ARIC Manuscript Proposal #2007

PC Reviewed: 10/9/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
The effect of inpatient surgery on long-term neurocognitive changes in a biethnic cohort: The ARIC Study

b. Abbreviated Title (Length 26 characters):
Surgery and cognitive decline

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

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

First author: **Charles Brown**
Address: Johns Hopkins Hospital
Department of Anesthesia and Critical Care Medicine
Zayed Tower 6208
1800 Orleans St. Baltimore, MD 21287

Phone: 410 955 7519 Fax: 410 955 0994
E-mail: cbrownv@jhmi.edu

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).
Name: **Rebecca Gottesman**
Address: Johns Hopkins Hospital
Department of Neurology
Meyer 6-113
600 N. Wolfe St.
Baltimore, MD 21287

Phone: 410 614 2381 Fax: 410 955 0672
E-mail: rgottesm@jhmi.edu

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

4. Rationale:
Dementia is a growing public health problem because of the increasing prevalence of the disease and the resources required to care for patients with disease progression. Although significant research efforts have focused on stopping or reversing dementia, 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.

The effect of acute illness on short-term cognitive decline has been characterized in varied clinical settings, but most efforts have focused on changes that occur immediately after illness or several months later. In the short term, the incidence of delirium in elderly patients undergoing surgery has been estimated to be as high as 52%.[2] Although acute changes represented by delirium often resolve in the short term, cognitive changes following delirium have been shown to persist months after surgery.[3,4] However, the role of critical illness in cognitive decline that persists months to years after an initial insult is less well studied.

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. Ehlenbach et al followed the cognitive status of 2929 individuals age 65 and older every 2 years using the Cognitive Abilities Screening Instrument (CASI).[5] Over a mean follow up of 6.1 years, a non-critical illness hospitalization was associated with a decline in the CASI of 1.01 points (95% CI 0.7-1.3; $p<0.001$), and a critical illness hospitalization was associated with a decline in the CASI of 2.14 points (95% CI 0.03-4.24; $p=0.047$). Moreover, the adjusted hazard ratio for development of incident dementia following a non-critical illness hospitalization was 1.4 (95% CI 1.1-1.7; $p=0.001$) and following a critical illness hospitalization was 2.3 (95% CI 0.9-5.7; $p=0.09$).

Similarly, the effect of hospitalization on cognitive decline was examined in a cohort of 1870 patients through the Chicago Health and Aging Project over a median of 9 years. In this study, the decline in global cognitive score accelerated 2.4 fold from pre-hospitalization to post-hospitalization. Severity of illness and length of hospitalization were each associated with faster decline, and the decline persisted over the length of follow-up.[6]

A significant limitation of both of these studies was that participants were admitted to hospitals for both medical and surgical indications. Although a mechanism for the cognitive decline found in these studies was not examined, evidence suggests that both anesthetic agents as well as common postoperative events such as delirium, systemic

inflammation, and sedative/analgesic medications all may play a role. These insults are particularly prevalent in the perioperative period, and so patients undergoing inpatient surgery may be particularly susceptible to cognitive decline. An additional limitation of these studies is that relatively few confounding variables were considered. The ARIC dataset allows adjustment for additional potential confounding variables, including apoE status—which has not been explored in previous studies examining the association between hospitalization and cognitive decline. We will expand on the confounding variables to include factors such as apoE status, diabetes, carotid disease, hypertension, depression, and disability measures.

Because of the increasing number of elderly patients presenting for surgery, it is crucial to know whether surgery or perioperative insults—including anesthesia, and post-operative care—increase the risk of cognitive decline or of the onset of dementia. Determining this association has practical implications. First, many operations are planned procedures and so allow time for full risk/benefit considerations and optimization of medical condition. Second, the perioperative insult can be modified through changes in both anesthetic, surgical, and recovery techniques. Finally, conclusions regarding long-term cognitive decline after medical admissions may not be generalizable to surgical patients because of differences in the patient population, hospital insults, and inflammatory response. If perioperative insults do indeed increase this risk, then efforts to refine the risk/benefit analysis for elective surgery and to determine strategies to modify this risk will be paramount.

5. Main Hypothesis/Study Questions:

1. A history of inpatient surgery will be associated with reduced or decreasing cognitive scores on the Delayed Word Recall test (DWR), Digit Symbol Substitution Test (DSST), and Word Fluency Test (WFT) from ARIC visit 2 (1990-2) to the ARIC Brain MRI and Carotid MRI visits (2004-6).

2. A history of inpatient surgery will be associated with the onset or progression of defined cerebral vascular or degenerative changes detected by MRI between ARIC visit 3 to the ARIC Brain MRI visit.

3. A history of inpatient surgery will be associated with admission to any hospital for dementia. The period of exposure for inpatient surgery will be from ARIC visit 2 until 2010, although we will also consider earlier time periods in separate analyses.

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 patients undergoing inpatient surgery during a defined exposure period to those patients not undergoing surgery. Data on surgical procedures and postoperative complications will be obtained using ICD discharge codes. The surgical exposure will be analyzed in several ways—(1) yes/no, (2) number of inpatient surgeries, (3) predicted cardiac risk of inpatient surgery, and (4) clinical severity of the admission.

In reference to item (3), Clinical Classification Software (CCS) developed by the Agency for Healthcare Research and Quality will be used to classify each procedure into clinically relevant procedure groups, using the 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.

In reference to item (4), an admission will be considered as including a critical illness using the methodology of Ehlenbach et al. 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.

We will also consider medical admissions in our analysis as either a confounding variable or as an exclusion criteria in a restricted analysis. We will utilize the methodology of Ehlenbach et al. to categorize medical admissions using ICD-9 codes as including a critical or non-critical illness.

Hypothesis 1. A history of inpatient surgery will be associated with decreasing cognitive scores on the DWR, DSST, and WFT from ARIC visit 2 (1990-2) to the ARIC Brain MRI and Carotid MRI visits (2004-6).

Exposures:

- Inpatient surgery (categorized in the four ways described above) between visit 2 and ARIC MRI visits. We will also consider shorter intervals of surgical exposure, such as ARIC visit 2 – visit 4, in other analyses.

Inclusion:

- We will include all individuals with cognitive data from ARIC visit 2 and ARIC MRI visits, or from ARIC visit 2 and visit 4.
- We will exclude those patients who scored below 5th percentile in any cognitive test at visit 2, had prevalent stroke at visit 2, or underwent neurosurgical procedures.
- We will conduct separate analyses using different groups of patients—
    1. In the primary analysis, we will use <u>all</u> patients with surgery during the defined exposure period,

2. In a secondary analysis, we will attempt to account for potential misclassification if there were a lag effect of surgery.
    a. We will use all patients with surgery during the defined exposure period, but exclude any patients with surgery in the 10 years prior.
    b. We will use all patients with surgery during the defined exposure period, and furthermore, include any more patients with surgery during the 10 years prior to the exposure period.

Outcome:

- Change in score of DSST, WFT, DWR from visit 2 to MRI visit or change in score from visit 2 to visit 4.

Data analysis

- We will conduct regression analysis to investigate the effect of inpatient surgery (exposure) on the change in cognitive scores (outcome). We will utilize separate models stratified by race and adjusting for age, sex, education, apoE status, hypertension, diabetes, smoking, hyperlipidemia, coronary artery disease, cerebrovascular disease, depression, disability, and medical admissions. We will consider utilizing propensity scores for undergoing surgery in the analysis; if we use them we will adjust for the propensity scores in the regression analyses.
- We will also conduct regression analysis using random effects mixed models with history of inpatient surgery predicting longitudinal change in score of DWR, WFT, and DSST. We will use all available cognitive data from ARIC visit 2,visit 3, visit 4, and ARIC Brain MRI or Carotid MRI visits. Similarly, we will use separate models stratified by race and adjusting for age, sex, education level, and apoE status. We expect to use random intercept only models including interaction terms between surgical status and follow-up as well as follow-up time and other risk factors, including hypertension, diabetes, smoking, hyperlipidemia and coronary artery disease as independent variables. Although we may be limited by sample size, we will compare slopes of change or absolute change in cognitive scores before and after surgical exposure.

Hypothesis 2. A history of inpatient surgery will be associated with the progression of defined MRI abnormalities from ARIC visit 3 to the ARIC Brain MRI visit.

Exposure:

- Inpatient surgery between visit 3 (1993-1995) and ARIC Brain MRI visit (2004-2006). We will also conduct separate analyses expanding the exposure period to visit 2 (1990-1992) – ARIC Brain MRI visit.

Inclusion/ Exclusion:

- All individuals with MRI data in visit 3 and the ARIC Brain MRI visit
- We will exclude those patients with prevalent stroke at visit 2, or who underwent neurosurgical procedures.
- We will conduct separate analyses using different groups of patients—
    1. In the primary analysis, we will use all patients with surgery during the defined exposure period,

2. In secondary analyses, we will attempt to account for potential misclassification if there were a lag effect of surgery.
    a. First, we will use all patients with surgery during the defined exposure period, but exclude any patients with surgery in the 10 years prior.
    b. Second, we will use all patients with surgery during the defined exposure period, and furthermore, include any patients with surgery in the 10 years prior.

- Based on previous publications, we anticipate approximately 980 patients will be analyzed.

Outcome:

- Change in MRI-assessed burden of infarcts, white matter hyperintensities, ventricle size, or sulci widening between visit 3 and ARIC Brain MRI visit, using methodology from Knopman et al.[7] and Gottesman et al.[8]

Statistical Analysis:

- We will conduct regression analysis to determine if inpatient surgery (exposure) predicts onset or progression in MRI defined abnormalities (new lacunar infarcts, white matter hyperintensities, ventricular size, sulci widening) between visit 3 and the ARIC Brain MRI visit adjusting for age, sex, education, apoE status, hypertension, diabetes, smoking, hyperlipidemia, coronary artery disease, cerebrovascular disease, depression, disability, and medical admissions. Because volumetric measurements are available from the Brain MRI visit and not from visit 3, we will use approaches similar to those described in Gottesman et al.[8] to analyze change in WMH volume, and will apply similar approaches to estimate change in ventricular and sulcal volume.

Hypothesis 3. A history of inpatient surgery will be associated with admission to any hospital for dementia.

Exposure:

- Any inpatient surgery between visit 2 and 2010. We will also consider shorter intervals of surgical exposure, such as ARIC visit 2 – visit 4, in other analyses.

Inclusion/Exclusion:

- We will include all patients from ARIC visit 2.
- We will exclude those patients scoring below 5th percentile in any cognitive test at visit 2, with prevalent stroke at visit 2, or who underwent neurosurgical procedures.
- We will conduct separate analyses using different groups of patients—
    1. In the primary analysis, we will use all patients with surgery during the defined exposure period,
    2. In secondary analyses, we will attempt to account for potential misclassification if there were a lag effect of surgery.

a. First, we will use all patients with surgery during the defined exposure period, but exclude any patients with surgery in the 10 years prior.
b. Second, we will use all patients with surgery during the defined exposure period, and furthermore, include any patients with surgery in the 10 years prior.

Outcome:

- Hospitalizations with diagnosis of dementia, using the methodology from Alonso et al.[9] Using data from visit 2 until 2004, there were 203 cases of dementia in this cohort. These numbers are expected to be higher with more accrued years of follow-up.

Statistical Analysis:

- We will use Cox proportional hazards analysis to determine if a history of inpatient surgery predicts the time from baseline to hospitalization for dementia or diagnosis of dementia, adjusting for age, education level, apoE status, and baseline cognitive scores. Additional models will also adjust for cardiovascular risk factors, including hypertension, diabetes, smoking, and hyperlipidemia. Data on inpatient surgery will be analyzed as several variables, including yes/no, number of inpatient surgeries, severity of inpatient surgery, and number of major complications.

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. We will attempt to determine and use any other records that might further describe the hospital admission to refine our exposure characterization.
2. Patients in the ARIC study were not yet elderly during the years in question, and so cognitive decline may not be evident by the ARIC Brain MRI visit. However, ARIC visit 5 will collect cognitive data in the now older cohort, so this current study will provide pilot data for a potential future study using ARIC visit 5 data.
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. Nevertheless, ARIC visit 5 will provide another time point.
4. There is a potential for selection bias based on survival differences among participants with different cognitive or surgical 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 did or did not undergo surgery. We will adjust for potential confounding variables in multivariable regression and through propensity score analysis.

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)?

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.

Christman A, Matsushita K, Gottesman R, Mosley T, Alonso A, Coresh J. Hill-Briggs F, Sharrett A , Selvin E. Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*. 2011 Jul; 54(7):1645-52. Epub 2011 Mar 1. PubMed PMID: 21360189.

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, Mosley TH, Catellier DJ, Coker LH, ARIC Study Brain MRI Study. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimers Dement. 2009 May;5(3):207-14.

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. In press.

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: 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.

REFERENCES

1. Brookmeyer R, Johnson E, Ziegler-Graham K. Forecasting the global burden of Alzheimer's disease. *Alzheimer's and Dementia.* 2007; 3: 186-191.

2. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009;119(2):229–236.

3. Selnes OA, Gottesman RF, Grega MA, Baumgartner WA, Zeger SL, Mckhann GM. Cognitive and neurologic outcomes after coronary-artery bypass surgery. *N Engl J Med*. 2012;366(3):250–257.

4. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367(1):30–39.

5. Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA*. 2010;303(8):763–770.

6. Wilson RS, Hebert LE, Scherr PA, Dong X, Leurgens SE, Evans DA. Cognitive decline after hospitalization in a community population of older persons. *Neurology*. 2012;78(13):950–956.

7. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. *Neurology*. 2011;76(22):1879–1885.

8. Gottesman R, Coresh J, Catellier D, Sharrett A. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2010.

9. Alonso A, Mosley TH, Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. *J Neurol Neurosurg Psychiatr*. 2009;80(11):1194–1201.