ARIC Manuscript Proposal # 2950

PC Reviewed: 02/14/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
The association of hospitalization and brain amyloid in the ARIC-PET study.

b. Abbreviated Title (Length 26 characters):
Hospitalization and brain amyloid

2. Writing Group:
Writing group members:
Charles Brown, David Knopman, Thomas Mosley, Alvaro Alonso, Rebecca Gottesman

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. CB

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3. Timeline:
6-9 months: analysis of data

3-6 months: writing of manuscript

4. Rationale:

Dementia and cognitive decline are growing public health problems in older adults, and identifying modifiable risk factors or strategies to attenuate the progression of cognitive decline is important. It is becoming clear that hospitalization in older adults is not benign, and may in fact be associated with long-term cognitive consequences. Characterizing the cognitive effect of hospitalization and potential mechanisms of this effect is crucial to identifying high-risk patients and to developing targeted prevention strategies.

Epidemiologic evidence supporting the association of hospitalization and cognitive decline/incident dementia

The deleterious effect of hospitalization on cognitive decline and incident dementia has been shown in several community-based cohort studies. First, Ehlenbach et al. followed the cognitive status of 2929 individuals age 65 and older every 2 years using the Cognitive Abilities Screening Instrument (CASI).[1] Over a mean follow up of 6.1 years, a non-critical illness hospitalization was associated with a decline in the CASI and an increased hazard ratio for incident dementia. The presence of critical illness exacerbated both cognitive decline and incident dementia. Second, in a separate cohort using data from the Chicago Health and Aging Project, the decline in global cognitive score accelerated 2.4 fold from pre-hospitalization to post-hospitalization.[2] Severity of illness and length of hospitalization were each associated with faster decline, and the decline persisted over the length of follow-up. Finally, using data from the ARIC study, our group found that hospitalization compared with no hospitalization was associated with greater decline in DSST scores (1.25 points greater decline, p=0.001) but no difference in DWRT or WFT score change.[3] Hospitalization compared with no hospitalization was also associated with a 57% higher odds of increasing ventricular size at follow-up. Each additional hospitalization, as well as having a critical illness, was associated with greater odds of changes in DSST scores and ventricular size. Finally, surgical hospitalization compared with no surgery was associated with greater odds of having increased ventricular size.

However, the mechanism behind these findings linking hospitalization and subsequent cognitive decline is unclear. One intriguing hypothesis is that events during hospitalization may promote brain amyloid deposition. In rodent models, volatile anesthetics have been shown to increase the oligomerization of amyloid-β (Aβ),[4] contribute to decreased clearance of Aβ,[5] and increase the production and phosphorylation of tau[6]—all changes consistent with models of dementia progression. In humans, several studies have shown changes in cerebrospinal fluid levels of Aβ, tau, and the ratio of Aβ:tau after surgery[7,8]; however, the long-term cognitive effects of these changes are unclear. There are even fewer studies examining the effect of critical illness on brain amyloid, although cognitive decline is now recognized as extremely common among survivors of critical illness.[9]

The ARIC-PET study[10] recruited 346 participants without dementia, ages 67-88 years, to undergo PET imaging with florbetapir, an isotope known to bind to Aβ in the brain, at 3 ARIC sites. Since hospitalization data are available in the ARIC cohort prior to the PET imaging, date from the ARIC-PET study provides a unique opportunity to examine the effect of hospitalization, surgery, and critical illness from midlife through late-life on late-life brain amyloid deposition. We hypothesize that hospitalization (as well as surgery and critical illness) will be associated with increased brain amyloid in late-life.

5. Main Hypothesis/Study Questions:

1. In the ARIC-PET cohort, participants with a history of hospitalization at any point during their followup will have increased amyloid deposition on brain imaging, compared to participants without a history of hospitalizations.

2. The association between hospitalization and amyloid deposition will be stronger among participants with increasing number of hospitalizations. Both surgical hospitalization and hospitalization with critical illness will be associated with greater amyloid deposition compared to patients with no hospitalization or hospitalization without surgery/critical illness.

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).

Study design: Prospective cohort study comparing brain amyloid among participants in the ARIC-PET study with prior hospitalization to those patients without hospitalization. Hospitalization status will be further characterized by number of hospitalizations, ±surgery, and ±critical illness, as was done in our previous ARIC paper. Data on hospitalization, surgical procedures, and critical illness will be obtained using ICD discharge codes.

Hospitalization as an exposure will be characterized in the following ways:

1. Hospitalization will be considered as yes/no (primary exposure).
2. Hospitalization will be considered as number of hospitalizations.
3. Hospitalization will be characterized as including critical illness vs. non-critical illness. We will use the methodology of Ehlenbach et al., [1] which specifies ICD-9 codes that represent severe illness occurring during that hospitalization. ICD-9 codes identifying a critical illness include shock (785.5 and all 5 digit breakouts), severe sepsis (995.92), acute respiratory failure (518.82 and 518.84), hypotension (458), respiratory or cardiac arrest (799.1 and 427.5), cardiopulmonary resuscitation (99.6, 99.63), and prolonged ventilation (96.72). These are all conditions that are unlikely to be present on hospital admission.

4. Hospitalizations will be characterized as including surgery or not, with further characterization as number of surgical hospitalizations, predicted cardiac risk of inpatient surgery, and including critical-illness. To classify surgical procedures, we will use Clinical Classification Software (CCS) developed by the Agency for Healthcare Research and Quality to classify procedure into clinically relevant procedure groups, using ICD-9 discharge codes. Then, the predicted level of cardiac risk associated with each of the CCS derived surgical procedure groups will be categorized as high, intermediate or low according to the American Heart Association Perioperative Guidelines.

Hypothesis 1: In the ARIC-PET cohort, participants with a history of hospitalization will have increased amyloid deposition on brain imaging, compared to participants without a history of hospitalizations.

Exposures:

- Inpatient hospitalization (yes/no)

Inclusion/Exclusion

- We will include all individuals enrolled in the ARIC-PET study.
- We will exclude participants who underwent neurosurgical procedures and 1 patient who was classified as having dementia.

Outcome

- The primary outcome will be a global cortical measure of amyloid, quantified as the standardized uptake value ratio (SUVR)
    - The SUVR will be calculated as a weighted average of the following regions: orbitofrontal, prefrontal, and superior frontal cortices, lateral temporal, parietal, and occipital lobes, precuneus, and anterior and posterior cingulates.
    - The SUVR value will be dichotomized at the sample median of SUVR 1.2, due to the highly skewed distribution, but we will also consider quartiles.
- We will consider specific regions of interest (ROI) contained within the global measure that are frequent locations of amyloid deposition, in addition to the global measure.

Data analysis

- We will conduct logistic regression analyses to investigate the effect of hospitalization (exposure) on amyloid deposition, as defined by SUVR>1.2 (outcome). We will utilize separate models stratified by race and adjusting for age, sex, education, and apoE status (model 1), and adding hypertension, diabetes, smoking, hyperlipidemia, congestive heart failure, and coronary artery disease at visit 5 (model 2). We will consider utilizing propensity scores for hospitalization in the analysis; if we use them we will adjust for the propensity scores in the regression analyses or match the groups using propensity scores before conducting the analysis.

- We will also conduct additional analyses, using the outcome of top quartile of global SUVR, and using SUVR for individual ROI
- We will conduct additional sensitivity analyses, in which participants are stratified by MCI status and presence of any APOE allele, as well as by race

Hypothesis 2: The association between hospitalization and amyloid deposition will be stronger among participants with increasing number of hospitalizations. Both surgical hospitalization and hospitalization with critical illness will be associated with greater amyloid deposition compared to patients with no hospitalization or hospitalization without surgery/critical illness.

Exposures:

- Number of hospitalizations,
- Surgical hospitalization vs. non-surgical hospitalization vs. no hospitalization;
- Critical-illness hospitalization vs. non critical-illness hospitalization, vs. no hospitalization

Inclusion/Exclusion

- We will include all individuals enrolled in the ARIC-PET study.
- We will exclude participants who underwent neurosurgical procedures, and 1 patient who was classified as having dementia.

Outcome

- The primary outcome will be a global cortical measure of amyloid, quantified as the standardized uptake value ratio (SUVR)
    - The SUVR will be calculated as a weighted average of the following regions: orbitofrontal, prefrontal, and superior frontal cortices, lateral temporal, parietal, and occipital lobes, precuneus, and anterior and posterior cingulates.
    - The SUVR value will be dichotomized at the sample median of SUVR 1.2, due to the highly skewed distribution, but we will also consider quartiles.
- We will also consider specific regions of interest (ROI) contained within the global measure that are frequent locations of amyloid deposition.

Data analysis

- Characterization of the exposure variable
    - To examine the effect of number of hospitalizations, we will use number of hospitalizations as the exposure variable, and consider whether spline terms or other categorization should be included.
    - To examine the effect of surgery, we will categorize participants as having no hospitalizations (reference), surgical hospitalizations, and hospitalizations without surgery. We will compare the effect of surgical hospitalization on brain amyloid compared to the other two groups.
    - To examine the effect of critical illness, we will classify participants as having no hospitalization (reference), hospitalization without critical

illness, and hospitalization with critical illness. We expect to find a dose effect, with the effect of critical illness hospitalizations on brain amyloid being greater than the other 2 groups.

- Similar to hypothesis 1, we will conduct logistic regression analysis to investigate the effect of each exposure on amyloid deposition, as defined by SUVR>1.2 (outcome). We will utilize separate models stratified by race and adjusting for age, sex, education, and apoE status (model 1), and adding hypertension, diabetes, smoking, hyperlipidemia, congestive heart failure, and coronary artery disease (model 2). We will consider utilizing propensity scores for hospitalization in the analysis; if we use them we will adjust for the propensity scores in the regression analyses or match the groups using propensity scores before conducting the analysis.
- We will also conduct additional analyses, using the outcome of top quartile of global SUVR, and using SUVR for individual ROI
- We will conduct additional sensitivity analyses, in which participants are stratified by MCI status and presence of any APOE allele

Methodological Limitations

1. The participants in the ARIC-PET study are a selected cohort who may not be representative of the entire ARIC cohort. In the manuscript, we will compare key features of the ARIC-PET cohort with the overall ARIC-NCS cohort, to address this limitation.
2. Deciding a particular SUVR cutoff to use as the outcome is difficult. Because this is an exploratory study, we chose to use the median value, but will also examine quartiles of SUVR. We could also use other published florbetapir thresholds, although there is no one uniformly accepted cutpoint in the literature.
3. There is a potential for residual confounding between the patients who were or were not hospitalized. We will adjust for potential confounding variables in multivariable regression and potentially through propensity score analysis.
4. We do not have access to key aspects of hospitalization, beyond type of surgery and presence of critical illness. The results of this study will be hypothesis-generating and may support future observational studies with more granular collection of hospitalization data.
5. The present study only examines participants who were dementia free and alive at the time of screening. Thus, there may be selection bias if the effect of hospitalizations on cognitive status precluded entry in the ARIC PET study. We will examine characteristics of patients in the ARIC PET study compared with the overall ARIC population to characterize potential selection bias more fully.
6. The present study will only examine brain amyloid at one time point, and cannot answer the question of how hospitalization affects change in amyloid deposition. However, repeat PET scans in this cohort will be available in the future to answer this question.

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 ICTDER03 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)?

Brown CH, Sharrett AR, Coresh J, Schneider AL, Alonso A, Knopman DS, Mosley TH, Gottesman RF. Association of Hospitalization with Long-Term Cognitive and Brain MRI Changes in the ARIC Cohort. Neurology 2015; 84: 1143-1453.

Gottesman RF, Schneider ALC, Zhou Y, Chen X, Green E, Gupta N, Knopman DS, Mintz A, Rahmim A, Sharrett AR, Wagenknecht L, Wong D, Mosley T. The ARIC-PET amyloid imaging study: Brain amyloid differences by age, race, sex, and APOE. Neurology 2016;87:473-480.

Gottesman RF, Schneider ALC, Zhou Y, Coresh J, Green E, Gupta, N, Knopman DS, Mintz A, Rahmim A, Sharrett AR, Wagenknecht LE, Wong DF, Mosley TH. Midlife vascular risk factors, APOE, and brain amyloid: The ARIC-PET study. Under review.

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _X___ No.