ARIC Manuscript Proposal # 2976

PC Reviewed: 5/9/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of sickle cell trait with measures of neurocognitive function in African Americans

b. Abbreviated Title (Length 26 characters): **Sickle cell trait and neurocognitive function**

2. Writing Group:

Writing group members: Hyacinth I. Hyacinth, Nemin Chen, Vimal Derebail, Melissa Caughey, Abhijit V. Kshirsagar, Richey Sharrett, Rebecca F. Gottesman, B. Gwen Windham, Nigel Key, Alvaro Alonso.

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

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3. Timeline: Obtain approval for manuscript proposal by June, submit to P & P by October and submit manuscript to journal by December, 2017.

4. Rationale:

Introduction [Rationale and background]:

Several studies show that vascular risk factors and biomarkers, especially small vessel disease, are also risk factors for cognitive decline (1). The prevalence of cerebral small vessel disease,

thought to be related to development of neurocognitive abnormalities, is significantly higher among African Americans than among whites (2, 3). Further, patients with sickle cell anemia (SCA) have been shown to have impairment in cognitive function; children (4) and adults (5) score lower on cognitive tests than controls and children are at risk for lower academic attainment in school (6). Silent cerebral infarction is common in children with SCA, (7) and correlates with poorer neurocognitive outcomes in children and adolescents with SCA (8). In a study of adults with SCA cortical and subcortical brain volumes were lower than controls after accounting for other factors including cerebrovascular lesions, and these lower volumes correlated with cognitive performance (9). These findings support clear association between sickle cell disease and the onset and severity of neurocognitive abnormalities. SCA is the homozygous state of the sickle beta-globin mutation and is prevalent in about 100,000 Americans. The heterozygous state, known as sickle cell trait (SCT) is prevalent in about 8% (over 3 million) of African Americans, besides Hispanics and other minority groups.
Recent studies suggest that individuals with SCT are at higher risk for microvascular health conditions including kidney disease (10), venous thromboembolism (11, 12) and perhaps stroke, although there is some debate on the latter (13-15) (unpublished REGARDS data shows no association with stroke). The exact mechanisms behind these associations is still unclear, but thought to be related to microvascular occlusive events from sickle red blood cells, inflammation and hypercoagulability already putatively associated with SCA-related silent infarcts and cognitive decline.

5. Main Hypothesis/Study Questions: We hypothesize that SCT will be associated with cognitive impairment in adults after accounting for possible confounding variables. Specifically, we will test whether;

1. SCT is associated with lower scores in neurocognitive tests using ARIC visit 2 data
2. SCT is associated with cognitive decline using ARIC visit 2, 4 and 5 data
    a. SCT is associated with more severe of cognitive decline.
3. SCT is associated with MRI measures of cerebral cortical injury (WMH lesions, hippocampus, frontal and posterior ROI volumetric measures) at visit 5.

Finally, we will explore whether SCT is associated with incidence of dementia in African Americans in ARIC, though we recognize this analysis is likely to be underpowered.

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).
This is a longitudinal observational study of the association of sickle cell trait (SCT) status with prevalence and incidence of neurocognitive impairment, and also radiological markers of neurocognitive impairment among African Americans in the ARIC cohort.

Inclusion criteria: African Americans with sickle cell genotyping data available, who completed neurocognitive testing in at least one of visits 2 (1991-1992), 4 (1996-1998) and/or 5 (2011-2013). Also, MRI data from visit 5 will be required for hypothesis 3.
Exclusion criteria: African American individuals with Sickle cell anemia (HbSS) or compound heterozygotes (HbSC, etc.).
Covariates:

Age, sex, and educational level (<high school, high school or >high school), study center, body mass index (continuous), diabetes mellitus status (defined as self-reported history of a physician's diagnosis or use of diabetes medication or based on fasting or random blood glucose diagnosis), history of alcohol use, self-reported history of smoking (current, former or never), APOE genotyping status (0, 1, or 2 E4 alleles), and stroke (self-reported history at baseline + adjudicated during follow-up).

Outcome data:

1. Global cognitive function measures at visits 2 (1991-1992), 4 (1996-1998) or 5 (2011-2013).
2. Cognitive domain specific scored (DWRT, DSST, WFRT) – all relevant visits
3. MRI derived cerebral cortical measures (hippocampal volume, posterior and anterior cortical ROI volume, cerebral WMH lesions (count).

Analysis Plan:
Analysis Q1:
Predictor: sickle cell trait status, i.e. SCT vs. non-SCT
Outcome: Global and domain specific cognitive testing scores at baseline (visit 2)
Analysis: Linear regression model to assess the relationship of SCT status with global and test specific (DWRT, DSST, WFRT) cognitive scores at visit 2. Analysis will be adjusted for relevant covariates as mentioned in earlier sections. We will also adjust for self-reported history of stroke in sensitivity analysis, to determine whether SCT is an independent predictor of increased risk for prevalence of cognitive abnormality.

Analysis Q2:
Predictor: sickle cell trait status, i.e. SCT vs. non-SCT
Outcome: decline in cognitive function (based on global and specific (DWRT, DSST, WFRT) cognitive function tests). Using visit 2, 4 and 5 cognitive assessment data.
Analysis: using linear regression fitted with a generalized estimating equation (GEE), relevant covariates. We will test the association of SCT with change in cognitive tests over time, following the recommendations from the NCS analysis working group (i.e. including interaction terms time x SCT, using splines for the time variable, adjusting for non-response using Multiple Imputation with Chained Equations).

Finally, we will explore the association of SCT with MRI derived measured of cerebral cortical injury.
Analysis Q3:
Predictor: sickle cell trait status, i.e. SCT vs. non-SCT
Outcome: Brain volume adjusted for intracranial volume, Hippocampal volume, posterior and anterior cortical ROI volume and presence of WMH lesions (counts) – visit 5 MRI
Analysis: Using linear regression model to assess the relationship of SCT status with Hippocampal volume, posterior and anterior cortical ROI volume. Analysis will be adjusted for relevant covariates such as CVD risk factors, age, sex, history of alcohol use, APOE genotyping status (0, 1, or 2 E4 alleles) and addition to baseline self-reported history of CVD. For this analysis, we will use MRI sampling weights in addition to correct for non-participation

All analysis will be adjusted for the first 4 principal components of global genetic ancestry to correct for population substructure/stratification.

We will also test for effect modification by sex, hypertension, diabetes, smoking status, hyperlipidemia/ statin use, atrial fibrillation and CKD (by GFR and albuminuria separately) using stratified models and interaction terms of each of the above with SCT status, using 0.10 to denote statistical significance.

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)?

1. MS 2174 - sickle cell trait and stroke (Caughey), which looks at the association of SCT with stroke, white matter intensities and lacunar infarcts measured at the visit 5 brain MRI
2. MS 2025 - SCT effect on CVD and CVA (Hyacinth)
3. MS 2375 Sickle cell trait and coronary heart disease (Hyacinth)

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

___ 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 ____ No.

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