cognitive decline will be greater in African Americans.

Hypothesis 5: The effect of T2DM on cognitive decline is partially mediated by higher fasting blood glucose levels, higher fasting blood insulin levels, vascular disease, and hypertension.

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).

Study design: Fourteen-year longitudinal study

Inclusion: Subset of ARIC participants who underwent a brain MRI at exam 3 and were invited to participate in the ARIC MRI and Neurocognitive Longitudinal Study.

Exclusion: None

Outcome: 1) Cognitive assessment results and age at each assessment over 4 waves: (Delayed Word Recall Test, Digit Symbol Substitutions Rest, and Word Fluency Test) (exam 2, exam 3, exam 4, post-exam 4 (second MRI)). 2) Age at death for participants who died prior to the 4th cognitive assessment. We will use age at cognitive assessments and age at death as the time-scales for our analyses.

Exposure: T2DM classification (all exams).

Covariates: DOB (to calculate age at each visit) (exam 1), date of each visit (to calculate age at each visit) (all exams), gender (exam 1), race (exam 1), educational attainment (exam 1), socioeconomic status (exam 1), duration of diabetes (for prevalent diabetes cases) (exam 1), fasting plasma glucose levels (all exams), fasting plasma insulin levels (all exams), anti-diabetic medication use (all exams), blood pressure/hypertension (sitting systolic and diastolic BP, antihypertensive medication use, and algorithm for hypertensive classification used in ARIC analyses) (all exams), vascular disease (stroke and stroke subtype, myocardial infarction, angina pectoris, intermittent claudication, congestive heart failure, peripheral arterial disease, ankle-brachial index, carotid intima-medial thickness) (prevalent at baseline and incident throughout study period), evidence of cerebrovascular disease on MRI (stroke and white matter disease) (first and second MRI), lipids (HDL, LDL, and total cholesterol and total triglycerides) (all exams), standing height (all exams), weight (all exams), BMI (all exams), waist circumference (all exams), vital exhaustion (Maastricht Vital Exhaustion Questionnaire) (exam 2), APOE genotype (exam 1), physical activity level (exam 2), alcohol intake (exam 2), cigarette smoking status (exam 2).

Summary of data analysis: We will use a joint model to simultaneously model cognitive decline and risk of death. This modeling approach accommodates selective survival effects by adjusting for participants who die earlier in the study period. The joint model is comprised of two sub-models that will use shared parameters: a sub-model for the repeated measures of cognitive function and a sub-model for age at death. We will use a linear mixed effects model[20] for cognitive function as a function of age and T2DM. We will use a piecewise exponential model[21] to assess the association between T2DM and age at death. The piecewise exponential model provides much of the flexibility of the Cox proportional hazards model, including the ability to include time-dependent covariates, such as T2DM, and has the advantage that we can easily combine the model with a model for repeated measures within existing software, for example, PROC NLMIXED in SAS, following approaches described by Guo and Carlin[22]. Additionally, the piecewise exponential model also allows time-dependent covariate effects, i.e. non-proportional hazards, by specifying different regression coefficients for different time intervals.

Anticipated methodologic limitations: Cognitive assessments were not obtained from participants who were ineligible for or would not consent to MRI, which limits generalizability.

Attrition from sources other than mortality could induce bias. Sample size may limit power to detect potential interactions.

7.a. Will the data be used for non-CVD analysis in this manuscript?
__x__ Yes ____ 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?
__x__ Yes ____ No
(This file ICTDER03 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)?
Most related manuscript proposals in ARIC:

1. 1700 Cognitive Function and Incident Dementia: The Atherosclerosis Risk in Communities (ARIC) Study. Andrea Christman (manuscript currently with co-authors)

2. 1284r Periodontitis as a potential risk factor for cognitive impairment in late life. James M Noble

3. 1418 Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study. Elizabeth Selwin

4. 1701 Incident heart failure and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) study. Jan Bressler

Most related publications in ARIC:

1. Knopman DS, Mosley TH, Catellier DJ, Coker LH, ARIC Study Brain MRI Study. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimers Dement.* 2009 May;5(3):207-14.

2. Young SE, Mainous AG, Carnemolla M. Hyperinsulinemia and cognitive decline in a middle-aged cohort. *Diabetes Care.* 2006 Dec;29(12):2688-93.

3. Knopman D, Boland L, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR. Cardiovascular risk factors and cognitive decline in middle-aged adults: the ARIC study. *Neurology.* 2001;56:42-8.

4. Knopman DS, Penman AD, Catellier DJ, Coker LH, Shibata DK, Sharrett AR, et al. Vascular risk factors and longitudinal changes on brain MRI: The ARIC study. *Neurology* 2011;76(22):1879-85.

5. Pavlik VN, de Moraes SA, Szklo M, Knopman DS, Mosley TH, Jr., Hyman DJ. Relation between cognitive function and mortality in middle-aged adults: the atherosclerosis risk in communities study. *Am J Epidemiol* 2003;157(4):327-34.

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

___ A. primarily the result of an ancillary study (list number* _____)

_x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _ 1999.01**__ _____ _____)**

*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.

Works cited

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