ARIC Manuscript Proposal #3929

PC Reviewed: 9/14/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Prevalence and outcomes of adult dehydration in individuals with sickle cell trait

b. Abbreviated Title (Length 26 characters): **Adult Dehydration in SCT**

2. Writing Group: Melissa Caughey, Vimal Derebail, Marcus Carden, Gerardo Heiss, Nigel Key, Abhijit Kshirsagar, Enrico Novelli

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

First author: **Melissa Caughey**
Address: UNC / NCSU Dept. of Biomedical Engineering

Phone: (919) 843-1841
E-mail: caughey@med.unc.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: **Gerardo Heiss**
Address: UNC Dept. of Epidemiology
E-mail: gerardo_heiss@unc.edu

3. Timeline: Manuscript to be completed within 1 year of proposal approval

4. Rationale:

Sickle cell trait (SCT) is the heterozygous form of sickle cell anemia and has a birth prevalence of 7-9% in Black Americans.[1] Although the SCT genotype is generally benign, it carries the risk of hemoglobin S polymerization and red blood cell sickling under conditions of hypoxia or extreme exertion.[2–4] Sickle cell nephropathy, thought to be caused by hemoglobin S polymerization in the low oxygen, hypertonic environment of the renal medulla,[5] is observed both with heterozygous and homozygous inheritance of the HbS gene.[6,7] In prospectively analyzed observational cohort studies, SCT has also been associated with incidence of albuminuria, chronic kidney disease, and end-stage renal disease.[8,9] However, less focus has been directed toward hyposthenuria, or the inability to concentrate urine, in individuals with SCT. Further, it is unknown whether SCT increases the risk of chronic dehydration or its associated outcomes.

Several small studies from the 1950s – 1960s reported an age-dependent worsening in urinary concentration ability among individuals with SCT, relative to non-carrier controls.[10–13] Although urine concentration following a 12 hour fluid restriction approached the normal range for very young children with SCT, evidence of hyposthenuria was apparent for all individuals with SCT over the age of 10.[12] Water loss due to urinary concentration defects may be compensated by polydipsia, or increased thirst, and potentially offset by adequate fluid intake. However, under strenuous conditions such as military training or endurance athletics, additional water loss through sweating or elevated respiration may tip the hydration balance for individuals predisposed to hyposthenuria, leading to hypertonicity, or a disproportionate loss of body water relative to sodium and potassium.[14] In laboratory settings, RBCs with hemoglobin S content are observed to sickle when exposed to hypertonic saline solution, both for homozygous (HbSS) and heterozygous (SCT) genotypes.[15] Under physiologically plausible conditions, hypertonic extracellular fluid is also observed to induce water efflux and sickling of hemoglobin S containing RBCs.[16] With water loss, the RBCs shrink and the hemoglobin S molecules become more closely packed together. The close proximity allows polymerization crosslinks and strand formations, which cause the RBC to distort and sickle.

In the general population of healthy adults with access to water, dehydration is thought to be uncommon.[17] With advanced age; however, dehydration may be as prevalent as 20% - 30%, with etiologies related to impaired thirst mechanism, diabetes, renal disease, or dementia. The prevalence of midlife dehydration has not been previously reported, for either the general population or individuals with SCT, nor are its associated long-term outcomes known.

5. Main Hypothesis/Study Questions:

-What is the prevalence of dehydration in middle-aged individuals with SCT? Does it differ from the general population without SCT?
-Do clinical or demographic factors associated with dehydration differ by SCT status?
-Is dehydration in SCT more often described as isotonic, hypertonic, or hypotonic?
-Are laboratory markers of dehydration at midlife associated with future hospitalizations for dehydration, and does risk of hospitalization for dehydration differ by SCT status?
-Is dehydration at midlife associated with early mortality, and if so do adjusted mortality risks differ by SCT status?

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 population: ARIC participants with and without SCT, with available blood analysis at ARIC visit 1

Exclusions:
-Sickle cell anemia (HbSS) or double heterozygosity for HbS and HbC (HbSC disease)
-Participants not fasting at least 8 hours prior to bloodwork

Derived variables;
Plasma osmolality: (2 x serum sodium + BUN / 2.8 + glucose / 18)
Dehydration: plasma osmolality > 295 mOsm/kg
Isotonic dehydration: serum sodium = 130 – 150 mEq/L
Hypotonic dehydration: serum sodium < 130 mEq/L
Hypertonic dehydration: serum sodium >150 mEq/L
Chronic kidney disease: eGFR <60 mL/min/1.73 m^2 using CKD-Epi formula

Hospitalization for dehydration
-ICD-9 discharge codes: 276.x
-ICD-10 discharge codes : E86.x, E87.0

Modeling approach
-Odds ratios of dehydration at ARIC visit 1 comparing SCT to no SCT
Odds ratios by demographic subgroups
Odds ratios by clinical subgroups (CKD, diabetes)
-Hazard ratios of hospitalization for dehydration, associated with laboratory markers at ARIC v1
Modification by SCT status
-Hazard ratios of mortality, associated with laboratory markers of dehydration at ARIC v1
Modification by SCT status

Model adjustments
-Demographics (*e.g.*, age, race, sex, ARIC center)
-Clinical factors (*e.g.*, diabetes mellitus, chronic kidney disease, diuretics use)
-Environmental factors (*e.g.*, cold vs. warm months for dehydration assessment)

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

___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)?

ms #2150 Sickle cell trait and venous thromboembolism.
This work was published in 2014

ms #2174 Is sickle cell trait a risk factor for stroke and cerebral small vessel disease?
This work was published in 2014

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* _____)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

Ancillary study # 2010.16 Sickle cell trait: a risk factor for kidney disease?
We have contacted the lead authors (Abhijit Kshirsagar , Vimal Derebail, and Nigel Key) and are collaborating with them on this proposal.

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.

Bibliography

1. Lorey FW, Arnopp J, Cunningham GC. Distribution of hemoglobinopathy variants by ethnicity in a multiethnic state. *Genet Epidemiol*. 1996;13:501–512.
2. Kark JA, Posey DM, Schumacher HR, Ruehle CJ. Sickle-cell trait as a risk factor for sudden death in physical training. *N Engl J Med*. 1987;317:781–787.
3. Martin TW, Weisman IM, Zeballos RJ, Stephenson SR. Exercise and hypoxia increase sickling in venous blood from an exercising limb in individuals with sickle cell trait. *Am J Med*. 1989;87:48–56.
4. O'Connor FG, Bergeron MF, Cantrell J, Connes P, Harmon KG, Ivy E, Kark J, Klossner D, Lisman P, Meyers BK, O'Brien K, Ohene-Frempong K, Thompson AA, Whitehead J, Deuster PA. ACSM and CHAMP summit on sickle cell trait: mitigating risks for warfighters and athletes. *Med Sci Sports Exerc*. 2012;44:2045–2056.
5. Brezis M, Rosen S. Hypoxia of the Renal Medulla — Its Implications for Disease. *N Engl J Med* 1995;332:647–655. Available from: http://www.nejm.org/doi/10.1056/NEJM199503093321006
6. Nath KA, Hebbel RP. Sickle cell disease: Renal manifestations and mechanisms. *Nat Rev Nephrol*. 2015;11:161–171.
7. Naik RP, Derebail VK. The spectrum of sickle hemoglobin-related nephropathy: from sickle cell disease to sickle trait. *Expert Rev Hematol* 2017;10:1087–1094. Available from: https://doi.org/10.1080/17474086.2017.1395279
8. Naik RP, Derebail VK, Grams ME, Franceschini N, Auer PL, Peloso GM, Young BA, Lettre G, Peralta CA, Katz R, Hyacinth HI, Quarells RC, Grove ML, Bick AG, Fontanillas P, Rich SS, Smith JD, Boerwinkle E, Rosamond WD, Ito K, Lanzkron S, Coresh J, Correa A, Sarto GE, Key NS, Jacobs DR, Kathiresan S, Bibbins-Domingo K, Kshirsagar A V., Wilson JG, Reiner AP. Association of Sickle Cell Trait With Chronic Kidney Disease and Albuminuria in African Americans. *JAMA* 2014;312:2115. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.15063
9. Naik RP, Irvin MR, Judd S, Gutiérrez OM, Zakai NA, Derebail VK, Peralta C, Lewis MR, Zhi D, Arnett D, McClellan W, Wilson JG, Reiner AP, Kopp JB, Winkler CA, Cushman M. Sickle Cell Trait and the Risk of ESRD in Blacks. *J Am Soc Nephrol* 2017;28:2180–2187. Available from: https://jasn.asnjournals.org/lookup/doi/10.1681/ASN.2016101086
10. Keitel HG, Thompson D, Itano HA. HYPOSTHENURIA IN SICKLE CELL ANEMIA: A REVERSIBLE RENAL DEFECT. *J Clin Invest* 1956;35:998–1007. Available from: http://www.jci.org/articles/view/103360
11. SCHLITT L, KEITEL HG. Pathogenesis of hyposthenuria in persons with sickle cell anemia or the sickle cell trait. *Pediatrics* 1960;26:249–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14442907

12. Francis YF, Worthen HG. Hyposthenuria in sickle cell disease. *J Natl Med Assoc* 1968;60:266–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5661193

13. COCHRAN RT. Hyposthenuria in Sickle Cell States. *Arch Intern Med* 1963;112:222. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.1963.03860020120016

14. Bhave G, Neilson EG. Volume Depletion versus Dehydration: How Understanding the Difference Can Guide Therapy. *Am J Kidney Dis*. 2011;58:302–309.

15. Perillie PE, Epstein FH. SICKLING PHENOMENON PRODUCED BY HYPERTONIC SOLUTIONS: A POSSIBLE EXPLANATION FOR THE HYPOSTHENURIA OF SICKLEMIA*. *J Clin Invest* 1963;42:570–580. Available from: http://www.jci.org/articles/view/104746

16. Carden MA, Fay ME, Lu X, Mannino RG, Sakurai Y, Ciciliano JC, Hansen CE, Chonat S, Joiner CH, Wood DK, Lam WA. Extracellular fluid tonicity impacts sickle red blood cell deformability and adhesion. *Blood*. 2017;130:2654–2663.

17. Taylor K, Jones EB. Adult Dehydration 2021. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32310416