PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Systematic review and meta-analyses on associations of endogenous testosterone concentration with health outcomes in community-dwelling men.
AUTHORS	Marriott, Ross; Harse, Janis; Murray, Kevin; Yeap, Bu

VERSION 1 – REVIEW

REVIEWER	Bigaran, Ashley Australian Catholic University, Mary Mackillop Institute for Health Research
REVIEW RETURNED	06-Mar-2021

GENERAL COMMENTS	The authors should be commended on this comprehensive systematic review and large individual participant meta-analysis of studies to clarify the relationship between endogenous sex hormones, specifically testosterone on incident all-cause deaths, and cardiovascular specific death in community-dwelling men. The authors only included prospective cohort studies using the gold standard method of mass spectrometry to assess testosterone. The methodology and meta-analysis appear sound and mostly aligns with the published protocol. The included data tables, forest plots, funnel plots and appropriate assessment of heterogeneity and bias supports this paper well. A possible addition to the discussion would be a section on the clinical implications of these findings. A few comments requiring further clarification: • Introduction – At present, the introduction is too brief and provides limited context of problem associated with declining testosterone in community-dwelling men. While the published protocol provides an excellent overview of the present issue, the introduction of this systematic review and meta-analysis should further elaborate on the broader health consequences associated with declining testosterone in the aging male and its potential relationship with the selected outcomes of all-cause mortality and cardiovascular death investigated in this review. • Line 82 – 'Too low' is too vague to describe hypogonadism. Please consider an alternative • Line 99 – The sub-group IPD meta-analyses for heart failure, myocardial infarction, stroke, colorectal cancer, lung cancer and prostate cancer were not included in this review. While I understand the analyses focused on the most frequently documented outcomes of all-cause death, and cardiovascular deaths, succinct characterizations of all papers included in this review (and outcomes outlined in the protocol) would be of interest. • Line 175 onwards – please include the associated citations for each study. • Supplementary material - Table S6 - Please add an abbreviations

	section to the bottom of Table S6, detailing all of the abbreviated words reported within the table.

REVIEWER	Li, Hongjun Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Department of Urology
REVIEW RETURNED	30-Mar-2021

GENERAL COMMENTS	The research is of important and interesting, but “Conclusions” (did not demonstrate associations of endogenous testosterone with CVD deaths or with all-cause mortality) was seemingly differ from other researches. This should be discussed carefully, and many sub-conclusions can be different from present total conclusion, due to many unadjusted factors and significant heterogeneity can interfere with the final conclusions. 5 years of follow-up data and testosterone monitoring was not long enough to judge the effectiveness of endogenous testosterone on the development of cardiovascular disease (CVD) events, all-cause mortality, cognitive decline, dementia, etc. The title (Systematic review: the Androgens In Men Study) is too broad and not proper. “Meta-analyses” and “adult men in the general community” should be included in title at least. The concept “endogenous testosterone” should be given more detailed definition and discussion, because testosterone exist in many different status including free-T, bio-available-T, SHBG-binding T..

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	Response
1. The authors should be commended on this comprehensive systematic review and large individual participant meta-analysis of studies to clarify the relationship between endogenous sex hormones, specifically testosterone on incident all-cause deaths, and cardiovascular specific death in community-dwelling men. The authors only included prospective cohort studies using the gold standard method of mass spectrometry to assess testosterone. The methodology and meta-analysis appear sound and mostly aligns with the published protocol. The included data tables, forest plots, funnel plots and appropriate assessment of heterogeneity and bias supports this paper well. A possible addition to the discussion would be a section on the clinical implications of these findings.	We thank the reviewer for these comments. Addressed: We have inserted one paragraph in the Discussion (lines 382-392) on clinical implications and to carefully discuss how our findings should be regarded.
2. Introduction – At present, the introduction is too brief and provides limited context of problem associated with declining testosterone in community-dwelling men. While the published protocol provides an excellent overview of the present issue, the introduction of this systematic review and meta-analysis should further elaborate on the broader health consequences associated with declining testosterone in the aging male and its potential	Addressed: The Introduction has been revised accordingly (lines 87-99).

Comment	Response
relationship with the selected outcomes of all-cause mortality and cardiovascular death investigated in this review.	
3. Line 82 – 'Too low' is too vague to describe hypogonadism. Please consider an alternative	Addressed: This sentence was removed in the revision to the Introduction section to address Reviewer 1 Comment 2.
4. Line 99 – The sub-group IPD meta-analyses for heart failure, myocardial infarction, stroke, colorectal cancer, lung cancer and prostate cancer were not included in this review. While I understand the analyses focused on the most frequently documented outcomes of all-cause death, and cardiovascular deaths, succinct characterizations of all papers included in this review (and outcomes outlined in the protocol) would be of interest.	Addressed: The other outcomes have been summarised in a grouped forest plot (hazard ratio outcomes; Supplementary figure 3) and table (cognitive function or decline; Supplementary table 10), added to the Supplementary Material file. Additional text describing these analyses has been added to the Methods (lines 166-167, 172-175) and to the end of the Results (lines 285-301). Text was also inserted to briefly describe selected articles which did not have suitable effect estimates reported but identified cohort studies with suitable data for the planned IPD metaanalyses (lines 226-232).
5. Line 175 onwards – please include the associated citations for each study.	Addressed: Citations have been added.
6. Supplementary material - Table S6 - Please add an abbreviations section to the bottom of Table S6, detailing all of the abbreviated words reported within the table.	Addressed: all abbreviations used in the table have been added.
Reviewer 2	
1. The research is of important and interesting, but “Conclusions” (did not demonstrate associations of endogenous testosterone with CVD deaths or with all-cause mortality) was seemingly differ from other researches. This should be discussed carefully, and many subconclusions can be different from present total conclusion, due to	It is a minimum of five years of follow-up data that was used as a selection criterion. The length of follow-up in selected studies ranged from 5 to 20 years. Only published estimates are summarised in this paper.
Comment	**Response**
many unadjusted factors and significant heterogeneity can interfere with the final conclusions. 5 years of follow-up data and testosterone monitoring was not long enough to judge the effectiveness of endogenous testosterone on the development of cardiovascular disease (CVD) events, all-cause mortality, cognitive decline, dementia, etc.	Addressed: The words “ranging from 5-20 years” was added to the Results text to clarify that the length of follow-up of selected studies was 5 years or longer (Line 221). Additional text was added to the Abstract (line 58) and to the Discussion (lines 342349) concerning the heterogeneity of estimates. We have inserted one paragraph in the Discussion (lines 370-380) to more comprehensively discuss methodological limitations and another (lines 382-392) to

	carefully discuss how our findings should be regarded.
2. The title (Systematic review: the Androgens In Men Study) is too broad and not proper. “Meta-analyses” and “adult men in the general community” should be included in title at least.	Addressed: We have changed the title to “Systematic review and meta-analyses on associations of endogenous testosterone concentration with health outcomes in community-dwelling men.” This change also reflects that this work does not reflect the entire contribution from the Androgens In Men Study, which (as outlined in the protocol article) will involve a series of IPD metaanalyses using participant-level data from each of the selected studies.
3. The concept “endogenous testosterone” should be given more detailed definition and discussion, because testosterone exist in many different status including free-T, bio-available-T, SHBGbinding T..	Addressed: What we mean by “endogenous testosterone” is clarified in the Introduction (lines 87-89), and also in the Methods, with respect to the presented meta-analyses (lines 145-148). Additional text has been added to the Discussion (lines 389-392) to draw out the distinction between endogenous and exogenous.