ARIC Manuscript Proposal #2915

PC Reviewed: 1/5/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
The effect of hospitalization and inpatient surgery on long-term neurocognitive changes, dementia risk, and brain MRI findings: The ARIC Study

b. Abbreviated Title (Length 26 characters):
Hospitalization, surgery, and cognitive decline

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **KW**

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3. Timeline:
3-6 months: analysis of data
1-2 months: writing of manuscript

4. Rationale:

Dementia and cognitive decline are growing public health problems in older adults. Estimates suggest that even modest reductions in disease onset or regression, such as by 1-2 years, would significantly decrease the global burden of the disease.[1] Thus, efforts to slow the onset or reduce the progression of dementia and cognitive decline are vital.

Hospitalization and critical illness may play a significant and previously unrecognized role in accelerating cognitive decline and increasing the risk of incident dementia through an unknown mechanism. A previous study, which followed 2,929 individuals age 65 and older every 2 years found that hospitalization for a non-critical illness was associated with cognitive decline and increased risk of incident dementia over a 6-year period. The risk of cognitive decline and incident dementia associated with a critical illness hospitalization was found to be even stronger.[2] In a separate study that examined the effect of hospitalization in 1,870 individuals over 9 years, the authors found a 2.4 fold increase in acceleration of global cognitive decline from pre-hospitalization to post-hospitalization that persisted over the length of follow-up. Greater illness severity and length of hospitalization were each associated with faster decline. [3]

Interpretation of the findings from each of these studies is limited by the consideration of relatively few confounding variables. Additionally, neither study examined whether the relationship between hospitalization and cognitive variables differed depending on whether patients were admitted for medical versus surgical indications. It is important to examine the individual effect of surgical hospitalizations in particular, because evidence suggests that both anesthetic agents as well as common postoperative events such as delirium, systemic inflammation, and sedative/analgesic medications all may play an important role in promoting cognitive decline. [4,5]

Our group recently published a manuscript in Neurology examining the associations between hospitalization, cognitive decline and MRI changes at the 2004-2006 ARIC visit.[6] We found that hospitalization, compared with no hospitalization, was associated with greater decline on the Digit Symbol Substitution Test (DSST) (p=0.001), but not on Delayed Word Recall test (DWRT) or Word Fluency Test (WFT). 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. Additionally, compared to hospitalization without surgery, surgical hospitalization was associated with increased ventricular size. Unlike the aforementioned studies, we were able to account for a wide range of potentially confounding variables, including APOE e4 status, diabetes, carotid disease, and hypertension.

Since the publication of this manuscript, cognitive and MRI data from visit 5 has become available. With the availability of this new data, we propose to examine the effect of hospitalization, inpatient surgery, and critical illness on cognitive change and structural MRI markers in an older cohort of patients. In light of the recent evidence linking infection and inflammation to cognitive decline[7] and structural brain changes[8], the current study will also extend previous work by determining whether acute infection during the course of hospitalization confers additional risk for cognitive decline and MRI abnormalities among older adults. Because age is likely the most important risk factor for cognitive decline after

hospitalization and surgery, it is especially important that medical and perioperative risk factors for late-life cognitive decline and neurodegeneration be identified to inform medical and surgical decision making.

5. Main Hypothesis/Study Questions:

1. A history of hospitalization and/or inpatient surgery will be associated with greater cognitive decline on the DWR, DSST, and WFT as measured by (a) absolute change from visit 4 (1996-1999) to visit 5 NCS (2011-2013), (b) change in slope after first hospitalization using data from visits 2 to 5, and (c) worse cognitive performance on the comprehensive cognitive battery at visit 5 NCS. Participants who experience a late-life (≥65 years of age) hospitalization and/or inpatient surgery will display greater cognitive decline than participants who only experience hospitalization and/or inpatient surgery in midlife.

2. A history of hospitalization and/or inpatient surgery from ARIC visit 2 until visit 5 will be associated with greater cerebral small vessel disease, degenerative changes, and reduced white matter integrity on brain MRI at visit 5 NCS.

3. A history of hospitalization and/or inpatient surgery from ARIC visit 2 until visit 5 will be associated with increased risk of mild cognitive impairment (MCI) and dementia at visit 5 NCS.

*Number of hospitalizations, severity, major surgery, and infection will also be used as exposures for each study question.

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 those participants with hospitalization and/or inpatient surgery during a defined exposure period to those participants without hospitalization. Data on hospitalization, surgical procedures, critical illness, and acute infection will be obtained using ICD-9 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.,[2] 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.
5. Hospitalizations will be characterized as either including an acute infection or not, with further characterization of the number of hospitalizations with infection. We will use the methodology of Cowan et al. (2016)[9] to classify acute infection using ICD-9 codes. ICD-9 codes for acute infection will include: (1) Respiratory: 460-466, 480-487, (2) urinary tract: 599.0, 595, 590, (3) skin and subcutaneous tissue: 680 to 686, (4) bacteremia: 790.7, (5) osteomyelitis: 730 to 730.2, and (6) other infectious diseases: 001 to 134.

1. A history of hospitalization and/or inpatient surgery will be associated with greater cognitive decline on the DWR, DSST, and WFT as measured by (a) absolute change from visit 4 to visit 5 NCS (2011-2013), (b) change in slope after first hospitalization using data from visits 2 to 5, and (c) poorer cognitive performance on the comprehensive cognitive battery at visit 5 NCS. Participants who experience a late-life (≥65 years of age) hospitalization and/or inpatient surgery will display greater cognitive decline than participants who only experience a hospitalization and/or inpatient surgery in midlife.

Exposures:

- Inpatient hospitalization (categorized in the five ways described above) between visit 2 and visit 5.

Inclusion:

- We will include all individuals with cognitive data at relevant visits.
- We will exclude those patients who scored below 5th percentile on any cognitive test at visit 2.
- A sensitivity analysis will conducted after excluding participants with documented neurological conditions (e.g., MS, stroke, TBI with residual cognitive impairment) and those who underwent neurosurgical procedures.

Outcome:

a) Change in score of DSST, WFT, and DWR from visit 4 to visit 5.
b) Change in the slope of cognitive decline following hospitalization.
c) Performance on the visit 5 NCS comprehensive cognitive battery.

Data analysis

a) We will conduct regression analysis to investigate the effect of hospitalization on cognitive change from ARIC visits 4 to 5 using change in score of DSST, WFT, and DWR. We will utilize separate models stratified by race and adjust for age, sex, education, APOE e4 status, hypertension, diabetes, smoking, hyperlipidemia, coronary artery disease, and heart failure at visit 4. We may also calculate propensity

scores for undergoing surgery and match the groups using propensity scores before conducting analyses.

b) To examine the effect of hospitalization on trajectory of cognitive change, we will conduct regression analysis using random effects mixed models with history of hospitalization and/or surgery predicting longitudinal change in score of DWR, WFT, and DSST, using all available cognitive data from ARIC visit 2, visit 3, visit 4, ARIC Brain MRI or Carotid MRI visits, and ARIC visit 5. We expect to use random intercept only models including interaction terms between hospitalization and/or surgery and follow-up. We will define time 0 as time of first hospitalization. We will estimate the change in cognitive scores before and after first hospitalization by including the main effect of time to estimate the slope prior to the first hospitalization and a linear spline term that allows the slope for time to change after the first hospitalization. We will use a second linear spline term to account for the increased rate of cognitive decline that occurs in late-life. Although we may be limited by sample size, we will compare slopes of change or absolute change in cognitive scores before and after hospitalization and how these slopes may differ by age of the participants.

c) We will also conduct regression analyses to investigate the effect of hospitalization on cognitive functioning using the comprehensive neurocognitive battery at ARIC visit 5. As in aim 1a, we will utilize separate models stratified by race and adjust for age, sex, education, APOE e4 status, hypertension, diabetes, smoking, hyperlipidemia, coronary artery disease, and heart failure. We may also calculate propensity scores for undergoing surgery and match the groups using propensity scores before conducting analyses.

- To examine the effect of age at hospitalization on cognitive decline, we will conduct regression analyses to determine whether the occurrence of these events in late-life versus midlife is associated with greater cognitive decline from visit 4 to visit 5 and poorer cognitive functioning at ARIC visit 5.
- We will conduct separate analyses to evaluate the effect of (1) number of hospitalization, (2) critical illness vs. non-critical illness, (3) major surgical vs. non-surgical hospitalization, and (4) acute infection vs. no infection on outcome variables.

Hypothesis 2. A history of hospitalization and/or inpatient surgery from ARIC visit 2 until visit 5 will be associated with greater cerebral small vessel disease, degenerative changes, and reduced white matter integrity on brain MRI at visit 5 NCS.

Exposure:

- Inpatient hospitalization (categorized in the five ways described above) between visit 2 and visit 5.

Inclusion/ Exclusion:

- All individuals with MRI data from visit 5 NCS.
- A sensitivity analysis will conducted after excluding participants with documented neurological conditions (e.g., MS, stroke, TBI with residual cognitive impairment) and those who underwent neurosurgical procedures.

Outcome:

- *Brain Volume:* Whole brain, ventricular, and hippocampal volume, as well as the composite variable, "Alzheimer's Disease Signature Region" will be used. Gray matter volume will be calculated using a semi-structured parcellation program. Analyses of brain volume will include adjustment for total intracranial volume.
- *White matter hyperintensity volume (WMH)*: WMH scores will be derived from proton density-weighted images extracted from the ARIC-NCS MRI scans obtained at visit 5/NCS. WMH burden will be determined using a quantitative computer-aided segmentation program which uses an algorithm to segment fluid-attenuated inversion recovery (FLAIR) images (FLAIR-histoseg) to measure the volumetric burden of leukoaraiosis [10]. All analyses using WMH will include adjustment for total intracranial volume.
- *Subclinical and lacunar infarction:* The presence of subclinical infarction and lacunar infarction will be determined for each patients using the ARIC-NCS MRI scans obtained at visit 5/NCS. Subclinical infarction will be defined as cortical and subcortical infarctions >3mm in size that do not correlate in time with the onset of neurological symptoms. Lacunar infarctions will be defined as subcortical infarctions between >3mm and <20mm in size [11].
- *Cerebral microbleeds:* The presence of cerebral microbleeds will be determined for each patient using the T2* GRE MRI sequences from the ARIC-NCS MRI scans obtained at visit 5/NCS. Microbleeds will then be classified according to their location as cortical or subcortical.
- *White matter microstructure:* Diffusion tensor imaging (DTI) will be used to evaluate axonal integrity. Whole brain measures of mean diffusivity (MD) and fractional anisotropy (FA) will be extracted from the ARIC-NCS MRI scans obtained at visit 5/NCS.

Data analysis:

- We will conduct linear and logistic regression analyses to determine if inpatient hospitalization (exposure) and/or inpatient surgery predicts MRI defined abnormalities at ARIC NCS visit 5, after adjusting for age, sex, education, APOE e4 status, hypertension, blood pressure, diabetes, smoking, hyperlipidemia, coronary artery disease, and heart failure.
- We will conduct separate analyses to evaluate the effects of (1) number of hospitalization, (2) critical illness vs. non-critical illness, (3) major surgical vs. non-surgical hospitalization, and (4) acute infection vs. no infection on outcome variables.

Secondary analysis:

- We may also examine the effect of inpatient hospitalization on brain volume changes from Brain MRI visit (2004-2006) to visit 5 NCS (2011-2013). Although differences in brain MRI acquisition techniques preclude the direct comparison of quantifiable MRI outcomes between the two visits, we will use a ranking system to compare change in whole brain, ventricular, and hippocampal volume between participants with and without hospitalization and/or inpatient surgery.

Hypothesis 3. A history of hospitalization and/or inpatient surgery from ARIC visit 2 until visit 5 will be associated with increased risk of mild cognitive impairment (MCI) and dementia at visit 5 NCS.

Exposure:

- Inpatient hospitalization (categorized in the five ways described above) between visit 2 and visit 5.

Inclusion/Exclusion:

- We will include all patients seen at ARIC visit 2.
- We will exclude those patients scoring below 5th percentile in any cognitive test at visit 2.
- A sensitivity analysis will conducted after excluding participants with documented neurological conditions (e.g., MS, stroke, TBI with residual cognitive impairment) and those who underwent neurosurgical procedures.

Outcome:

- MCI and dementia diagnosed at ARIC visit 5.

Data analysis:

- We will use logistic regression to determine if a history of hospitalization predicts diagnosis of MCI or dementia, adjusting for age, education level, APOE e4 status, and baseline cognitive scores. Additional models will also adjust for cardiovascular risk factors, including hypertension, diabetes, smoking, and hyperlipidemia.
- We will conduct separate analyses to evaluate the effects of (1) number of hospitalization, (2) critical illness vs. non-critical illness, (3) major surgical vs. non-surgical hospitalization, and (4) acute infection vs. no infection on outcome variables.

Methodological limitations:

1. Data on inpatient exposure will be limited to ICD-9 codes from each hospital discharge. However, ICD-9 codes can be used to identify surgical procedures and select postoperative critical illness, and have been used in a cohort of general admissions as an exposure variable linked with long-term cognitive decline.
2. We have reported results of a similar study using cognitive data prior to the ARIC MRI visits. However, since increasing age is a clear risk factor for cognitive decline after hospitalization and/or surgery, it is also important to examine the magnitude of these changes in older adults.
3. The cognitive data are collected at relatively few time points, so we will not have data on the intermediate time points of cognitive change in the main analyses. We will use mixed models to account for all available data.
4. There is a potential for selection bias based on survival differences among participants with different cognitive or hospitalization status. We will compare demographic and co-morbidity information among those patients with different survival times to determine the likelihood of this bias.

5. 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.
6. There are missing data at visit 5. We will conduct the primary analyses using only patients with available data. We will conduct sensitivity analyses as recommended by the ARIC analysis committee to account for missing data using imputation, including use of MICE and IPAW as appropriate.

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)?

Related Manuscript Proposals

2551 Midlife and late life vascular risk factors and white matter integrity assessed using diffusion tensor imaging: the ARIC-NCS study

2351 Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI

#1771 Cognitive, vascular risk factor and APOE genotype predictors of hippocampal volume

2266 Associations between brain vascular imaging features and regional volumetrics

Related ARIC Manuscripts

Alonso A, Mosley T, Gottesman R, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalization associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. J Neurol Neurosurg Psychiatry 2009; 80: 1194-1201.

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, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH Jr. Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort : Atherosclerosis Risk in Communities (ARIC) Study. Stroke 2010, 41:3-8:

Knopman DS, Penman AD, Catellier DJ, Coker LH, Shibata DK, Sharrett AR, Mosley TH Jr. Vascular risk factors and longitudinal changes on brain MRI: The ARIC study. Neurology. 2011 May 31;76(22):1879-85.

Pathan SS, Gottesman RF, Mosley TH, Knopman DS, Sharrett AR, Alonso A. Association of lung function with cognitive decline and dementia: the Atherosclerosis Risk in Communities (ARIC) Study. Eur J Neurol. 2011 Jun;18(6):888-98.

Schneider A, Sharrett A, Patel M, Alonso A, Coresh J, Mosley T, Selnes O, Selvin E, Gottesman R. Education and cognitive change over 15 years: The ARIC Study. JAGS. 2012; 60: 1847-1853.

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* 1999.01)

___ 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.

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 __X__ Yes ____ No.

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