ARIC Manuscript Proposal #2996

PC Reviewed: 06/06/17   **Status:** _____   **Priority: 2**
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: Association between Infection with Herpes Simplex Virus-Type 1, Cytomegalovirus, and Helicobacter Pylori, and Cognitive Decline in the Atherosclerosis in Communities (ARIC) Study

   b. Abbreviated Title (Length 26 characters): Infection and Cognition

   2. Writing Group: Kristen M. George, Aaron R. Folsom, Faye L. Norby, Pamela L. Lutsey, B. Gwen Windham

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _KMG_ **[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: Finish by August 2017

4.   Rationale:

   Cognitive decline reflects a continuum of cognitive changes that can range from normal aging to pathologic decline, a change in cognition that exceeds the decline expected due to aging

alone. [1][2] Cognitive changes among older adults are important because pathologic decline indicates increased risk of mild cognitive impairment and dementia. [2] Chronic infections with herpes simplex virus type 1 (HSV-1), helicobacter pylori, and cytomegalovirus (CMV), have been suggested as possible risk factors for cognitive decline. These common infections were first identified as having a potential role in the pathogenesis of atherosclerosis and coronary heart disease by way of systemic inflammation. [3] However, no statistically significant association has been found between HSV-1, CMV, and h. pylori and cardiovascular diseases including coronary heart disease (CHD), carotid intimal-medial thickening, or atherosclerosis in the ARIC cohort. [4][5][6][7] Despite the lack of association with CVD, there is renewed interest in the role chronic infection may play in neurocognition. Recent studies indicate that these chronic infections can lead to inflammation involving the central nervous system potentially leading to cognitive decline. [8]

5.   Main Hypothesis/Study Questions:

We hypothesize that ARIC participants whose visit 1 serum tested positive for antibodies to HSV-1, CMV, or h. pylori will have an accelerated rate of cognitive decline over 20 years compared to participants whose serum tested negative.

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).

Design: As part of case-cohort studies of CVD conducted in ARIC, a stratified random sample (n=556) of participants was tested for serum antibodies to HSV-1, h. pylori, and CMV at visit 1. For the present analysis, a prospective study will be conducted using this sample to assess the association between these three infections and cognitive decline between visits 2 and 5.

Exclusions: All participants missing serum antibody measures to HSV-1, h. pylori, and CMV or missing baseline covariates as well as African Americans in MN and MD.

Exposure: Serum antibodies to HSV-1, h. pylori, and CMV measured at visit 1 within the cohort stratified random sample

Outcome: Change in cognition over 20 years of follow-up. Cognitive change will be measured using scores from the Delayed Word Recall (DWR) Test, Digit Symbol Substitution (DSS) Test, and Word Fluency (WF) Test. Measures taken at visits 2, 4, and 5 will be converted to z-scores standardized to visit 2.

Covariates from visit 1: age, sex, race (MS-blacks, NC-whites, NC-blacks, MN-whites, and MD-whties), APOE ε4, income, education,
Covariates from visit 2: body mass index (BMI), smoking status, hypertension, diabetes, prevalent coronary heart disease (CHD), prevalent stroke, drinking status, HDL cholesterol, and total cholesterol

Analysis: Linear regression with generalized estimating equations (GEE) will be used to assess the association between HSV-1, h. pylori, and CMV infections and 20-year cognitive decline. Models will include an unstructured correlation matrix and robust variance to estimate the average difference in trajectory of cognitive test score between those whose serum tests positive for antibodies to infection and those that test negative. HSV-1, CMV, and h. pylori infections will be interacted with time to model rates of change in cognitive test scores by infection status. Time will be modeled as a linear spline with a knot at year 6 to account for the gaps between visits (6 years between visits 2 and 4 and 14 years between visits 4 and 5).

Models will be adjusted for baseline (visit 1 or 2) covariates. We will explore interacting covariates with time.
 Model 1: age, sex, race, APOE ε4, income, education,
 Model 2: plus body mass index (BMI), smoking status, hypertension, diabetes, prevalent
 coronary heart disease (CHD), prevalent stroke, drinking status, HDL cholesterol, and total
 cholesterol.
For each infection, an analysis will be run to assess change in z-score for the three cognitive tests separately. Additionally, we will conduct a fourth analysis using a composite global z-score.

Due to attrition and selection bias, we will include (a) inverse probability of attrition weights and (b) weights to correct for the cohort random sample selection probabilities.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ 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? __X__ 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)?

Based on our thorough search, there are no related manuscript proposals.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __ _ Yes __X_ No

11.b. If yes, is the proposal
   ___ **A. primarily the result of an ancillary study (list number* _____)**
   ___ **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 ____ Yes __X_ No.

References:
   [1] Salthouse T. Consequences of Age-Related Cognitive Declines. *Annu Rev Psychol*. 2012; 63: 201-06.
   [2] Plassman BL, Williams JW, Burke JR, et al. Systemic Review of Factors Associated with Risk for and Possible Prevention of Cognitive Decline in Later Life. *Ann Intern Med*. 2010; 153(3): 183-93.
   [3] Roivainen M, Viik-Kajander M, Palosuo T, et al. Infections, Inflammation, and the Risk of Coronary Heart Disease. *Circ*. 2000; 101: 252-57.
   [4] Sorlie PD, Nieto FJ, Adam E, et al. A Prospective Study of Cytomegalovirus, Herpes Simplex Virus 1, and Coronary Heart Disease: The Atherosclerosis in Communities (ARIC) Study. *Arch Intern Med*. 2000; 160(13): 2027-32.
   [5] Folsom AR, Nieto FJ, Sorlie P, et al. Helicobacter pylori Seropositivity and Coronary Heart Disease Incidence. *Circ*. 1998; 98: 845-50.

[6] Nieto FJ, Adam E, Sorlie P, et al. Cohort Study of Cytomegalovirus Infection as a Risk Factor for Carotid Intimal-Medial Thickening, a Measure of Subclinical Atherosclerosis. *Circ*. 1996; 94: 922-7.

[7] Sorlie PD, Adam E, Melnick SL, et al. Cytomegalovirus/herpesvirus and Carotid Atherosclerosis: The ARIC Study. *J Med Virol*. 1994; 42(1): 33-7.

[8] Mawanda F and Wallace R. Can Infections Cause Alzheimer's Disease? *Epidemiol Rev*. 2013; 35(1): 161-80.