ARIC Manuscript Proposal # 3058

PC Reviewed: 10/3/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of late-life glycemia status with 3-year late-life cognitive decline and incident MCI/dementia: The ARIC Study

b. Abbreviated Title (Length 26 characters): Diab incident MCI/dem v6

2. Writing Group:
Writing group members: Andreea Rawlings (first); Richey Sharrett; Marilyn Albert; Josef Coresh; Beverly Gwen Windham; Melinda C. Power; David Knopman; Keenan Walker; Sonia Davis; Thomas Mosley; Rebecca Gottesman, Liz Selvin (senior)

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

First author: **Andreea Rawlings, PhD MS**

Address: Oregon State University, College of Public Health and Human Sciences
Milam Hall 155
2520 SW Campus Way
Corvallis, OR 97331

Phone: 541-737-5522
E-mail: arawlin2@jhu.edu

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).

Name: Elizabeth Selvin
Address: Johns Hopkins University
2024 E Monument Street, Suite 2-600
Baltimore MD 21287

Phone: 410-614-3752 Fax: 410-955-0476
E-mail: eselvin@jhu.edu

3. Timeline: 6-9 months; manuscript submission spring 2018.

4. Rationale:

Studies have documented that compared to persons without diabetes, persons with diabetes have greater cognitive decline and risk of dementia[1–4]. Our work in ARIC has shown faster cognitive decline from midlife to late-life in persons with prediabetes and diabetes compared to those without, and in persons with poorly controlled diabetes (HbA1c ≥7%) compared to those with well-controlled diabetes (HbA1c<7%)[5]. However, results from studies examining diabetes assessed in late-life with subsequent risk of cognitive decline and dementia have been mixed[8–13].

The ARIC Neurocognitive Study (ARIC-NCS) provides a unique opportunity to characterize glycemic patterns and diabetes durations using 25 years of data spanning mid-life to late-life. This approach may better capture the complexity, and cumulative effects, of the disease, such as longer duration and greater exposure to hyperglycemia, oxidative stress, and hyperinsulinemia, and the development of micro- and macrovascular complications. Additionally, it allows us to examine how selection (at visit 5) may impact estimates of cognitive decline in older age.

Understanding the life-course of diabetes and glycemia can give us insight into the etiologically relevant time window for intervention. It can also inform whether more intensive glucose management in older adults (and area of great debate) is associated with adverse cognitive outcomes.

Our aims for this study are 1) to characterize glycemic patterns and diabetes duration using 25 years of data (from visits 1-5), 2) to examine associations between glycemia status at visit 5 with subsequent cognitive decline, incident dementia, and incident mild cognitive impairment (MCI, from visits 5-6), and 3) to examine if selection at visit 5 has an impact on subsequent cognitive decline.

5. Main Hypothesis/Study Questions:

<u>Aim 1</u>

To characterize glycemic patterns and diabetes duration from mid-life to late-life (visits 1-5)

<u>Aim 2</u>

To examine associations between glycemia status at visit 5 (characterized in Aim 1), with cognitive decline, incident dementia, and incident MCI

Hypothesis: Persons with longer duration of prediabetes and diabetes in late-life, compared to persons without diabetes or with newly diagnosed diabetes, will have greater late-life cognitive decline and conversion to MCI and dementia

<u>Aim 3</u>

To examine the impact of selection to visit 5 on estimates of subsequent cognitive decline, incident dementia, and incident MCI

Hypothesis: Accounting for ARIC participants who are alive but did not attend visit 5 will strengthen estimated associations between glycemia status and subsequent cognitive decline, incident dementia, and incident MCI

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, using visit 5 as baseline

Aim 1: Characterizing glycemia patterns from mid-life to late-life
Summary of proposed analyses:
In preliminary analyses, we will use self-report, medication, and glucose information (because of its availability at all study visits) to categorize glycemia status at visits 5. We will investigate adding HbA1c (visit 2, 5), the oral glucose tolerance test (visit 4), and a definition including confirmation across tests, which is more consistent with clinical practice.

For participants who attend visits 1-5, we will define glycemia status as follows:
- No diabetes: no self-reported diagnosis, no medication use, and fasting glucose <100 mg/dL
- Prediabetes: no self-reported diagnosis, no medication use, and fasting glucose 100-125 mg/dL
- Diabetes: self-reported diagnosis, medication use, or fasting glucose ≥126 mg/dL

For participants without diabetes at visit 1-4, we will use annual follow-up data to identify new cases of diabetes to estimate diabetes duration between visits 4 and 5.

We anticipate characterizing glycemia status at visit 5, the main exposure, using prediabetes, diabetes, and duration, based on information from visits 1-5. For example, one possibility is the 6-level variable below:
- No diabetes (reference)
- Prediabetes (developed in mid-life)
- Prediabetes (developed in late-life)
- Short duration diabetes (<5 years)
- Intermediate duration diabetes (5-10 years)
- Long duration diabetes (>15 years)

Aim 2**:** Examining the associations between glycemia status at visit 5 (characterized in Aim 1), with cognitive decline, incident dementia, and incident MCI

Exclusions
We will exclude participants who did not attend visit 5 or who lack cognitive status (normal, MCI, or dementia) and cognitive performance (domain scores) data, persons of non-white or non-black race, or non-white and in Maryland or Minnesota field centers, and persons with dementia.

Outcomes

We will use the following variables created by the coordinating center, which are briefly described below.

Dementia incidence between visit 5 and 6: Dementia incidence will be analyzed in two separate groups:

Persons examined at Visit 5. Dementia will be defined using both the information from the full Visit 6 examination with expert committee diagnosis and information captured in AFU interviews using the Six Item Screener (SIS) and the Ascertain Dementia 8-item Informant Questionnaire (AD8). Date of dementia onset will be captured using the SIS and AD8, and dementia diagnosis will be confirmed at Visit 6 in those who attend Visit 6. Participants who attended Visit 5, but not Visit 6, and have SIS and AD8 information available from the AFU will also be included.

Persons alive at Visit 5 who did not attend Visit 5. In order to evaluate potential selection effects of Visit 5 attendance, we will examine separately those participants who did not attend Visits 5, but have available SIS and AD8 data during this period. Their rate of probable dementia based on SIS and AD8 data will be compared with the similarly-defined probable dementia among Visit 5 attendees.

Cognitively normal: defined as all cognitive domains scores are >-1.5 Z scores or an absence of decline in the full ARIC cognitive battery of >0.055 standard deviations per year (ARIC Visit 6 Manual 17)

Mild cognitive impairment (MCI): defined as at least one domain score ≤ -1.5 Z scores, a CDR sum of boxes between >0.5 and ≤3, an FAQ ≤5, and a decline on the full ARIC cognitive battery of >0.055 standard deviations per year (ARIC Visit 6 Manual 17).

Dementia: defined based on these three criteria being met – (1) FAQ > 5 or CDR sum of boxes > 3, and (2) at least 2 domain scores ≤ -1.5 Z scores, and (3) a decline since visit 5 on the full ARIC cognitive battery of >0.055 standard deviations per year (ARIC Visit 6 Manual 17).

Cognitive change: We will examine change in cognitive function from visit 5 to visit 6 in domains of memory, language, and processing speed and executive function (tests included in each domain are shown below). Tests will be summarized using a latent variable approach, as previously described[20].

<u>Memory Composite</u>
Logical Memory I & II
Incidental Learning
Delayed Word Recall Test (DWRT)

<u>Language</u>
Animal Naming
Boston Naming Test
Word Fluency Test (WFT)

Processing speed and executive function
Trail Making Test-A
Trail Making Test-B
Digit Span Backwards
Digit Symbol Substitution Test (DSST)

Covariates
We will evaluate the following variables as confounders: age, age squared (to allow for the usually observed accelerated cognitive decline), sex, race-center, education, cigarette smoking and alcohol use status, body mass index, physical activity, total cholesterol, HDL, triglycerides, hypertension, coronary heart disease, history of stroke, and *APOE* ε4 status. Covariates will be assessed at visit 5.

Statistical analysis
We will use Cox proportional hazards regression, with sensitivity analysis using logistic regression (described below) to examine the association between the 6-level exposure variable and incident MCI and dementia. This analysis will be restricted to persons categorized as being cognitively normal at visit 5.

We will use linear regression to examine the association between the 6-level exposure variable with late-life cognitive decline. This analysis will be restricted to participants with cognitive data at visit 5. We will examine changes in global cognitive score and changes in domain-specific cognitive scores.

We will use three models for these analyses:
Model 1: Crude/unadjusted
Model 2: Model 1 + age, gender, race/field center, education (demographic model)
Model 3: Model 2 + physical activity, alcohol consumption, smoking, body mass index, apoE, hypertension, hypertension medication use, cholesterol, self-reported health compared to others, history of coronary heart disease, and history of stroke (demographic and cardiovascular model)

Aim 3: Examining the impact of selection to visit 5 on estimates of subsequent cognitive decline, incident dementia, and incident MCI

Approximately 40% of persons who were alive during visit 5 (2011-2013) did not attend visit 5. Persons who did not attend were older and were more likely to have cardiovascular risk factors (diabetes, hypertension, be current smokers, have higher BMI, etc) at earlier study visits.

We have auxiliary information on persons who did not attend visit 5, including prior visit information and the annual follow-up calls. We will use inverse probability of attrition weighting to reweight the participants who attended visit 5 to represent all participants alive at visit 5. We will use a logistic regression model (outcome=attended visit 5, yes/no) with predictors from visits 1-4 and AFU.

We will then rerun the analyses described in Aim 2, to estimate the associations between glycemia status at visit 5 (characterized in Aim 1), with cognitive decline, incident dementia, and incident MCI.

Effect Modification

We will examine possible effect modification by history of coronary heart disease, history of stroke, sex, race, and *APOE* ε4 status through the use of stratified analyses.

Sensitivity analyses

- In analyses of cognitive changes, we will use inverse probability of attrition weighting (IPAW) to account for drop-out between visits 5 and 6 (for aims 2 and 3)
- We will use logistic analyses instead of Cox. The long latency of dementia (usually decades) makes it unlikely that persons would have true "incident" dementia in the relatively short time between visits 5 and 6. Rather, participants are on a trajectory and convert between visits 5 and 6, which makes a logistic regression more appropriate. Additionally, follow-up time should be relatively similar for all participants between visits 5 and 6, with variability in times due to when participants originally attended the study visits. Thus, persons would essentially have equal follow-up times, which need to be accounted for in Cox models.
- We will explore alternative definitions of diabetes using HbA1c from visits 2 and 5, and using self-report and medication use only (we will only examine diabetes and duration, not prediabetes, in this latter definition). We will also explore differences in glycemia associations by glucose-lowering medication use.

Limitations/Challenges

- Different measures of glycemia are available at different study visits (A1c visits 2, 5; glucose visits 1-5; OGTT visit 4; no biomarkers during AFU)
- Cognitive decline between visits 5 and 6 may be small and limit our ability to detect differences in cognitive function across glycemia groups
- Given the large gap between visits 4 and 5, misclassification in glycemia status is likely, and would bias results toward the null
- We will not be able to rule out the possibility of residual confounding

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# 2511. Vascular risk factors and brain amyloid deposition: The ARIC-PET Study. Gottesman et al.

MP# 2120a. Mid-life vascular risk factors for Mild Cognitive Impairment in the ARIC NCS Study. Knopman et al.

MP# 2120b. Incidence of Dementia and its relationship to midlife vascular risk factors in ARIC. Gottesman et al.

MP# 2120c. Prevalence of Mild Cognitive Impairment and Dementia and Their Relationship to Diabetes and Hypertension in ARIC. Knopman et al.

MP#2606. Biomarkers of hyperglycemia, 20-year cognitive decline, and dementia risk: the Atherosclerosis Risk in Communities Study. Rawlings et al

MP#2160. Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study.

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* __2009.29__)

___ 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.

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, approved manuscripts using 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 ____ Yes __X__ No.

References

1 Reijmer YD, van den Berg E, Ruis C, Kappelle LJ, Biessels GJ. Cognitive dysfunction in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2010; **26**: 507–19.

2 Ryan JP, Fine DF, Rosano C. Type 2 diabetes and cognitive impairment: contributions from neuroimaging. *J Geriatr Psychiatry Neurol* 2014; **27**: 47–55.

3 Biessels GJ, van der Heide LP, Kamal A, Bleys RL, Gispen WH. Ageing and diabetes: implications for brain function. *Eur J Pharmacol* 2002; **441**: 1–14.

4 Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. *Endocr Rev* 2008; **29**: 494–511.

5 Rawlings AM, Sharrett AR, Schneider ALC, *et al.* Diabetes in Midlife and Cognitive Change Over 20 Years: A Cohort Study. *Ann Intern Med* 2014; **161**: 785–93.

6 Rawlings AM, Sharrett AR, Mosley TH, Ballew SH, Deal JA, Selvin E. Glucose Peaks and the Risk of Dementia and 20-Year Cognitive Decline. *Diabetes Care* 2017; : dc162203.

7 Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Heal* 1998; **88**: 1337–42.

8 Whitmer R, Sidney S SJ, Johnston S YK. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005; **64**: 277–82.

9 Walker KA, Power MC, Gottesman RF. Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review. 2017. DOI:10.1007/s11906-017-0724-3.

10 van Vliet P. Cholesterol and late-life cognitive decline. *J Alzheimers Dis* 2012; **30 Suppl 2**: S147-62.

11 Power MC, Tchetgen EJ, Sparrow D, Schwartz J, Weisskopf MG. Blood pressure and cognition: factors that may account for their inconsistent association. *Epidemiology* 2013; **24**: 886–93.

12 Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J* 2012; **42**: 484–91.

13 Xu W, Qiu C, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. *Diabetes* 2009; **58**: 71–7.

14 Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. *Lancet Neurol* 2006; **5**: 87–96.

15 Bagg W, Whalley GA, Gamble G, Drury PL, Sharpe N, Braatvedt GD. Effects of improved glycaemic control on endothelial function in patients with type 2 diabetes. *Intern Med J* 2001; **31**: 322–8.

16 Di Flaviani A, Picconi F, Di Stefano P, *et al.* Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients. *Diabetes Care* 2011; **34**: 1605–9.

17 Rizzo MR, Marfella R, Barbieri M, *et al.* Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. *Diabetes Care* 2010; **33**: 2169–74.

18 Cui X, Abduljalil A, Manor BD, Peng C-K, Novak V. Multi-scale glycemic variability: a link to gray matter atrophy and cognitive decline in type 2 diabetes. *PLoS One* 2014; **9**: e86284.

19 Zhong Y, Zhang XY, Miao Y, *et al.* The relationship between glucose excursion and cognitive function in aged type 2 diabetes patients. *Biomed Environ Sci* 2012; **25**: 1–7.
20 Gross AL, Power MC, Albert MS, *et al.* Application of Latent Variable Methods to the Study of Cognitive Decline When Tests Change over Time. *Epidemiology* 2015; **26**: 878–87.