ARIC Manuscript Proposal # 3042

PC Reviewed: 9/12/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of midlife cognition, cognitive decline, and education with late-life cerebral β-amyloid deposition

b. Abbreviated Title (Length 26 characters): midlife cognition with PET

2. Writing Group:
Writing group members: Andreea M Rawlings (first); A Richey Sharrett; Thomas H Mosley; Dean Wong; Rebecca F Gottesman (senior/last), others welcome

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]**

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3. Timeline: All data is currently available, we plan to submit for publication within 12 months of approval of the manuscript proposal.

4. Rationale:

Cognitive ability in early adulthood appears to track well to late-life[1]. Several studies[2–4] have documented associations between cognitive or school performance measured during childhood and the prevalence of dementia in old age, with one study finding associations with performance in children as young as 11 years old[3].

In one study, lower cognitive performance at age 22 was associated with specific markers of Alzheimer's Disease (AD), including Braak Stage and neurofibrillary tangles, in late life[2]. In the ARIC study, cognitive performance and 6-year cognitive decline assessed in late midlife (mean age ~60) were both associated with incidence of hospitalized dementia occurring years later[5]. Higher level of education has been consistently associated with lower risk of dementia[6], a finding replicated in ARIC-NCS[7].

These associations have been interpreted as manifestations of cognitive reserve[8,9]. The reserve associated with cognitive ability may be represented by neural structural differences, as has been shown for the ability to speak two or more languages[10].

Participants in the ARIC study had their cognitive performance assessed in midlife. More than 300 participants of ARIC subsequently underwent florbetapir PET in late-life (approximately 20 years after assessment of vascular risk factors, cognition, and education) allowing for comparisons between midlife factors and late-life β-amyloid deposition. Our aim is to examine the association of education level, midlife cognitive performance, and midlife cognitive trajectories with late-life cerebral β-amyloid deposition.

5. Main Study Questions:

Aim 1

To examine the association between cognitive function assessed at visits 2 and 4 (separately) with cerebral β-amyloid deposition measured on PET.
Hypothesis: we hypothesis that cognitive function in midlife will be associated with AB deposition in late-life

Aim 2

To examine the association between change in cognitive function from visits 2 to visit 4 with cerebral β-amyloid deposition measured on PET.
Hypothesis: we hypothesis that change in cognitive function in midlife will be associated with AB deposition in late-life

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

Non-concurrent cross-sectional design using information from visits 2 and 4 with PET markers at visit 5

Exclusions

We will exclude participants who meet any of the following criteria:

- Did not undergo ARIC-PET
- Race other than black or white
- Missing covariates (described below)
- Prevalent stroke at visit 2

Exposure – cognitive function at visit 2 and 4, change in cognitive function from visit 2 to 4

- Cognitive function was assessed at visit 2 and 4 using the following tests:
    - Delayed word recall test (DWRT)
    - Digit symbol substitution test (DSST)
    - Word fluency test (WFT)
    - For each test, we will calculate a Z score by subtracting the test mean and dividing by the standard deviation. We will also create a global measure of cognitive performance by averaging the Z scores the three tests. We will also consider the use of latent variables in place of the individual tests (work developed by Alden Gross, MP#2215)
- Cognitive change from visit 2 to visit 4
    - We will use the difference between individual test scores and also create a global composite of the difference in scores between the visits
- Education:
    - We will examine education categorized as: less than high school, high school or GED or vocational, or college or professional education
    - We will also examine education continuously as years of education

Outcome – Standardized Uptake Volume Ratio (SUVR) by ARIC-PET

- The standardized uptake value ratio (SUVR) is a measure of relative β-amyloid presence, calculated as the standardized uptake value of florbetapir (% of injected dose per kg of body weight) in a specific region of interest (ROI) divided by the standardized uptake value in the cerebellum.
- We will use global cortical SUVR for this analysis, a weighted average (based on ROI size) of the following regions: precuneus, orbitofrontal cortex, prefrontal cortex, superior frontal cortex, lateral temporal lobe, parietal lobe, occipital lobe, anterior cingulate, and posterior cingulate. In secondary analyses we will examine associations between the exposure variables and specific ROIs. Because of the skewed distribution of SUVR, we will dichotomize it at the median value of 1.2, with values >1.2 classified as "elevated". As no standard cut-point has been established, we will examine other cut-points as well.

Covariates

We will evaluate the following variables as covariates: age, sex, race, body mass index, education, systolic and diastolic blood pressure, hypertension, hypertension medication

use, diabetes, diabetes medication use, APOE genotype, smoking, alcohol use, diabetes duration, and physical activity.

Statistical Analysis:
We will characterize our analytic population using means/standard deviations or percent for all covariates. We will use logistic regression to characterize the association between the exposures and dichotomized SUVR. Because of the high prevalence of elevated SUVR (50% by definition), logistic regression over estimates prevalence estimates. As a result, we will also use log-binomial and Poisson regression with robust variance estimation to estimate prevalence estimates.

Effect Modification
We will examine possible effect modification by age, race, sex, and APOE genotype.

Sensitivity analyses
We will consider the following sensitivity analyses:

- We will use inverse probability weighting to account for study dropout or death between visits 2 and 5
- Exclude participants with incident stroke during follow-up (between visits 2 and 5)

Challenges/Limitations

- We may have limited power in some analyses
- Selection bias of who ends up with an MRI is of concern and may limit generalizability of our study
- 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? 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)?

MP #2466: The ARIC-PET amyloid imaging study: differences in brain amyloid deposition by age, race, sex, and APOE genotype (Gottesman)
MP #2511: Vascular risk factors and brain amyloid deposition: The ARIC-PET study (Gottesman)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? **__x__ Yes ____ No**
ARIC NCS

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.

References

1. Plassman BL, Welsh K a, Helms M, Brandt J, Page WF, Breitner JC. Intelligence and education as predictors of cognitive state in late life: a 50-year follow-up. *Neurology*. 1995;45(8):1446-1450. doi:10.1212/WNL.45.8.1446.
2. Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: Findings from the Nun Study. *Neurobiol Aging*. 2005;26(3):341-347. doi:10.1016/j.neurobiolaging.2004.06.019.
3. Whalley LJ, Starr JM, Athawes R, Hunter D, Pattie a, Deary IJ. Childhood mental ability and dementia. *Neurology*. 2000;55:1455-1459. doi:10.1212/WNL.55.10.1455.
4. Dekhtyar S, Wang H-X, Scott K, Goodman A, Koupil I, Herlitz A. A Life-Course Study of Cognitive Reserve in Dementia--From Childhood to Old Age. *Am J Geriatr Psychiatry*. 2015;23(9):885-896. doi:10.1016/j.jagp.2015.02.002.
5. Schneider AL, Gottesman RF, Mosley T, et al. Cognition and incident dementia hospitalization: results from the atherosclerosis risk in communities study. *Neuroepidemiology*. 2013;40(2):117-124. doi:10.1159/000342308000342308.
6. Valenzuela M, Brayne C, Sachdev P, Wilcock G, Matthews F. Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter population-based cohort. *Am J Epidemiol*. 2011;173(9):1004-1012. doi:10.1093/aje/kwq476.
7. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimer's Dement (Amsterdam, Netherlands)*. 2016;2(January):1-11. doi:10.1016/j.dadm.2015.12.002.
8. Gottesman RF, Rawlings AM, Sharrett AR, et al. Impact of Differential Attrition on the Association of Education with Cognitive Change Over 20 Years of Follow-up: The ARIC Neurocognitive Study. *Am J Epidemiol*. 2014;179(8):956-966. doi:10.1093/aje/kwu020.
9. Sharrett AR. Is cognitive aging predicted by educational level? *Am J Epidemiol*. 2012;175(8):760-761. doi:10.1093/aje/kwr513.
10. Perani D, Abutalebi J. Bilingualism , dementia , cognitive and neural reserve. *Curr Opin Neurol*. 2015;28(6):618-625. doi:10.1097/WCO.0000000000000267.
11. McGurn B, Deary IJ, Starr JM. Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. *Neurology*. 2008;71(14):1051-1056. doi:10.1212/01.wnl.0000319692.20283.10.