ARIC Manuscript Proposal #2544

PC Reviewed: 5/12/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Arterial Stiffness and β-Amyloid Deposition in the ARIC-PET Study

b. Abbreviated Title (Length 26 characters): PWV & Brain β-Amyloid

2. Writing Group:

Writing group members: Timothy Hughes (first author), Rebecca Gottesman (last/ senior author), Lynne Wagenknecht, Laura H. Coker, other ARIC investigators are welcome, especially those involved in the ARIC PET study.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __TMH__ **[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:

May 2015 - P&P committee
June - receive data
October – Draft of manuscript to coauthors

4. Rationale:

Recent studies from our group and other show that blood pressure[1-3] and arterial stiffness[3] are associated with the extent of β-amyloid deposition in the brain visible on PET scans. Further, greater central arterial stiffness, measured by pulse wave velocity (PWV) was strongly associated with the longitudinal accumulation of β-amyloid in the brain over two

years in non-demented elderly adults[4]. We showed that arterial stiffness is related to both the evidence of β-amyloid deposition and white matter disease in the brain independent of common covariates, including antihypertensive medication use and current blood pressure. However, the mechanisms linking peripheral vascular measures and β-amyloid deposition in the brain remain unclear.

Our previous research[3, 4] suggests that arterial stiffness may be an underlying mechanism linking peripheral hypertension to evidence of cerebral small vessel disease (cSVD) and β-amyloid deposition in the brain, in accordance with the two-hit hypothesis for dementia. However, our previous study was done in a modest sample (n=91) of very elderly adults (ages 81-93) in a follow-up to the Gingko Evaluation of Memory study. These results are promising but need to be replicated in a slightly younger cohort of elderly adults at risk for cognitive impairment, such as those in the ARIC-PET Study. The ARIC-PET study is a uniquely ideal study for this aim for several reasons. First, ARIC-PET is an ongoing study of β-amyloid florbetapir PET imaging at three sites. Second, it has the unique attribute of including African-American individuals who are both at a higher risk for hypertension and stroke. Finally, this study builds on the comprehensive assessment and characterization of cardiovascular disease over 20+ years of follow-up and includes additional measures of subclinical cardiovascular disease that may be associated with β-amyloid deposition in the brain.

5. Main Hypothesis/Study Questions:

1) Arterial stiffness will be associated with the extent of β-amyloid deposition in the brain in the ARIC-PET cohort.
2) The associations between arterial stiffness and β-amyloid deposition will be modified by APOE-4, diabetes status, hypertension status and race.
3) Individuals with the greatest amount of arterial stiffness will have a greater burden of both cSVD (e.g. white matter hyperintensities, cerebral microbleeds) and greater β-amyloid deposition.

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).

The data requested for this proposal is already collected as part of the ARIC Study and ARIC-PET. The proposed analysis will use β-amyloid florbetapir PET data collected in ARIC-PET (n=346, 2011-14), and PWV measured at ARIC visit 5 (n>6000, 2011-13). Analyses will be restricted to those persons with both florbetapir PET and PWV data from ARIC visit 5. All participants with a PET scan will have had a brain MRI at ARIC visit 5.

For hypothesis 1, we will evaluate the normality of PWV and florbetapir standard uptake value ratio (SUVR) data and use appropriate statistical methods. A global cortical mean

SUVR will be calculated using a weighted average of 9 regions of interest and will be used as the primary outcome. The first part of the analysis will use SUVR as a continuous variable using general linear models and then we will use logistic regression with a cutpoint of SUVR>1.1 to determine β-amyloid positivity. We plan to use the same cutpoints and to adjust all models for age, sex, race, cognitive status and antihypertensive treatment at the ARIC-PET visit, plus additional covariates to be used in Dr. Gottesman's primary ARIC-PET papers.
For hypothesis 2, we will determine if the relationships between PWV and β-amyloid differ by diabetes status, hypertensive status, African American race and APOE-4 genotype using multivariable models described in hypothesis 1 with the addition of interaction terms between arterial stiffness and potential effect modifiers. Interaction terms with a $p<0.15$ will lead to stratified analyses to further examine effect modification.
Hypothesis 3 will incorporate the visit 5 MRI data using the number of cerebral microbleeds and white matter hyperintensities as biomarkers of cSVD. To examine the joint effect of high cSVD and high β-amyloid deposition, we propose to: first, create a cSVD score based on high/low white matter hyperintensities (based on a median split) combined with cerebral microbleeds (0 = no microbleeds, 1 = one or more microbleeds), and then combine this with high/low β-amyloid status to define four groups (e.g. neither, only high cSVD, only high β-amyloid, and both high cSVD and high β-amyloid).

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 (only APOEε*4 genotyping)

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)?

There are currently two manuscript proposals using amyloid imaging (Dr. Gottesman's #2466 and #2511). One of these uses the entire ARIC PET cohort to determine the relationships between brain amyloid deposition, midlife hypertension and subclinical vascular risk factors. The other proposal looks for differences in amyloid deposition by demographic factors. Through conversations with Dr. Gottesman, she will not include pulse wave velocity in her analyses and allow me to use it this analysis proposal.
To the best of our knowledge there at not any submitted ARIC proposals that use both pulse wave velocity and brain measures. The closest proposal would be that of Dr. Michelle Snyder (#2246) which uses pulse wave and retinal photography.

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.

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. Langbaum JB, Chen K, Launer LJ, et al. Blood pressure is associated with higher brain amyloid burden and lower glucose metabolism in healthy late middle-age persons. Neurobiology of aging 2012;33:827 e811-829.
2. Toledo JB, Toledo E, Weiner MW, et al. Cardiovascular risk factors, cortisol, and amyloid-beta deposition in Alzheimer's Disease Neuroimaging Initiative. Alzheimer's & dementia : the journal of the Alzheimer's Association 2012;8:483-489.
3. Hughes TM, Kuller LH, Barinas-Mitchell EJM, et al. Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults. Neurology 2013.
4. Hughes TM, Kuller LH, Barinas-Mitchell EJ, et al. Arterial Stiffness and beta-Amyloid Progression in Nondemented Elderly Adults. JAMA neurology 2014.