ARIC Manuscript Proposal #2511

PC Reviewed: 3/10/15 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Vascular risk factors and brain amyloid deposition: The ARIC-PET Study

b. Abbreviated Title (Length 26 characters): Vascular risk factors in ARIC-PET

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; 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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3. Timeline: 3-6 months; planned manuscript preparation and submission by summer 2015

4. Rationale:

Several lines of evidence have led investigators to suggest that vascular disease contributes to the etiology of Alzheimer's Disease (AD).[1-6] Major vascular risk factors-- elevated blood pressure (BP),[7-10] smoking,[10,11] and elevated cholesterol levels,[8,12]— all, especially when measured in

midlife, and diabetes, even when assessed only later in life,[2,10,13-15] are known to predict, years later, both dementia and AD specifically.

What remains unclear is whether vascular risk factors simply contribute to the cognitive dysfunction seen in patients with dementia, which would explain the observed associations, or if they actually lead to neuropathologic changes that lead to AD. The direct evidence here is conflicting: diabetes[16] and elevated midlife BP[17] were related to neurofibrillary tangles, neuritic plaques and reduced brain weight in autopsied Japanese men from Honolulu, but another study found no association of diabetes with AD pathology.[18] Mild, moderate and severe cerebral atherosclerosis showed strong odds ratios for neuritic plaques - 1.6, 3.3, and 5.1, respectively, in analyses based on 1,054 autopsies from the National Alzheimer's Disease Database.[19] Smaller studies found large vascular differences between decedents with proven AD and comparable controls: stenosis in 75% vs. 44% in cerebral arterioles[20] and in 22% vs. 5% in Circle of Willis arteries,[21] and small cortical infarcts in 32% of cases vs. 2.5% of controls.[22] Two large studies (the Honolulu[23] and Nun studies[24]) reported no associations between neuritic plaques and lacunes or microinfarcts.

In this proposal, we plan to use data from the ARIC-PET study to evaluate associations between vascular risk factors and late-life amyloid deposition, as measured by florbetapir PET. Florbetapir PET (AV-45, Amyvid) is an FDA-approved isotope which is felt to bind to amyloid in the brain. Nondemented individuals with increased Amyvid binding had decreased memory performance, and AV-45 retention differed significantly ($p<0.001$) among normals (N=78), MCI (N=60), and AD (N=45) patients.[25] Higher uptake has been linked to steeper cognitive decline.[26,27] In addition, based on our as-of-yet unpublished initial analyses (MP #2466), we note significant differences in amyloid deposition, in the ARIC-PET cohort, by racial group: African-Americans in ARIC-PET had, on average, 0.10 points higher florbetapir SUVR values, (95% CI 0.04-0.16) than their white counterparts, independent of age and sex and apoE status. For this reason, we think there is particular importance in evaluating whether vascular risk factors differentially effect amyloid deposition by race.

5. Main Hypothesis/Study Questions:

1. Aβ deposition by PET will be associated with each of the following: a diagnosis of midlife (visit 1) hypertension, midlife diabetes, midlife hypercholesterolemia, and midlife current smoking status. In addition, composite ARIC stroke risk score will be associated with higher levels of brain amyloid by PET.
2. The associations described in #1 will not differ in race-stratified models, but inclusion of i.e. hypertension in the race/amyloid models will attenuate or lead to a null effect for the association between race and amyloid (we anticipate that differences in vascular risk factor prevalence will explain the apparent racial differences). We anticipate that this will be especially true for hypertension.
3. We will also explore the same vascular risk factors also from late-life (from ARIC-NCS, so relatively concurrent with the PET scans).

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). Analyses to include non-concurrent followup (hypotheses 1 and 2, above) as well as cross-sectional data (hypothesis 3, above).

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) 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 or 1.2 (each to be analyzed, as these have both been used in prior literature).

Other variables: We will include race, center, sex, and age information from ARIC baseline and visit 5 (age), as well as apoE genotype from prior ARIC measurement. In addition, hypertension (v1) and systolic and diastolic blood pressures, diabetes, hypercholesterolemia, and smoking status will all be assessed from visit 1 as well as from ARIC-NCS. The composite ARIC stroke risk score[28] will be used from visit 1 as well. Level of educational attainment as a covariate will be included in models. The third hypothesis will include vascular risk factor status from visit 5/ ARIC-NCS.

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 (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 each of the separate vascular risk factors described above. We acknowledge that there are a number of other risk factors or markers of potential interest but anticipate including these in subsequent papers (for instance, in a manuscript on subclinical vascular markers and brain PET).

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)?
My own proposal 2466, but no other proposals since these are the first papers using ARIC-PET data.

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

11b. 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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