December 22, 2016

Josef Coresh
ARIC Publications Committee

Dear Dr. Coresh,

The following is a point by point response to your comments regarding ARIC manuscript proposal #2911.

Comment 1. Can you clarify the sample size of individuals with hormone data?

Response:

The hormone data is available in the following number of participants (from Visit 4):

Testosterone:	**10,666**
DHEAS:	**10,659**
SHGB:	**10,593**

My proposal lists the approximate number of participants that will be included in my analysis: "All analyses will be stratified by sex/HRT status [postmenopausal women not taking HRT (N≈3,897), postmenopausal women taking HRT (N≈2,392), and men (N≈5,019)]."

Comment 2. We were not clear of the source of the data – is this a recent ancillary study initiated at Baylor (2013.21) or another study? Ancillary study 2006.16 mentioned in the proposal. Is Brad Astor's study with visit 4 assays but I do not recall measurements of hormones in that study.

Response:

This is data from ancillary study 2013.21. In the attached, updated version of the manuscript proposal, I have additionally listed 2013.21 in section 11.b.

Sincerely,

Nick Roetker, MPH
PhD Student in Epidemiology
University of Minnesota

ARIC Manuscript Proposal #2911

PC Reviewed: 12/15/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Prospective study of endogenous hormones and incidence of venous thromboembolism

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members:

Nicholas Roetker
Richard MacLehose
Ron Hoogeveen
Christie Ballantyne
Saonli Basu
Mary Cushman
Aaron Folsom

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

First author: **Nicholas Roetker**
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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).

Name: **Aaron Folsom**
Address: Division of Epidemiology and Community Health
University of Minnesota
1300 South Second Street, Suite 300
Minneapolis, MN 55454

Phone: 612-626-8862 Fax: 612-624-0315
E-mail: folso001@umn.edu

3. Timeline:

We anticipate a draft ready to submit for Publications Committee Review in spring 2017.

4. Rationale:

Exogenous female steroid hormones, including oral contraceptives and hormone replacement therapy, are established risk factors for venous thromboembolism (VTE) in women.[1] Whether endogenous levels of other steroid hormones such as dehydroepiandrosterone sulfate (DHEAS) and testosterone or steroid hormone regulators such as sex hormone-binding globulin (SHBG) are related to VTE risk is incompletely studied.

Testosterone is the principal male hormone (i.e., androgen) and decreases gradually with age,[2] and men with lower testosterone have higher risk of all-cause mortality.[3] DHEAS is an inactive precursor of DHEA, which subsequently gets converted into active sex steroids in peripheral tissues.[4,5] Although its physiological function is not completely understood,[4] DHEAS levels decline sharply with increasing age, leading to a decrease in peripheral levels of androgens and estrogens,[5] and low DHEAS is also associated with higher risk of all-cause mortality in men.[6] Studies in women have shown that endogenous levels of testosterone and DHEAS may be associated with the coagulation factor fibrinogen and fibrolytic markers.[7–9] Given that the incidence of VTE rises substantially with age (0.5–1 cases per 1,000 person-years before midlife compared to 5–7 cases per 1,000 person-years by age 80[10]) and the possible connection of testosterone and DHEAS with hemostatic factors, endogenous testosterone and DHEAS should be studied as potential risk factors for VTE. Two prospective studies found no evidence of an association of plasma testosterone with VTE risk in men and women,[11,12] but exploring this association further in another study population could be useful.

SHBG is a plasma glycoprotein that binds with high affinity to biologically active androgens (e.g., testosterone but not DHEA) and estrogens, thus transporting and regulating the bioavailability of these hormones.[13] SHBG levels increase with age in men, although prospective, population-based studies in men (and women) have not shown SHBG to be associated with mortality.[14,15] However, studies have reported associations of SHBG with a number of coagulation factors and fibrolytic markers in women.[7,8] As such, SHBG should be studied as a potential risk factor for VTE. One very small case-control study in women found a possible association between elevated plasma SHBG and VTE (OR: 1.92, 95% CI: 0.74, 5.00), but SNPs related to SHBG levels were not associated with VTE, suggesting that the observed association was confounded.[16] Additional studies examining the association between SHBG and VTE risk are needed.

5. Main Hypothesis/Study Questions:

Lower DHEAS and testosterone and higher SHBG are associated with higher risk of VTE in both women and men.

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: prospective with baseline at Visit 4 (1996-98)

Endpoints: VTE incidence

Exposures: plasma DHEAS, testosterone, and SHBG

Exclusions: prevalent VTE or use of anticoagulants at baseline (visit 4), cancer by visit 4, missing plasma hormone measures, missing data on HRT, premenopausal women at visit 4, men taking estrogen or testosterone, racial/ethnic group other than white or black.

Covariates: age, sex, race, HRT, BMI, smoking, diabetes, eGFR

Analysis: All analyses will be stratified by sex/HRT status [postmenopausal women not taking HRT (N≈3,897), postmenopausal women taking HRT (N≈2,392), and men (N≈5,019)]. First we will examine associations of each hormone exposure with covariates. Then we will use linear splines to model the relationship of hormone exposures with risk of VTE and estimate hazard ratios using Cox proportional hazards models.

If we find an association for DHEAS, we will use CHS (measured in ≈N=4,000) as a replication sample.

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.)

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___x___ Yes _____ No

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- MS# 748 (Endogenous hormones and atherosclerosis; submitted by Sherita Hill Golden)

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11.b. If yes, is the proposal

_x__ A. primarily the result of an ancillary study (list number* 2006.16 and 2013.21)

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*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

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

First author: **Nicholas Roetker**
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