ARIC Manuscript Proposal # 1418

PC Reviewed: 09/09/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

b. Abbreviated Title (Length 26 characters): Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study

2. Writing Group:

Writing group members: Elizabeth Selvin; Rebecca Gottesman; Hong Zhu; Alvaro Alonso; Josef Coresh; Richey Sharrett; Thomas Mosley; others welcome

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

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3. Timeline: the proposed project is an analysis of existing data; we anticipate it will take 6-12 months from the availability of the HbA1c data (~October 2008) to submission of manuscript to ARIC Publications Committee.

4. Rationale:

Diabetes is associated with an increased risk of cognitive decline and the development of dementia (1-5). Although more controversial, there is some evidence that individuals with diabetes are more likely to develop Alzheimer's disease as compared to their non-diabetic counterparts (5-8). Associations are likely to be particularly strong when metabolic status is measured in middle age rather than later in life. The biological mechanisms linking diabetes to impaired cognition remain unclear and data examining possible mediators of this association are sparse (4). Individuals with diabetes are at increased risk of stroke (9-12) and it is postulated hyperglycemia itself may contribute to microvascular changes and eventually brain ischemia. A possible mechanism is advanced glycation end products (AGEs). AGEs accumulate in the setting of hyperglycemia and are thought to contribute to diabetic vascular disease (13-16); they have also been hypothesized to directly contribute to the pathogenesis of dementia, including the Alzheimer's form (17-20).

Hemoglobin A_{1c} (HbA_{1c}) is an integrated measure of circulating glucose levels, and its measurement is central to the management of glucose control in persons with diabetes. Recent epidemiologic studies have demonstrated that HbA1c is a marker of cardiovascular risk and total mortality among persons without diabetes (9;21-29). Several previous studies have assessed the association between HbA1c and cognitive function in persons with type 2 diabetes (25) but little is known about the association of HbA1c with cognitive decline and the development of dementia across the spectrum of glucose abnormalities (30).

5. Main Hypothesis/Study Questions:

The overarching objective of this proposal is to examine the association between HbA1c, a marker of exposure to elevated glucose levels, and measures of cognitive function and incident hospitalization for dementia in individuals with and without diabetes in the ARIC cohort.

> Hypothesis 1: Higher hemoglobin A1c levels in persons with and without diabetes will be independently associated with decline in cognitive function.
>
> Hypothesis 2: Higher hemoglobin A1c levels in persons with and without diabetes will be independently associated with risk of hospitalization for dementia.

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: Prospective cohort study with Visit 2 as baseline.

Exposure: HbA1c (Visit 2 only). HbA1c data will be available ~Oct 2008 on all participants with stored whole blood at Visit 2 (Ancillary Study 2006.15). Main analyses will be conducted using diabetes-stratified quartiles of HbA1c. We will also model clinically relevant cut-points of HbA1c (<6, 6-7, 7-8, >8) in persons with diabetes.

Diabetes status: Diagnosed diabetes defined by a physician diagnosis or diabetes medication use at either Visit 1 or Visit 2. Additional analyses will be conducted incorporating individuals with undiagnosed diabetes (fasting glucose >126 mg/dl or non-fasting glucose >200 mg/dl).

Covariates (assessed at Visit 2 unless otherwise noted): Age, sex, waist-hip ratio, body mass index, total, LDL- and HDL-cholesterol, hypercholesterolemia (total cholesterol ≥240 mg/dl or taking cholesterol lower drugs in the prior 2 weeks), prevalent coronary heart disease (Visit 1,Visit 2, or incident between visit 1 & Visit 2), triglycerides, mean systolic and diastolic blood pressures, blood pressure medication use, hypertension status, smoking, alcohol consumption, Baeke physical activity score (Visit 1 only), education level (Visit 1 only), occupational status (Visit 1 only), depressive symptoms (Visit 2) assessed using a 21-item questionnaire on Vital Exhaustion

Potential stratifying/subgroup variables of interest: fasting status, glucose, diabetes medication use.

Outcomes:

Cognitive Function at Visits 2 and 4: Change in cognitive function from Visit 2 (1990-1992) to Visit 4 (1996-1998) (Visit 4 score – Visit 2 score). In the ARIC Study, cognitive functioning was assessed at Visits 2 and 4 using three standardized tests: the Delayed Word Recall Test (DWRT)(31;32), the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R)(33), and the Word Fluency Test (WFT)(33) of the Multilingual Aphasia Examination (34). Trained examiners administered the cognitive tests in a standardized order during one session in a quiet room. Examiner performance was monitored by audio tape recording. Recordings were reviewed locally and shared across centers to ensure consistency with testing procedures.

- Visit 2 cognitive function variables (cnfa01, cnfa02, cnfa03, cnfa04) in datafile, *CNFA*
- Visit 4 cognitive function variables (cnfc1, cnfc2, cnfc3, cnfc4) – datafile: *CNFC04*

Incident hospitalization or death due to dementia: time to first hospitalization for dementia defined by ICD-9 or -10 hospital discharge code. Previous analyses (Alonso et al) indicate there are 203 post-Visit 2 hospital discharge-defined dementia cases using the following ICD codes: Alzheimer's disease (331.0), vascular dementia (290.4) or dementia of other etiology (290.0, 290.1, 290.2, 290.3, 290.9, 294.1, 294.2, 294.8, 294.9, 331.1, 331.2, 331.8, 331.9).

Exclusions: history stroke or TIA, scoring below the sex- and race-specific 5th percentile on any of the cognitive tests of interest at Visit 2, medications in the past 2 weeks such as narcotics, anti-psychotics and others which are associated with sedation as a primary CNS side effect, or missing variables of interest.

Sensitivity analyses: we will conduct sensitivity analyses using definitions of diabetes incorporating undiagnosed cases (based on fasting glucose >126 mg/dl or non-fasting glucose >200 mg/dl). For analyses of cognitive decline, we will conduct sensitivity analyses excluding

persons aged <50 years at the second visit as previous show that cognitive decline is thought to be negligible before the age of 60 years.

Analyses:

Aim 1: linear models of 6-year change in cognitive function score (Visit 4-Visit 2) by diabetes-specific quartiles of HbA1c for each measure of cognitive function, controlling for covariates of interest. We will also create a binary variable classifying individuals as having cognitive decline or not and conduct logistic regression analyses examining the association between diabetes-specific quartiles of HbA1c and cognitive decline for each measure of cognitive function and a combined global definition of cognitive decline during the 6-year period (35). We will conduct a secondary analysis categorizing individuals into quartiles of decline and compare those with greatest cognitive decline to those with minimal or no decline using a logistic regression model.

Aim 2: time-to-event models (Cox proportional hazards) to compare the risk of incident hospitalization for dementia by diabetes-specific quartiles of HbA1c after adjusting for covariates of interest. We will confirm the proportionality of the hazards across HbA1c quartiles.

Major limitations: As with any observational study, we will not be able to rule out the possibility of residual confounding. Misclassification of our outcomes is also a potential problem, but unlikely to be differential by HbA1c level. We are also unlikely to see large changes in cognitive function during the 6 year period of interest as this is a middle-aged cohort and large, population-level declines in dementia are generally seen at older ages. We will conduct analyses excluding individuals age <50 at Visit 2 to assess the magnitude of this problem. Using hospitalizations to identify cases of dementia is likely to highly underestimate the true incidence of the condition. Nonetheless, this is likely to be a highly specific case definition. This is also a heterogeneous outcome and we anticipate that we will not have a sufficient number of cases to separate out types of dementia (e.g. Alzheimer's vs vascular 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 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? ____ Yes __X__ 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"? ____ Yes ____ No

8.c. If yes, is the author aware that some DNA data is not allowed to be used by 'for profit' groups. Is this data being used by a 'for profit' organization? If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded?

____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)?

ARIC	1365	Midlife cardiovascular risk factors and risk of dementia hospitalization in a biracial cohort: the ARIC study	Alonso, A		05-13-2008	A	2	
ARIC	148	Correlates of cognitive function in middle-aged adults	Cerhan, JR		03-05-1992	A	1	PubMed 1998
ARIC	314	Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study.	Mosley, TH		05-11-1995	A	1	PubMed 1996
ARIC	672	Changes in cognitive test scores in the ARIC cohort over a 6-year period (Visit 2 to Visit 4) and their correlation with vascular risk factors	Knopman, DS		07-21-1999	A	2	2001
ARIC	757	Relationship between cognitive function measured in middle-age and all cause mortality in a US population cohort: The Atherosclerosis Risk in Communities (ARIC) Study	Pavlik, VN		01-16-2001	A	2	2003
ARIC	762	Cognitive functioning as a predictor of ischemic stroke incidence	Alves de Moraes, SA		01-16-2001	A	1	PubMed 2003
ARIC	1010	Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study.	Beydoun, MA		05-06-2004	A	2	PubMed 2007
ARIC-HbA1cV2-200305	1011	Stability of haemoglobin A1c (HbA1c) measurements from frozen whole blood samples stored for over a decade.	Selvin, E		05-06-2004	A	2	PubMed 2005
ARIC	1024	Glycemic control and coronary heart disease risk in persons with and without diabetes: The Atherosclerosis Risk in Communities Study	Selvin, E		07-27-2004	A	2	PubMed 2005
ARIC	1067	Glycemia (haemoglobin A1c) and incident stroke: The ARIC Study	Selvin, E		03-11-2005	A	2	PubMed

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* __2003.05 *and* 2006.15 _)

___ 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.

_ES_

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