ARIC Manuscript Proposal # 3119

PC Reviewed: 2/13/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

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

b. Abbreviated Title (Length 26 characters): Vascular/amyloid contributions

2. Writing Group:

Writing group members: Rebecca Gottesman (first and corresponding author); Thomas Mosley (last author); Aozhou Wu; David Knopman; Dean Wong; Yun Zhou; Lynne Wagenknecht; A. Richey Sharrett; Arman Rahmim; Josef Coresh.

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 2018

4. Rationale:

Our own studies in ARIC have emphasized the importance that vascular risk factors play, especially when measured in midlife, in subsequent risk for dementia.[1] Some of these

have been implicated in Alzheimer's Disease (AD) specifically, when defined clinically,[2,3] and some autopsy series have suggested associations between vascular risk factors (i.e. hypertension) and neuropathologic changes concerning for AD,[4] or associations between atherosclerosis in the circle of Willis and AD neuropathologic changes.[5,6] Evidence of a more direct link between vascular risk and AD neuropathology has been strengthened with our publications from the ARIC-PET study demonstrating that a greater number of midlife vascular risk factors (of hypertension, hypercholesterolemia, obesity, smoking, and diabetes) was associated with elevated brain amyloid,[7] which, by leading hypotheses accumulates to cause AD, with a suggestion that this association might be even stronger among carriers of an APOE e4 allele, a finding suggested by other authors as well[8]. It is likely that the observed effect of vascular risk on cognitive change and dementia is not entirely mediated via an effect on amyloid or other AD neuropathology, however.

Understanding the relative contributions of vascular risk, particularly in midlife, and brain amyloid, among individuals without dementia, on cognitive performance and its change, is critical in understanding stages at which dementia may be preventable and may further identify targets for potential prevention. Among patients with AD, the presence of infarcts appears to be associated with worse cognition,[9] and two autopsy studies have demonstrated that measures of cerebrovascular disease (including lacunar infarcts and microinfarcts) and AD were each independent predictors of pre-mortem dementia status.[10,11] Another study demonstrated that "vascular brain injury", defined by infarction and white matter hyperintensities, had a greater influence on cross-sectional cognitive function than did extent of amyloid, without evidence of an interaction between amyloid and vascular risk;[12] in the Mayo Clinic Study of Aging a similar additive but not multiplicative effect of vascular risk and brain amyloid on cognition has been reported.[13] Others, however, have found evidence for a synergistic worsening in cognition among individuals with both elevated vascular risk and elevated amyloid burden.[14] Given this inconsistency in studies to date, this remains an important question to answer, and one that has not been well explored in individuals from the normal to mild cognitive impairment range, and that has particularly not considered midlife vascular risk, which is most important otherwise for both cognition and amyloid deposition.

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, each, with cognitive status and its change.

5. Main Hypothesis/Study Questions:

1. Both amyloid PET SUVR and midlife vascular risk factors will be associated independently with *cognitive status* (a)cognitive performance and b)normal/ MCI status) at the time of ARIC visit 5 (concurrent to the ARIC-PET imaging visit).
2. Both amyloid PET SUVR and midlife vascular risk factors will be associated independently with *change in a) cognitive performance* b) *status* from ARIC visit 5 (concurrent to the ARIC-PET imaging visit) to ARIC visit 6 (including the PET clinic visit, at approximately the halfway point between visits 5 and 6).
3. There will be evidence of an interaction between vascular risk and amyloid PET SUVR on cognitive function/ status. We will define "vascular risk" both as a binary

variable: (above/ below median vascular risk, defined by the visit 1 ARIC stroke risk score), and as a categorical variable (number of midlife vascular risk factors, as defined in our previous paper evaluating this with amyloid PET outcome).

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, cross-sectional data, and longitudinal followup after ARIC visit 5.

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. For the analysis, we will exclude the one individual in ARIC-PET who ultimately was given an adjudicated research diagnosis of dementia (at visit 5), and all non-black, non-white ARIC participants.

Outcome: **Cognitive status** at visit 5 (hypotheses 1,3): domain and global Z-scores and factor scores from ARIC-NCS. We hypothesize that vascular risk factors will be more strongly associated with the executive function and attention domains and amyloid will be more strongly associated with memory. Also, MCI versus normal cognition status at visit 5 based on adjudicated diagnoses.

For analyses of **cognitive change**, (hypotheses 2,3): Change in cognitive factor scores across three visits: ARIC visit 5, PET clinic visit (at least 2 years after visit 5, and approximately halfway between visits 5 and 6), ARIC visit 6. Also, conversion of cognitive status (from visit 5 to visit 6, using adjudicated diagnoses) from normal to MCI or dementia, or from MCI to dementia (to be defined as a binary variable: any conversion/ no conversion; or as a categorical ordinal variable: conversion by 2 categories (normal to dementia), conversion by 1 category (normal to MCI or MCI to dementia), no conversion but impaired (MCI to MCI), vs no conversion (normal to normal). To identify new dementia cases in these varying definitions of conversion, we will use surveillance dementia diagnoses to allow for more complete data availability (this will not allow us to identify more MCI cases, however, since surveillance does not allow diagnosis of MCI).

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; their use as time-varying covariates will be considered. We will consider them individually but also as a tally, as previously used in analyses with ARIC-PET data;[7] the number of risk factors present in midlife (out of hypertension, diabetes, hypercholesterolemia, smoking, and obesity) will be tallied. The composite ARIC stroke risk score[15] will be used from visit 1 as well, for hypothesis 3, to categorize individuals into above- versus below-median vascular risk. Level of educational attainment as a covariate will be included in models.

Standardized Uptake Volume Ratio (SUVR) by ARIC-PET, in prespecified regions of interest. Focus for this analysis is on global mean cortical SUVR, which is a weighted average of other regions commonly involved in AD. The SUVR's will be evaluated as continuous variables as well as a binary variable based on our previously reported cutpoint of 1.2.

Data analysis: In hypotheses 1, for 1a) cognitive performance, we will evaluate linear regression models with both vascular risk factors (separately and the number of midlife risk factors, categorized as 0,1, or 2+) and SUVR as independent variables in the same model, with further adjustment for demographics and APOE genotype. The same analysis (1b) but in a logistic regression (MCI yes/no) for cognitive status will be repeated. For hypothesis 2a, linear mixed models will be used to evaluate cognitive change, but with similar independent variables. For 2b, a logistic regression (any conversion yes/no) or multinomial logistic regression (several categories of conversion) will be explored. For hypothesis 3, we will explore stratified models, and also formally test for interaction, to evaluate the impact of SUVR on the above-described cognitive outcomes in the presence or absence of elevated vascular risk.

Potential Limitations: Loss to follow-up of the ARIC-PET cohort could make analyses of cognitive change difficult (Aim 2a), although with the use of adjudicated dementia diagnoses we will still be able to evaluate new dementia cases. Power may be limited if the number of individuals with conversion are low, and may be especially problematic for the interaction aim. If power remains a concern, or if there is significant loss to follow-up for ARIC-PET participants at visit 6 with inadequate number of events (MCI/ dementia conversion), we will consider formal adjudication of cognitive status for individuals at the time of the ARIC-PET clinic visit, which was done after the ARIC PET scan and represents an approximate midpoint between visits 5 and 6. This would allow us to identify people with conversion after the PET scan but before visit 6.

Given the potential concern that change in cognition from visit 5 to 6 does not consider pre-visit 5 cognition, which is likely influenced by not only midlife vascular risk factor status but also amyloid status, we will repeat the primary analyses but only among individuals with normal cognition at visit 5. We have chosen not to consider cognitive trajectory from visits 2 through 6 because we don't have PET amyloid imaging until visit 5.

Finally, we may consider using measures of small vessel disease on MRI (white matter hyperintensities, microhemorrhages, lacunes) to evaluate interaction between vascular risk and amyloid on cognition, since it is likely that vascular effects are mediated via many of these cerebrovascular changes.

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)?
2120c (Midlife vascular risk factors and incident dementia; Gottesman et al), 2511 (Vascular risk factors and brain amyloid; Gottesman et al); 3054 (Brain structural MRI abnormalities predict dementia, MCI, and cognitive decline in an older population; Wu et al).

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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