ARIC Manuscript Proposal # 3199

PC Reviewed: 7/10/18  Status: ____  Priority: 2
SC Reviewed: _________  Status: ____  Priority: ____

1.a. Full Title:
Endogenous Sex Hormones and Cognitive Decline among Men and Post-Menopausal Women in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Sex Hormones and Cognitive Decline

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:
Analyses will be performed over Summer/Fall 2018. Abstract is planned for December 2018 submission to AGS 2019 meeting and full manuscript draft by June 2019.

4. Rationale:

Cognitive decline and dementia are major concerns in increasing aging populations. The Atherosclerosis Risk in Communities Study (ARIC) previously demonstrated that the prevalence of dementia and mild cognitive impairment (MCI) was 9% and 21%, respectively, at ARIC visit 5, which was similar to the prevalence found in other populations. (1) Knopman et al. reported that prevalence of dementia and MCI increased with advancing age and that there were differences in prevalence between men and women. Men had higher prevalence of MCI (p<0.001); whereas women had higher prevalence of dementia, but the difference was not statistically significant. (1) While sex differences in cognitive function have been documented in other studies, mechanisms behind differences in cognitive decline in men and women are not well elucidated. (2, 3)

Traditional vascular risk factors that are present in mid-life have been associated with increased risk for later life cognitive decline and dementia risk. (4-6) Conversely, ideal cardiovascular health in mid-life is associated with lower risk. (7-9) However, given the burden of cognitive decline in older adults, there still remains a need to identify novel contributors to cognitive decline/dementia risk, as well as further understanding of sex differences, in order to guide future preventive strategies for both men and women.

Endogenous sex hormone levels, particularly higher androgen levels in post-menopausal women, might be a potential factor associated with cognitive decline. We have recently shown that among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA), that a more androgenic sex hormone profile, particularly higher testosterone/estradiol ratio and higher testosterone levels, were associated with a more adverse cardiovascular risk profile and with increased risk for incident cardiovascular disease (CVD), coronary heart disease (CHD), and heart failure (HF) events over 12-years of follow-up. (10) Among men, the opposite pattern has been seen. Prior epidemiological studies have shown that lower testosterone levels are associated with worse CVD and HF outcomes, as well as worse functional capacity, (11, 12) suggesting that low testosterone may be a marker of a poorer health state in men.

Prior studies have suggested that endogenous sex hormones, estrogens and androgens, may play a role in cognitive function as well; however their roles in age-related changes and sex-related differences remain uncertain. (13-16) In the Melbourne Women's Midlife Health Project, among post-menopausal women (N=148, mean age=60 years), higher estradiol levels and lower ratio of testosterone to estradiol were associated with better semantic memory performance in a 2-year follow-up. (16) This suggests that a more androgenic and less estrogenic pattern of sex hormones may adversely affect cognitive function. However this study was limited by small sample size, inclusion of only women, lack of diversity of study population, and short follow-up time.

Sex hormone binding globulin (SHBG) is a testosterone transport protein; higher levels of SHBG indicate lower levels of free testosterone for a given total testosterone level. Higher levels of SHBG levels have been shown to be associated with worse verbal memory in older men free of
dementia. In a prospective cohort (N=731, mean age 77 years), Muller et al. found that higher levels of endogenous SHBG was associated with Alzheimer’s Disease in elderly men and women.

There is even more paucity of data regarding interventional trials of hormone therapy. In the DHEA and Well-Ness (DAWN) Trial, supplementation of dehydroepiandrosterone (DHEA), an endogenous sex steroid and biosynthetic precursor to estrogen and androgen, resulted in no benefit in cognitive function after 1 year. The DAWN participants (N=110 men, N=115 women, ages 55-85 years) were not selected based upon endogenous DHEA levels and were treated with 50 mg per day of supplemented DHEA. Thus, the effects of low levels of endogenous DHEA and age-related changes in cognition remain unclear despite clinical trials of supplemented DHEA.

In sum, there is a need to better understand the role of endogenous sex hormones in mid-life with late-life cognitive performance and dementia risk; such information could provide insight into prevention strategies as well as the assessment of future cognitive risk. The ARIC cohort is well suited to investigate this relationship of endogenous sex hormones with cognitive decline. We propose to examine whether endogenous sex hormones measured in late midlife (at ARIC visit 4) are associated with later life dementia and cognitive decline among men and post-menopausal women in ARIC, which provides a large biracial cohort with a long follow up (20 years between Visit 4 and Visit 6), with robust adjustment for confounding factors.

5. Main Hypotheses/Study Questions:

Longitudinal study: To determine whether increased androgens (total testosterone, testosterone/SHBG ratio, and DHEA) are associated with cognitive change over a 20-year follow up (ARIC visit 4 to ARIC visit 6) and incident risk of adjudicated dementia over this same period

Hypotheses:
1. Elevated levels of androgens (total testosterone, testosterone/SHBG ratio, and DHEA) will be associated with greater cognitive decline and with incident dementia risk over 20-year follow up in post-menopausal women.
2. Conversely, in men higher androgens (testosterone and DHEA) will be associated with less cognitive decline and lower risk for incident dementia.

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 Design: The baseline of our analyses will be ARIC Visit 4, the first time sex hormones were measured in the whole cohort (plasma total testosterone, DHEA, and SHBG). Estradiol was not measured in the full cohort and will not be included in this analysis. Study design will be cross-sectional (ARIC Visit 4, 1996-1998) and longitudinal (ARIC Visit 4: 1996-1998 through ARIC visit 6: 2016-2017).
Participants:
All participants with measured sex hormones and cognitive testing from ARIC Visit 4 will be included. We will exclude participants with prevalent dementia and stroke that occurred before ARIC visit 4, participants who are neither white nor black, black participants from the Minnesota and Washington County field centers, and pre-menopausal women. There were 4093 men and 3131 post-menopausal women enrolled in the ARIC Study who had sex hormones [total testosterone, DHEA and SHBG] measured at Visit 4 (1996-98).

In sensitivity analyses we will exclude women currently taking hormone therapy (HT).

Sex Hormone Ascertainment:

Sex hormone levels were measured from blood samples obtained from participants at Visit 4 (1996-1998). Blood samples were obtained in the morning and plasma was stored at -80° C. SHBG and DHEA were measured from the same plasma samples, and plasma total testosterone was measured in 2012, by liquid chromatography mass spectrometry.

Albumin was not available at visit 4 to calculate bioavailable and free testosterone levels. However since total testosterone is bound only loosely to albumin (i.e. bioavailable) but tightly bound to SHBG (not bioavailable), we will examine the total testosterone/SHBG ratio as a surrogate for bioavailable testosterone.

Covariates:

Demographic factors: age, sex, race/field center

Socioeconomic and lifestyle factors: education, smoking, alcohol consumption, physical activity, body mass index (BMI)

Cardiovascular health factors: systolic blood pressure (SBP), use of antihypertensive medications, diabetes, estimated glomerular filtration rate (eGFR), total cholesterol, HDL-cholesterol, use of lipid-lowering medications, and prevalent coronary heart disease (CHD)

Hormonal factors (women): Use of hormone therapy and years since menopause

Genetic factors: APO e4 genotype

All covariates will be from ARIC Visit 4 except as noted: Educational status will be derived from Visit 1, APO e4 from Visit 2, and physical activity from Visit 3.

Outcome Ascertainment:

Cognitive function will be analyzed using a composite global z-score of three cognitive function tests: Delayed Word Recall Test (DWR), Digit Symbol Substitution Test (DSS), and Word
Fluency Test (WFT).(21) We will use cognitive data measured at ARIC Visit 4 (the baseline for the present analysis), Visit 5, and Visit 6.

We will also evaluate incident dementia, following the ARIC standardized algorithms.(1) Dementia was ascertained using a variety of methods in ARIC.(4, 22) First, participants who were present at the ARIC-NCS (Visit 5) had dementia adjudicated by an expert committee of eight clinicians including four physicians and four neuropsychologists.(22) Second, dementia was also adjudicated using predefined criteria for participants who were alive at visit 5 but did not attend the visit, those who were deceased, and a random sample of participants by using the Telephone Interview for Cognitive Status–Modified (TICSm) or informant telephone interviews using a modified version of the Clinical Dementia Rating (CDR) scale and the Functional Activities Questionnaire.(22) Lastly, dementia was ascertained using prior discharge records using ICD-9 codes or death certificate codes for dementia (290.0, 290.1, 290.2, 290.3, 290.4, 290.9, 294.1, 294.2, 294.8, 294.9, 331.0, 331.1, 331.2, 331.8, 331.9).(4, 22, 23)

Statistical analysis:

Sex hormone levels will be modeled as log transformed continuous variables (per 1 SD) or as categorical variables (tertiles) due to the skewed distribution. Analyses will be performed for testosterone, DHEA, SHBG, testosterone/ SHBG ratio. All analyses will be stratified by sex.

Our primary outcome will be a global Z-score, calculated as the average of these 3 individual Z-scores (DWR, DSS, WFT) at each study visit and standardized using the visit 4 global Z-score mean and standard deviation (SD).

We will use multivariable adjusted linear mixed effects models with random intercepts and slopes to determine the longitudinal (20-year change) association of sex hormones with cognitive outcomes (the global Z-score, and the individual Z-scores for DWR, DSS, WFT).

We will also use multivariable adjusted Cox proportional hazard regression to estimate the hazard ratios (HR) and 95% confidence interval (95% CI) between sex hormones at visit 4 and incident dementia over entire follow-up.

These sex-stratified models will be progressively adjusted as follows:

Model 1: will adjust for age and race/field center

Model 2: will additionally adjust for education, BMI, smoking status, current alcohol use, and physical activity

Model 3: will additionally adjust for SBP, antihypertensive meds, total and HDL-cholesterol, lipid-lowering medications, diabetes, prevalent CHD, and eGFR

Model 4: will additionally adjust for APO e4

Sensitivity analysis:
We will exclude women taking hormone therapy.

We will perform both a complete case analysis, as well as use multiple imputations by chained equations (MICE)(24) methods to account for missing data, imputing for both missing cardiovascular risk factors variables (in model 3) and missing outcomes (for those who did not return for Visits 5/6).

Mild cognitive impairment (MCI) was assessed as visit 6. As an alternative outcome, we will also consider a non-concurrent cross-sectional analysis of sex hormones measured in mid-life (visit 4) with late life mild cognitive impairment (MCI) at visit 6. For this analysis we would use multivariable-adjusted logistic regression.

7.a. Will the data be used for non-CVD analysis in this manuscript?  _X_ Yes   ____ No

Yes – This is cognitive research, but we believe that this is directly related to CVD risk factors and cardiovascular health.

b. If Yes, is the author aware that the file ICTDER02 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

8.a. Will the DNA data be used in this manuscript?  _X_ Yes   __ No

We will include APO e4 genotype status on our Model 4 for the participants included.

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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.csecc.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)?

ARIC Manuscript Proposal #3064 (Subramanya): Endogenous Sex Hormone Levels and Risk for Incident Heart Failure Among Men and Post-Menopausal Women: The Atherosclerosis Risk in Communities Study.

- This is another proposal from our group. The outcome in #3064 is HF not dementia. Thus there is no overlap. Dr. Subramanya is included as a co-author on the current proposal
ARIC Manuscript Proposal #2923 (Berger): Prospective study of the association between endogenous testosterone and incidence of atrial fibrillation

- The outcome for #2923 is Afib, not dementia. Thus there is no overlap. Both Dr. Michos and Dr. Ballatyne are co-authors on this proposal.

There are numerous other ARIC proposals related to cognitive decline, but none of them are examining the relationship of sex hormones with cognitive decline.

ARIC Manuscript Proposal #3091 (DiBiase): gravidity and parity and cognitive function. Our proposal is not examining gravity and parity, so there is no overlap.

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)* __________ __________ __________)

   AS #2013-21. Led by Dr Christie Ballantyne and Dr Ron C. Hoogeveen, includes all ARIC participants at visit 4. Dr. Ballantyne and Dr. Hoogeveen are included as co-authors on this current proposal.

ARIC-NCS # 2008.06

12. 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.

   Understood

REFERENCES


