ARIC Manuscript Proposal #3475

PC Reviewed: 9/10/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Factors predicting optimum testosterone levels in men: The Androgens In Men Study.

b. Abbreviated Title (Length 26 characters): AIMS paper 1

2. Writing Group:

Writing group members: Bu Yeap (UWA), Kevin Murray (UWA), Ross Marriott (UWA), Christie Ballantyne (ARIC), David Couper (ARIC), Adrian Dobs (ARIC), authors from each of the other AIMS cohort studies. Order to be later determined.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____

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3. Timeline:

Task	2019							2020				
	J	J	A	S	O	N	D	J	F	M	A	M
Data applications & transfer to UWA	X	X	X	X								
Harmonisation of datasets		X	X	X								
AIMS paper 1 analyses			X	X	X							
AIMS paper 1 drafting				X	X	X						
Submit to ARIC Steering Committee for review and approval (paper 1 of 4)							X					

Notes:

- Funding for the position of project manager and statistician presently exists until 20 May 2020.
- Four meta-analysis papers are planned for the AIMS project, plus an additional protocol article for the project. Remaining time is to be spent on these other papers.
- Harmonisation and analysis scripting tasks will commence whilst waiting for remaining IPD datasets from the other component studies.

4. Rationale:

Low testosterone concentrations are associated with a range of poorer health outcomes in older men,[1-5] but whether it is a biomarker for underlying ill-health or a causal factor for disease remains unclear.

Currently, testosterone treatment is recommended for men who have symptoms and signs of androgen deficiency and low testosterone concentrations, due to disease of the hypothalamus, pituitary or testes (organic or pathological hypogonadism).[6-9] Randomised controlled trials of testosterone treatment in older men with low-normal testosterone concentrations without organic hypogonadism have shown modest benefits on sexual function, anaemia and bone density, but not on cognition over 12 months.[10-14] The effect of testosterone on the cardiovascular system remains unclear.[15, 16] However, the selection criteria of these trials was such that the screening to enrolment ratio was 65:1, a highly selected population of older men.[10, 11, 16] Importantly, the trials were underpowered for outcomes of cardiovascular events, incidence of dementia or fracture, and for mortality risk.[16]

Therefore, an international collaboration of prospective cohort studies examining the associations of sex hormones with these outcomes will clarify the influence of sex hormone exposures on key health outcomes in men, provide information on lifestyle measures that maintain endogenous testosterone production and identify the scope and optimal recruitment criteria for future trials of testosterone therapy. These data will also allow reference ranges for testosterone in men across ages to be refined to inform recommendations for clinical practice.

References cited:

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2. Yeap BB, Alfonso H, Chubb SAP, Handelsman DJ, Hankey GJ, Almeida OP, et al. In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. J Clin Endocrinol Metab. 2014;99(1):E9-E18.
3. Yeap BB, Alfonso H, Chubb SAP, Hankey GJ, Handelsman DJ, Golledge J, et al. In older men, higher plasma testosterone or dihydrotestosterone is an independent predictor for reduced incidence of stroke but not myocardial infarction. J Clin Endocrinol Metab. 2014;99(12):4565-73.
4. Ford AH, Yeap BB, Flicker L, Hankey GJ, Chubb SAP, Handelsman DJ, et al. Prospective longitudinal study of testosterone and incident depression in older men: The Health In Men Study. Psychoneuroendocrinol. 2016;64:57-65.
5. Ford AH, Yeap BB, Flicker L, Hankey GJ, Chubb SAP, Golledge J, et al. Sex hormones and incident dementia in older men: The health in men study. Psychoneuroendocrinol. 2018;98:139-47.
6. Yeap BB, Grossmann M, McLachlan RI, Handelsman DJ, Wittert GA, Conway AJ, et al. Endocrine Society of Australia position statement on male hypogonadism (part 2): treatment and therapeutic considerations. Med J Aust. 2016;205:228-31.
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8. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society* Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(5):1715-44.
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10. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. N Engl J Med. 2016;374:611-24.
11. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Lessons from the testosterone trials. Endocr Rev. 2018;39:369-86.
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13. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, Ellenberg SS, Cauley JA, Ensrud KE, et al. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: A controlled clinical trial. JAMA Intern Med. 2017;177:471-9.
14. Resnick SM, Matsumoto AM, Stephens-Shields AJ, Ellenberg SS, Gill TM, Shumaker SA, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA. 2017;317:717-27.
15. Budoff M, Ellenberg SS, Lewis CE, Mohler ERI, Wenger NK, Bhasin S, et al. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. JAMA. 2017;317:708-16.
16. Yeap BB, Page ST, Grossmann M. Testosterone treatment in older men: clinical implications and unresolved questions from the Testosterone Trials. Lancet Diabetes Endocrinol. 2018;6:659-72.

5. Main Hypothesis/Study Questions:

The objective of this first manuscript is to investigate factors predicting optimal testosterone levels in men. Defining optimal testosterone concentrations in men will involve consideration of age plus other key risk factors for disease. Accordingly, the hypothesis is specific to an IPD meta-analysis cross-sectional investigation of previously identified associations between endogenous testosterone concentration and key social, demographic, lifestyle, and health factors, for the purpose of clarifying the nature of these associations. (Subsequent proposed

investigations will focus on associations between endogenous testosterone and risk of incident health outcomes in men: cardiovascular events/diagnoses, cancers, cognitive decline, dementia).

Hypothesis:

There is an (are) independent association(s) between endogenous testosterone concentration in men and variable(s) representing key social, demographic, lifestyle and health factors (e.g., participant age, marital status, BMI, physical activity, medical conditions and medications).

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.

- Prospective cohort study.
- Paper 1 will analyse variables collected at baseline (date of entry into the cohort: see below).

Inclusion/exclusion criteria.

Males with androgen concentrations measured using mass spectrometry who, at baseline (time of blood sample collection for testosterone assay: 1996-98):

- were not taking androgens
- were not taking anti-androgen medications
- with no prior orchidectomy.

Outcome variables

- Androgen concentration in serum/plasma samples, as measured using mass spectrometry.
- Androgens will include total testosterone, and, if available, Sex Hormone Binding Globulin (SHBG), estradiol, luteinizing hormone (LH)
- Note: Outcomes for the subsequent planned papers 2-4 are of incident events using follow-up time-to-event data, namely: diagnoses of cardiovascular disease, cardiovascular deaths, all-cause deaths (Paper 2); deaths from cancer (Paper 3); diagnoses of cognitive impairment and dementia (Paper 4). Separate Manuscript Proposals for these papers will be subsequently submitted. Similar covariates, as listed in this proposal, are planned for inclusion in those papers.

Other variables

- Known risk factors, confounders, structural, and identifier variables for IPD data
- Paper 1 will analyse data collected at baseline (time of blood sample collection for testosterone assay: 1996-98), which is the date of entry into the cohort (follow-up data to be analysed in Papers 2 to 4). The baseline date for each individual is the date at which serum/plasma samples for assaying androgen levels were taken (Visit 4 1996-98).

- Variables will include: Person ID, Date, Site, ethnicity, marital status, age, body mass index, smoking status, alcohol consumption, blood pressure, hypertension (yes/no based on clinician assessment, absolute BP measures, or self-report of prior medical assessment), physical activity level (from Visit 3 1993-95, as not available from Visit 4), education level, self-reported (general) health.

Data analysis

- One-stage IPD random-effects meta-analysis.
- Linear models (LMs) or Generalised Linear Models (GLMs) will be used to model the relationships between the covariates (independent variables) and hormone variables (dependent variable).
- Suspected non-linear relationships, at the scale of the linear predictor, will be investigated and modelled appropriately (e.g., splines with pre-set knot locations and linear boundary constraints). Suitable measures of effect size will be presented.
- Contour-enhanced funnel plots will be constructed to visually assess patterns in estimates of effect sizes and precision among studies and possible selection bias and/or publication bias.
- The relative amount of heterogeneity will be estimated and forest plots presented. Subgroup or meta-regression analyses may be conducted if pronounced heterogeneity is estimated.

Complexities

- IPD level data are not available from all component studies, so aggregate level data will be sought from at least one additional study, and any others identified from systematic review. Aggregate-level data will be formally incorporated into the meta-analysis and compared against the IPD-level only meta-analysis to assess/evaluate potential biases in estimates.

- Harmonization for some variables where recorded differently by the different component studies (e.g., physical activity, alcohol consumption). The project manager is requesting data for some of these variables in multiple formats, which might help facilitate harmonization in these circumstances.

7.a. Will the data be used for non-CVD analysis in this manuscript? _✓_ Yes ____ 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 _✓_ 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/mantrack/maintain/search/dtSearch.html

   _____ Yes ___✓__ No

   Three published papers (PMID: 25584720, 27729576, 31133217) looked at the association of measured testosterone level at baseline with incident risk of cardiovascular outcomes, which is similar to AIMS planned paper 2 (not this proposal, which is for paper 1 only). A point of difference with the planned articles for the AIMS project is that they are IPD meta-analyses that incorporate data from multiple component studies, including the ARIC study. Accordingly, the planned AIMS papers will complement the above-listed articles, but with a much broader scope of inference (i.e., none of the other overlapping ARIC studies are IPD meta-analyses).

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 (list number* _____)

_✓_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* AS #2013.21**)**

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.