ARIC Manuscript Proposal #2466

PC Reviewed: 11/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The ARIC-PET Amyloid Imaging Study: Differences in Brain Amyloid deposition by Age, Race, Sex, and ApoE genotype

b. Abbreviated Title (Length 26 characters): The ARIC-PET Study

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; Andrew Crabb; Xueqi Chen

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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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).

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3. Timeline: 3-6 months; planned abstract submission ASAP (November 2014) for the Human Amyloid Imaging conference (January 2015), with manuscript preparation soon after

4. Rationale:

The prevailing hypothesis behind the pathophysiology of Alzheimer's disease focuses on the accumulation of brain amyloid in amyloid-β (Aβ) plaques. Once the disease is

apparent clinically, most of the pathologic deposition of Aβ plaques associated with this neurodegenerative disease and much of the neuronal loss has already occurred, making it too late to treat the disease effectively. Therefore, research emphasis has been on identifying individuals *at risk* for AD, or with preclinical disease but without advanced pathologic changes.[1] Individuals with preclinical disease can be identified by imaging Aβ plaques with PET using [18]F-labeled AV-45, approved by the FDA in 2012 for evaluation of cognitive impairment in persons in whom a diagnosis of Alzheimer's disease is being considered, as florbetapir (Amyvid).

The novel development of radioactive isotopes that bind to brain amyloid has permitted study of Aβ's contribution to dementing illnesses before death, and even before any cognitive decline. Specifically, the development of the ligands [^{11}C]-Pittsburgh compound B (PiB)[2] and [18F]-AV-45[3] (florbetapir, Amyvid) permits us to image fibrillar β-amyloid using PET scans. Florbetapir, used in ADNI 2, has a longer half-life than PiB, is highly correlated with PiB uptake,[4] and, as stated above, is FDA-approved. Positive florbetapir scans (by a binary rating or by standardized uptake value ratio (SUVR)) have been associated with Aβ on autopsy.[5] Higher uptake has been linked to worse cognition in normal[6] and AD patients,[7] and with steeper cognitive decline.[8,9]

Dementia is more prevalent in African Americans than in Caucasians,[10-12] although AD neuropathologic findings are found with equal prevalence in both groups,[13,14] suggesting that a larger component of dementia in African-Americans may be due to vascular disease. In addition, typical AD risk factors may have different associations with clinical AD in African-Americans than in Caucasians. Carrying an apoE ε4 gene has stronger associations with AD in Caucasians than in African-Americans,[15] with some studies suggesting that, in African-Americans, AD is independent of apoE genotype.[16]

Very few studies with amyloid imaging include a biethnic population. The ARIC-PET study is an ongoing ARIC ancillary study of ~350 nondemented persons from three ARIC sites: Jackson, MS; Washington County, MD; and Forsyth County, NC. As of November 6, 2014, 346 participants have completed PET scanning with florbetapir, and repeat post-PET clinic evaluations for these participants (with a complete neurocognitive battery similar to Stage II from ARIC-NCS) have been initiated. All participants completed the ARIC-NCS Stage III evaluation with Brain MRI, and persons meeting criteria for dementia based on cognitive testing and CDR scores alone (not based on fully adjudicated diagnoses, since these were not completed at the time of ARIC-PET selection) were excluded from ARIC-PET inclusion. This manuscript represents the initial description of the PET imaging data, with particular focus on differences in amyloid deposition by age, race, sex, and apoE status.

5. Main Hypothesis/Study Questions:

1. Aβ deposition by PET will be higher in association with higher age. This will be especially true for a composite mean global cortical measure incorporating brain regions typically with amyloid deposition in association with Alzheimer's disease, and for other specific regions usually involved in Aβ deposition in AD: precuneus, posterior cingulate, and the orbitofrontal cortex.
2. Aβ deposition by PET will be higher in association with more ApoE ε4 alleles. The same regions will preferentially show these associations as described in #1, above.

3. We have no a priori hypotheses about differences in Aβ deposition by race or sex. We hypothesize, however, that the associations described in #2, above, are only seen in Caucasian and not in African-American participants.

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 (nearing completion of imaging; final sample size will be at least 346 (already completed) and may be up to 350 participants. Cross-sectional analysis for this manuscript.

Inclusion criteria: 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) by ARIC-PET, in prespecified regions of interest. Focus for this analysis is on : global mean cortical SUVR, precuneus SUVR, orbitofrontal cortex SUVR, and posterior cingulate SUVR. 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.

Other variables: Focus will be on descriptive characteristics, so for this manuscript we will use race, center, sex, and age information from ARIC baseline and visit 5 (age), as well as apoE genotype from prior ARIC measurement.

Data analysis: We will explore the SUVR data for normality, to see if transformation or quintile analysis of the values should be considered; we will use linear regression or ordinal logistic regression, respectively, for these analyses, with SUVR as the dependent variable. 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 cutpoint as used in previous papers. Race, age, sex, and number of ApoE ε4 alleles will be explored as independent variables, with additional models evaluating an interaction between race and number of ApoE ε4 alleles.

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? ____ 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)?
No current related proposals, as this is the first paper using data from ARIC-PET.

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.

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