ARIC Manuscript Proposal # 2822

PC Reviewed: 8/9/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Subclinical cerebrovascular disease and brain amyloid deposition: The ARIC-PET Study

b. Abbreviated Title (Length 26 characters): Brain MRI and amyloid

2. Writing Group:

Writing group members: Rebecca Gottesman (first and corresponding author); Thomas Mosley (last author); David Knopman; Dean Wong; Yun Zhou; Lynne Wagenknecht; A. Richey Sharrett; Edward Green; Arman Rahmim; Naresh Gupta; Akiva Mintz ; Cliff Jack; Brian Caffo; Zeyi Wang; Timothy Hughes.

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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3. Timeline: 3-6 months; planned abstract submission late summer/ fall 2016; manuscript submission spring 2017.

4. Rationale:

Clinical stroke is one way in which vascular risk factors might adversely impact cognition,[1] and increase risk for dementia and perhaps Alzheimer's disease (AD), although it is more likely that other subclinical brain changes, probably on the same pathophysiologic spectrum as clinical stroke, are contributors to dementia and AD. Both subclinical infarcts and leukoaraiosis, or white matter hyperintensities (WMH), are manifestations of brain microvascular disease, with strong associations with hypertension,[2,3] including in our own studies in ARIC,[4] and other vascular risk factors including smoking[5] and diabetes.[3] These brain microvascular changes been associated with cognitive impairment and cerebral atrophy (including regions usually involved in AD),[6] with similar results showing WMH as important risk factors for cognitive decline in other studies.[7]

Data are conflicting as to the role of brain microvascular disease in AD, pointing to the need for further, well-designed studies in this area. While some studies have suggested that microvascular disease and AD neuropathologic changes are uncorrelated (or that persons with a large amount of one type of pathology have relatively little of the other[8-10]), other pathologic studies suggest the opposite, with microvascular changes (including WMH) found more frequently in brains of AD patients than in similarly-aged controls.[11,12] Unfortunately, survivor bias limits the likelihood that persons with both severe small vessel disease and severe AD neuropathology are evaluated, and AD neuropathologic changes themselves can impact blood brain barrier permeability and alter cerebral perfusion, which in turn can lead to WMH,[12] leading to possible reverse causality (AD causing WMH and its progression).

The use of [18F]-AV-45[13] (florbetapir, Amyvid) permits us to image fibrillar β-amyloid (the accumulation of which, by leading hypotheses, is the cause of AD), using PET imaging; presence of florbetapir uptake has been associated with Aβ on autopsy,[14] and higher uptake has been linked to steeper cognitive decline.[15,16] In the ARIC-PET study (2011-2013), 346 nondemented participants who had been in ARIC-NCS, and had completed stage 3 (with brain MRI) through ARIC-NCS, completed florbetapir PET imaging within a year of the brain MRI scans. We found in this study that amyloid levels were elevated in black participants as compared to white participants,[17] and that those associations were independent of other major vascular risk factors and WMH volume, suggesting that WMH volume globally was not the entire reason for the racial disparities observed. A manuscript in preparation (and presented in abstract form at the Human Amyloid Imaging conference) is evaluating midlife vascular risk factors and late-life brain amyloid; individual risk factors do not appear to be associated with increased brain amyloid, but a cumulative increasing burden of midlife risk factors is associated, in a dose-response type of pattern, and with increasing effect among carriers of an APOE ε4 allele, with late-life brain amyloid, among nondemented individuals. Many of these risk factors are also associated with increasing brain small vessel disease, so it is critical to understand the direct effect of brain small vessel disease on brain amyloid in order to further understand the full relationship and mechanism of how elevated vascular risk might impact brain amyloid and the development of AD.

In this manuscript, we will evaluate the cross-sectional association between brain small vessel disease and brain amyloid, among participants from the ARIC-PET study. Beyond evaluating global burden of brain small vessel disease and global brain amyloid, we will evaluate regional increases in both small vessel disease and amyloid to determine if these are associated with one another (increased small vessel disease in regions where amyloid is increased).

5. Main Hypothesis/Study Questions:

1. Global cortical Aβ deposition by PET will be associated with increased white matter hyperintensity volume (on brain MRI) and subclinical infarcts on brain MRI.
2. Global cortical Aβ deposition by PET will be associated with abnormal white matter tract connectivity, defined using diffusion-tensor imaging (DTI) from MRI scans (lower fractional anisotropy and higher mean diffusivity).
3. Associations observed in #1 and #2, above, will be stronger in blacks compared to white participants.
4. Associations observed in #1 and #2, above, will be stronger in APOE ε4 carriers compared to noncarriers.
5. Regional increased uptake in Aβ will co-occur in regions with higher WMH volume and abnormal tract connectivity.

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).

Analysis of all participants in completed ARIC-PET study (N= 346 completed scans (one additional person was not able to complete the scan so her data is not usable). All analyses will be cross-sectional, using brain MRI data from ARIC-NCS and PET data from ARIC-PET.

Inclusion criteria (for inclusion in ARIC-PET; all of these persons will be included in analysis): persons with a CDR of 3 or lower, and also with a FAQ of 5 or lower, and with a brain MRI (from ARIC-NCS) within 12 months of recruitment. MMSE cannot be "low" (<19 for African-Americans and <21 for Caucasians) at the time of visit 5/ NCS. All participants were required to be able to give their own consent.
Exclusion criteria for involvement in ARIC-PET: We excluded individuals with history of: (1) radiation therapy, chemotherapy, or surgery in the 6 weeks preceding the ARIC-PET visit; or (2) clinically significant liver or renal dysfunction; (3) prolonged QT interval; (4) drug or alcohol abuse. We will allow use of anticholinergic medications or memantine if the dose has been stable for ≥3 months preceding the PET scan.

Outcome: Standardized Uptake Volume Ratio (SUVR) of florbetapir (amyloid) by ARIC-PET, in prespecified regions of interest. For hypotheses 1-4, global mean cortical SUVR, which is a weighted average (based on region-of-interest (ROI) volumes) of regions known to be typically impacted in AD. The SUVR's will be evaluated as continuous variables as well as a binary variable based on a hypothetical cutpoint explored in prior literature of an SUVR of 1.1 or 1.2 (each to be analyzed, as these have both been used in prior literature). Separate regional SUVR values will also be evaluated for hypothesis 5.

Brain MRI data will include the white matter hyperintensity (WMH) volume variable from the ARIC-NCS MRI scans; all analyses of this variable will include adjustment for total intracranial volume. In addition, mean diffusivity and fractional anisotropy will be analyzed (hypothesis 2), and analyses will be repeated including WMH volume as a covariate, to determine if any associations with abnormal connectivity are independent of WMH volume. Infarcts will be evaluated both as present/ absent as well as number of

infarcts on MRI (cortical and subcortical; these will be evaluated separately as well as together), as predictors of brain amyloid.

For hypothesis 1, to combine WMH and brain infarcts, we will evaluate these in the same model, and consider presence of any infarcts or top third of WMH volume as evidence of larger small vessel disease burden.

Other variables: We will include race, center, sex, and age information from ARIC baseline (race, center, sex) and visit 5 (age), as well as apoE genotype from prior ARIC measurement. In addition, hypertension and systolic and diastolic blood pressures, diabetes, hypercholesterolemia, and smoking status will all be assessed from ARIC-NCS. Level of educational attainment as a covariate will be included in models.

Data analysis: Our primary analysis will consider regression and linear models and logistic regression. As mentioned, we will include ICV as a potential confounder. In addition to region-at-a-time analyses, we will explore multivariate outcome models to see if regional inter-dependence adds precision to results. We will explore the SUVR data for normality, to see if transformation of the values should be considered; quantile regression will be explored if interpretable transformations are not successful. Separate models will be evaluated for the separate global measure as well as ROI's as described. We will also evaluate logistic regression models including the binary SUVR>1.1 (or 1.2) cutpoint as used in previous papers. The covariates described above will be explored as independent variables, with additional models evaluating an interaction between race and APOE, each (hypotheses 3 and 4), and each of the separate brain MRI markers.

For hypothesis 5, for regional analyses, separate analyses will be done for SUVR and WMH volumes (and DTI measurements) in the primary regions involved in AD (insula, precuneus).

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 #2466, #2544, #2511.

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.
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.

Bibliography and References Cited

1. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/ american stroke association. *Stroke.* 2011;42(9):2672-2713.
2. Gottesman RF, Coresh J, Catellier DJ, et al. Blood pressure and white matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) Study. *Stroke.* 2010;41:3-8.
3. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI. *Neurology.* 2011;76(22):1879-1885.
4. Gottesman RF, Coresh J, Catellier DJ, et al. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke.* 2010;41(1):3-8.

5. Power MC, Deal J, Sharrett AR, et al. Smoking and white matter hyperintensity progression: The ARIC-MRI Study. *Neurology.* 2015;84(8):841-848.
6. Knopman DS, Griswold ME, Lirette ST, et al. Vascular imaging abnormalities and cognition: Mediation by cortical volume in non-demented persons: ARIC-NCS Study. *Stroke.* 2015;46(2):433-440.
7. Tosto G, Zimmerman ME, Carmichael OT, Brickman AM, Alzheimer's Disease Neuroimaging Initiative. Predicting aggressive decline in mild cognitive impairment: the importance of white matter hyperintensities. *JAMA Neurology.* 2014;71(7):872-877.
8. Jagust W, Zheng L, Harvey DJ, et al. Neuropathological basis of magnetic resonance images in aging and dementia. *Ann. Neurol.* 2008;63(1):72-80.
9. Mungas D, Reed BR, Jagust WJ, et al. Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. *Neurology.* 2002;59(6):867-873.
10. Lo RY, Jagust WJ, Alzheimer's Disease Neuroimaging Initiative. Vascular burden and Alzheimer disease pathologic progression. *Neurology.* 2012;79(13):1349-1355.
11. Jellinger KA, Mitter-Ferstl E. The impact of cerebrovascular lesions in Alzheimer disease-- a comparative autopsy study. *J. Neurol.* 2003;250(9):1050-1055.
12. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's disease-- lessons from pathology. *BMC Medicine.* 2014;12:206.
13. Wong DF, Rosenberg PB, Zhou Y, et al. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45. *Journal of Nuclear Medicine.* 2010;51(6):913-920.
14. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging B-amyloid pathology. *JAMA.* 2011;305(3):275-283.
15. Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol.* 2012;72(4):578-586.
16. Doraiswamy PM, Sperling RA, Johnson K, et al. Florbetapir F 18 amyloid PET and 36-month cognitive decline:a prospective multicenter study. *Mol Psychiatry.* 2014.
17. Gottesman RF, Schneider ALC, Zhou Y, et al. The ARIC-PET Amyloid Imaging Study: Brain Amyloid Differences by Age, Race, Sex, and APOE. *Neurology.* 2016;Epub ahead of print.