ARIC Manuscript Proposal #2698

PC Reviewed: 1/12/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Hemostatic Factors and Long-term Cognitive Change

b. Abbreviated Title (Length 26 characters): Hemostasis and Cognitive Change

2. Writing Group:

Writing group members:

Aozhou Wu, MHS; and (alphabetically) Alvaro Alonso, MD, PhD; Josef Coresh, MD, PhD; Aaron R. Folsom, MD, MPH; Rebecca F. Gottesman, MD, PhD; Alden L. Gross, PhD, MHS; Andreea M. Rawlings, MS; A. Richey Sharrett, MD, DrPH; Andrea L.C. Schneider, MD, PhD; others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AW **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Vascular contributions to cognitive decline as well as dementia have been highlighted, mainly as brain vascular abnormalities, including large, lacunar and micro-infarcts[1], white matter hyperintensities and microhemorrhages[2]. Besides the well-known roles that cerebral atherosclerosis and lipohyalinosis play in the pathogenesis of these vascular abnormalities, hemostatic abnormalities have also been proposed as potential causes,[3] and therefore they too may impact cognitive function. In the coagulation process, fibrinogen, as one of the main substrates, is transformed to fibrin strands, which is further cross-linked by the complex of Factor VIII and von Willebrand factor (VWF), to produce blood clots. Elevated plasma level of fibrinogen, factor VIII or VWF may reflect a hypercoagulable status[4]. On the other hand, d-dimer, as the product of fibrinolysis process, is also positively associated with the level of coagulation. Therefore, increased levels of the hemostatic markers mentioned above in plasma indicate a high level of blood clot formation, which may result in brain vessel damage, lead to cerebral infarcts, and thus may contribute to cognitive impairment. Evidence from cross-sectional[4-6] and prospective studies[7-9] have suggested associations of hemostatic factors, including fibrinogen[7, 10], VWF[10], factor VIII[7] and d-dimer[10, 11] with dementia. However, most studies examining the association have been limited to severe cases – dementia patients or cohorts with relatively short duration of follow-up time, leaving uncertainty with respect to causality and to reference to the community-dwelling aging population as well as lacking quantitative estimates of the association with long-term cognitive change.

5. Main Hypothesis/Study Questions:

Study Aims:

1. Assess the longitudinal association between the level of fibrinogen, von Willebrand factor (VWF) and Factor VIII at visit 1 and 20-year cognitive decline from visit 2 to visit 5.
2. Assess the longitudinal association between the level of d-dimer at visit 3 and 20-year cognitive decline from visit 2 to visit 5.

Hypothesis:

Higher hemostatic factor levels are independently associated with greater long-term cognitive decline.

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

We will utilize a longitudinal study design with visit 2 as study baseline.

Study population

Inclusion Criteria:

All visit 2 ARIC participants with valid hemostatic factors measurement.

Exclusion Criteria:

We will exclude participants who are neither white nor African-American and non-white in Washington Co. and Minnesota, without education information. In addition, we will exclude participants with stroke diagnosis at or prior to visit 2 and exclude the cognition test if the participant was on CNS-altering medications (neuroleptics or benzodiazepines) at the corresponding study visit to minimize the impact of prevalent disease status on cognitive change. To minimize the impact on hemostasis measurement, we will also exclude those with atrial fibrillation (AF) or venous thromboembolism (VTE) diagnosis at or within 6 months prior to the hemostatic factor measurements, as well as those on anticoagulation medication at the two study visits for hemostatic factors measurements (visit 1 and visit 3).

Exposure

Hemostatic factors:
Fibrinogen, VWF and Factor VIII measured at visit 1
D-dimer measured at visit 3

Outcome

Cognitive test score changes:
Cognitive test scores measured at visit 2, visit 4 and visit 5, including: the delayed word recall test (DWRT), the digit symbol substitution test (DSST), and the word fluency test (WFT). Standardized z-scores (standardizing to visit 2) will be used for each test. A Global score will be calculated by summing the z-scores of the three tests and then standardized to the global scores at visit 2. Cognitive test score changes will be estimated using random effect model.
In addition, cognition change will also be evaluated using latent variables derived from cognitive tests, named factor scores. Latent variables for cognition domains (memory, executive/functioning speed, language) will be constructed incorporating multiple cognitive test resources in ARIC study using method developed by Dr. Alden L. Gross. Detailed method was descripted in ARIC MSP #2215 and the published manuscript (PubMed ID 26414855).

Covariates

For most covariates, we will use the measurements at study baseline (visit 2) including: age, gender, race-field center, smoking status (current, former, never), alcohol consumption (current, former, and never), body mass index (BMI), apolipoprotein E ε4 genotype, hypertension status, diabetes status, history of coronary heart disease. One exception is for the covariates measured only at visit 1: education level (< high school, high school or equivalent, > high school). Another exception is for covariates that may have more evident immediate effect on the hemostasis status than its long-term effect, including: use of aspirin and estrogen; or stronger association with hemostasis than cognition, e.g. kidney function. For these covariates, measurements taken at the corresponding visits for measuring hemostatic factors will be used.

Statistical Analysis Plan

I. Missing data imputation:

To account for informative drop-out and population attrition, we will impute the missing cognitive test results in visit 4 and 5 due to participants' loss to follow up as well as

missing covariates listed above using the multiple imputation with chain equation method, as per the recommendations from the ARIC-NCS Analysis Workgroup. We will use the same detailed methods as described in ARIC MSP #2523.

II. Primary Analysis:

We will use exposures measured at visit 1 (fibrinogen, VWF, and Factor VIII) or visit 3 (d-dimer) and outcome - cognitive tests results in visit 2, 4 and 5 to conduct the longitudinal analysis. Cognitive test scores will be standardized to visit 2 measurements using the mean and standard deviation of the scores at visit 2. The level of hemostatic factors will be analyzed as both categorical (based on quintiles) and continuous. Random effect models will be used to accommodate the correlation between repeated cognitive test measures over time. To model the association with cognition change trajectories, both random intercept and random slope will be included. An independent correlation structure for the two random effects will be assumed. The time-frame will be the time since visit 2, and cognitive test scores at visit 2, 4, and 5 will be modeled as dependent variables. To allow the flexibility of cognitive changes, we will add a linear spline with a knot at the intermediate point of visit 4. Interaction terms between exposure and time-spline will be included as the primary variables of interest. For each exposure, and for the four exposures considered together, four nested models will be constructed adjusting for different covariates. Model 1 will include exposures, outcome and only the demographic covariates: age, age square term, race-field center, and education level. Model 2 will further adjust for common cardiovascular risk factors, including: smoking status, alcohol consumption, BMI, apolipoprotein E ε4 genotype, hypertension status, diabetes status. Model 3 will include comorbidity status, i.e. history of CHD and kidney function in addition to covariates in model 2. Model 4 will further adjust for the use of aspirin and estrogen. Time-interaction terms, which contribute to the slope of cognitive change, will be included for following covariates: age, age squared, sex, race-field center, education, BMI, apolipoprotein E ε4 genotype, hypertension status, diabetes status, history CHD and kidney function. Non-linearity will be checked for the exposure-outcome association when treating hemostatic factors' level in continuous scale. Appropriate modeling approaches will be adopted to address the non-linear association if there is any.

III. Sensitivity Analysis:

a) Interaction and Subgroup analysis:

Interaction effects with cognitive slopes will be checked with the following covariates: gender, race, BMI, diabetes status, hypertension status at baseline, kidney function at the time of exposure measurement, and apolipoprotein E ε4 genotype.

Subgroup analysis using the same method as in primary analysis will be conducted in the subgroups of different gender, race, diabetes status, and other covariates that have significant modification effects on exposure-outcome association.

b) Impact of stroke, AF, and anticoagulation as well as CNS-altering medications used:

To assess the robustness of the results, we will censor participants at the time point of clinical stroke, AF diagnosis, anticoagulation medications or CNS-altering medications use after study baseline from the primary analytical population.

c)Re-do the analysis using non-imputed data with inverse probability weighting to account for informative missingness and cohort attrition.

Limitations

One of the limitations is that we don't have measurements of hemostatic factors at the study cognitive baseline (visit 2). Instead, the effects of fibrinogen, VWF and Factor VIII were lagged for 3 years from the measurements (visit 1), and d-dimer was measured 3 year after baseline, which harms study's temporality. In addition, d-dimer was measured about 6 years after the measurements of fibrinogen, VWF and Factor VIII, which makes their effects on cognitive change less comparable as the markers may reflect the hemostasis status at different life-stage and the measurements are also subject to temporal change.

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? ____ Yes __X__ 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"? ____ 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)?
To our knowledge, there are no ARIC proposals specifically focusing on Hemostatic factors and cognitive change. The proposal #2456, leaded by Dr. Aaron Folsom, evaluated the association assessment between hemostatic factors and stroke. The proposal #847r, led by Dr.Rebecca Gottesman, evaluated the association between hemostatic factors and MRI-detected cerebral infarction in a case-control design and suggested the biological possibility for the effect of hemostasis on cognition change through cerebral infarction. We will utilize the imputation method developed in the proposal #2523 and latent variable method developed in the proposal #2215. Key authors of these proposals contributed to the current proposal and appropriate coordination will be made.

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* 2008.06)

___ 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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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.

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