ARIC Manuscript Proposal # 3419

PC Reviewed: 6/18/19  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Assessment of pathways associated with low dehydroepiandrosterone sulfate levels in old adults using aptamer-based proteomics – Atherosclerosis Risk in Community Study

b. Abbreviated Title (Length 26 characters): Proteomics of low DHEA-S

2. Writing Group:
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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]

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3. Timeline: Analysis is anticipated to begin as soon as approval is obtained. The manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation is anticipated to take place within one year of approval of the proposal.

4. Rationale:
Circulating dehydroepiandrosterone (DHEA) and its sulfate, DHEA-S, decline with age and low DHEA/DHEA-S levels have been shown to be associated with cardiometabolic disease and mortality in older adults (1-3). In our ongoing study (MSP#3366), we have found that in older men and women, there appears to be a threshold of very low DHEA-S level below which individuals have increased risk for heart failure (HF) hospitalization and all-cause death over long-term follow-up. Moreover, in individuals without prevalent cardiovascular disease, very low levels of DHEA-S were also associated with higher levels of biomarkers indicative of subclinical myocardial injury (i.e. higher high sensitivity troponin T and N terminal proB-type natriuretic peptide) on cross-sectional analyses. Our findings suggest a potential insufficiency state in DHEA-S in some individuals with older age that may impact cardiovascular health, though the mechanism is currently unclear.

HF has become increasingly common with the aging population and carries a significant burden of morbidity and mortality. Very low DHEA-S levels appear to be a risk marker independent of traditional risk factors for heart failure. Therefore, a better understanding of the mechanism leading to very low levels of DHEA-S may be important in elucidating new strategies and targets in the risk assessment and management of HF. In this study, we aim to leverage the SomaLogic proteomics dataset from ARIC to identify proteins and pathways associated with DHEA-S levels in older adults. Moreover, while DHEA-S levels are thought to decrease with age in general, we and others have shown previously that there is a high degree of heterogeneity in change in DHEA-S level during aging. Therefore, we further propose to examine the proteomics signature associated with change in DHEA-S levels with advancing age.

5. Main Hypothesis/Study Questions:
There are unique proteomic signatures associated with very low concentration of DHEA-S in older adults and with significant decreases in DHEA-S level with aging.

1. What are the proteomic signature associated with circulating DHEA-S level?

2. What is the proteomic signature associated with a very low DHEA-S level (below the 15th percentile sex specific cutpoint of the study population)?

3. What are the proteomic signature associated with change in DHEA-S level over time?

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 methodological limitations or challenges if present).

Study Design:
For study questions 1 and 2, we will employ a cross-sectional design with ARIC visit 5 as the index visit. Individuals without prevalent cardiovascular disease (CVD: coronary heart disease, ischemic stroke or HF hospitalization) at the time of ARIC visit 5 and who had DHEA-S level measured at visit 5 will be included.

For analyses involving the change in DHEA-S levels, individuals without prevalent CVD at the time of visit 5 who had both measurements of DHEA-S at visits 4 and 5 will be included.

Sex mismatched samples (n=81) in the SOMAScan proteomics data will be excluded.

Exposures:
We will use proteomic data from SOMAScan v.4 obtained from ARIC visit 5. SOMAScan v.4 includes 4,931 serum proteins.

Outcomes:
1. Visit 5 DHEA-S level as a continuous variable.

2. Visit 5 DHEA-S level categorized as ≥ and < 15th percentile sex specific cutpoint.

3. Absolute and percent change in DHEA-S concentrations from visit 4 to visit 5 categorized into quartiles.

Covariates:
Age, race-center, total cholesterol, HDL cholesterol, systolic blood pressure, use of hypertensive medication, current smoking, diabetes status, body mass index, use of lipid lower medication, eGFR, testosterone, SHBG, use of hormone replacement therapy
**Statistical Analysis:**
*Analyses will be performed for men and women separately.*

**Association between circulating protein measures with DHEA-S concentration:**
1. Linear regression for continuous outcomes
2. Logistic regression for dichotomous outcomes
3. Regularized regression using Elastic Net

**Pathway Analyses:**
1. Targeted assessment of protein associations to known biomarkers for aging: GDF8, GDF11, GDF15, C1Q, Klotho, etc.
2. Causal pathway analyses using Ingenuity Pathway Analysis.

**Significance:** Proteome-wide significance will be defined based on a Bonferroni-corrected p-value of 9.46e-6.

**Sensitivity Analysis:**
- Interaction testing between the SOMAScan proteins with age (≥ vs < the median age) and race (white vs black).
- Stratified analyses by age and race.
- SOMAScan flagged proteins: Some proteins have been flagged by SOMALogic based on analytic performance. Sensitivity analyses will be performed including proteins with differing levels of “allowable” flagging by the SOMAScan system.

**Limitations:**
1. We acknowledge that both DHEA-S and other serum proteins measured by the SOMAScan may be influenced by the natural aging process, which may potentially confound any associations between proteins and DHEA-S levels that are found. We will be adjusting for age in our regression models. In addition, we will also test for interaction and stratify by age as part of our analyses.
2. In the change analyses, we are assessing association of SOMAScan proteins at the end of the change period (visit 5) rather than at the beginning (visit 4) as visit 4 proteomics data for this cohort is currently not available. This may make interpretation of the relationships between serum proteins/pathways and change in DHEA-S levels more difficult.
3. There is currently a lack of cortisol, ACTH stimulation test available for the entire ARIC study population. Therefore, the standardize methodology of determining adrenal insufficiency is not available to directly answer the question of whether very low DHEA-S is reflective of an adrenal insufficiency state in the elderly. However, we hope that leveraging proteomics analyses using the Soma Logic assay will shed light on relevant proteins and pathways associated with low DHEA-S concentration and how this is related to increased risk for HF events.
4. Cross sectional design does not allow assessment of temporal relationship between exposure and outcome.
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

_____ 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)?

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study *
___ 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