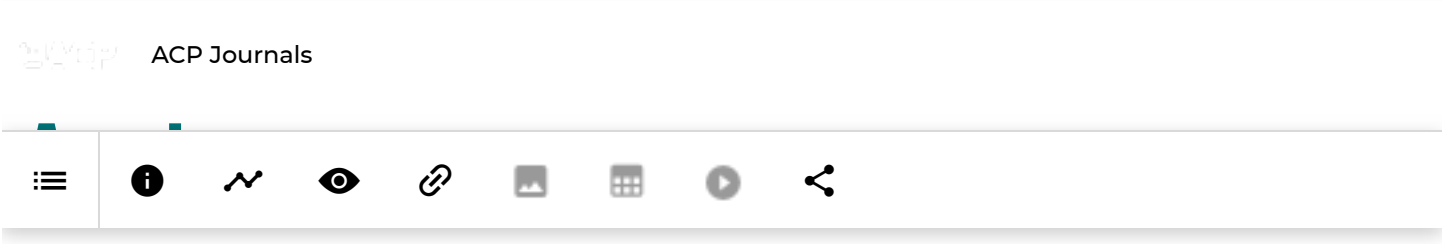

Abstract

Background:

Whether circulating sex hormones modulate mortality and cardiovascular disease (CVD) risk in aging men is controversial.

Purpose:

To clarify associations of sex hormones with these outcomes.

Data Sources:

Systematic literature review to July 2019, with bridge searches to March 2024.

Study Selection:

Prospective cohort studies of community-dwelling men with sex steroids measured using mass spectrometry and at least 5 years of follow-up.

Data Extraction:

Independent variables were testosterone, sex hormone–binding globulin (SHBG), luteinizing hormone (LH), dihydrotestosterone (DHT), and estradiol concentrations. Primary outcomes were all-cause mortality, CVD death, and incident CVD events. Covariates included age, body mass index, marital status, alcohol consumption, smoking, physical activity, hypertension, diabetes, creatinine concentration, ratio of total to high-density lipoprotein cholesterol, and lipid medication use.

Data Synthesis:

Nine studies provided individual participant data (IPD) (255 830 participant-years). Eleven studies provided summary estimates (n = 24 109). Two-stage random-effects IPD meta-analyses found that men with baseline testosterone concentrations below 7.4 nmol/L (<213 ng/dL), LH concentrations above 10 IU/L, or estradiol

concentrations below 5.1 pmol/L had higher all-cause mortality, and those with testosterone concentrations below 5.3 nmol/L (<153 ng/dL) had higher CVD mortality risk. Lower SHBG concentration was associated with lower all-cause mortality (median for quintile 1 [Q1] vs. Q5, 20.6 vs. 68.3 nmol/L; adjusted hazard ratio [HR], 0.85 [95% CI, 0.77 to 0.95]) and lower CVD mortality (adjusted HR, 0.81 [CI, 0.65 to 1.00]). Men with lower baseline DHT concentrations had higher risk for all-cause mortality (median for Q1 vs. Q5, 0.69 vs. 2.45 nmol/L; adjusted HR, 1.19 [CI, 1.08 to 1.30]) and CVD mortality (adjusted HR, 1.29 [CI, 1.03 to 1.61]), and risk also increased with DHT concentrations above 2.45 nmol/L. Men with DHT concentrations below 0.59 nmol/L had increased risk for incident CVD events.

Limitations:

Observational study design, heterogeneity among studies, and imputation of missing data.

Conclusion:

Men with low testosterone, high LH, or very low estradiol concentrations had increased all-cause mortality. SHBG concentration was positively associated and DHT concentration was nonlinearly associated with all-cause and CVD mortality.

Primary Funding Source:

Medical Research Future Fund, Government of Western Australia, and Lawley Pharmaceuticals. (PROSPERO: CRD42019139668)

Supplemental Material

Supplemental Material

DOWNLOAD | 3.08 MB

References

1.

Yeap BB, **Alfonso H**, **Chubb SA**, **et al**. Reference ranges and determinants of testosterone, dihydrotestosterone, and estradiol levels measured using liquid chromatography-tandem mass spectrometry in a population-based cohort of older men. J Clin Endocrinol Metab. 2012;97:4030-4039. [PMID: 22977273] doi: 10.1210/jc.2012-2265

Crossref | PubMed | Google Scholar

2.

Marriott RJ, **Murray K**, **Adams RJ**, **et al**. Factors associated with circulating sex hormones in men: individual participant data meta-analyses. Ann Intern Med. 2023;176:1221-1234. [PMID: 37639720] doi: 10.7326/M23-0342

Link | Google Scholar

3.

Shi Z, **Araujo AB**, **Martin S**, **et al**. Longitudinal changes in testosterone over five years in community-dwelling men. J Clin Endocrinol Metab. 2013;98:3289-3297. [PMID: 23775354] doi: 10.1210/jc.2012-3842

Crossref | PubMed | Google Scholar

SHOW ALL REFERENCES

Comments

4 Comments

Sign In to Submit A Comment

Scott Selinger, MD, FACP • Dell Medical School, Dept. of Internal Medicine • 23 May 2024

Testosterone-mortality link will likely be twisted in the name of "Men's Health"

I appreciate the rigorous efforts by Yeap and colleagues to clarify the association between sex hormones and all-cause mortality. I fear this will distill down through media attention to further pressure from the ascendant “men’s health” industry to further drive testosterone prescribing in vulnerable populations. It should be noted that the increased mortality identified occurred at total testosterone levels 20-30% below the current lower limits of normal identified by major societal guidelines for diagnosing hypogonadism, a fact likely to be unmentioned in a practice already overrun with guideline-discordant treatment. This is especially salient for two reasons. First, the publicized takeaways from TRAVERSE have been that testosterone gel therapy did not increase mortality in a group at high risk for cardiovascular events. However, most men treated for hypogonadism are receiving injectable testosterone, which have shown a greater risk of cardiovascular events, hospitalizations and deaths compared to gels, peeling away reassurances of non-maleficence. Second, the average of the median ages for the included studies is over 60 and much of the research on hypogonadism entails this older population, most new prescriptions are going towards a younger population for which there is much less data on safety and efficacy of treatment for, as well as prevalence of, hypogonadism. The messaging I would hope could come from the work done by Yeap in concert with those of TRAVERSE are that very low testosterone levels in older men are indeed a risk marker for death and disease. However, similar to other health data linked to increased mortality such as chronic mild hyponatremia and anemia, low levels of HDL, and short sleep duration, which have all shown no improvement or worsened mortality through pharmacotherapy, low testosterone does not appear to be an effective target for treatment to improve any of these major outcomes. We must move beyond the publicized mantra of “make low T high” towards addressing and preventing its associated comorbid conditions.

References:

1. Dubin JM, Jesse E, Fantus RJ, Bennett NE, Brannigan RE, Thirumavalavan N, Halpern JA.

Guideline-Discordant Care Among Direct-to-Consumer Testosterone Therapy Platforms. JAMA Intern Med. 2022 Dec 1;182(12):1321-1323. doi: 10.1001/jamainternmed.2022.4928. PMID: 36469030; PMCID: PMC9855289.

2. Layton JB, Meier CR, Sharpless JL, Stürmer T, Jick SS, Brookhart MA. Comparative Safety of Testosterone Dosage Forms. JAMA Intern Med. 2015;175(7):1187–1196. doi:10.1001/jamainternmed.2015.1573

3. Lincoff AM, Bhasin S, Flevaris P, Mitchell LM, Basaria S, Boden WE, Cunningham GR, Granger CB, Khera M, Thompson IM Jr, Wang Q, Wolski K, Davey D, Kalahasti V, Khan N, Miller MG, Snabes MC, Chan A, Dubcenco E, Li X, Yi T, Huang B, Pencina KM, Travison TG, Nissen SE; TRAVERSE Study Investigators. Cardiovascular Safety of Testosterone-Replacement Therapy. N Engl J Med. 2023 Jul 13;389(2):107-117. doi: 10.1056/NEJMoa2215025. Epub 2023 Jun 16. PMID: 37326322.

4. Selinger S, Ancha N, Frei CR. Testosterone Prescribing in Texas, 2018-2021. J Gen Intern Med. 2023 Nov;38(15):3436-3438. doi: 10.1007/s11606-023-08316-y. PMID: 37436571; PMCID: PMC10682327.

Shiu Lun Au Yeung 1, Shan Luo 1, C Mary Schooling 1,2 • 1School of Public Health, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong Special Administrative Region, 2 School of Public Health and Health Policy, City University of New York • 7 June 2024

Association of low testosterone in poor health: Correlation or causation?

We read with great interest the systematic review by Yeap et al., which summarizes the existing prospective cohort studies on the associations of testosterone and related hormones with cardiovascular outcomes.[1] Yeap et al., concluded that men with low testosterone had increased risk of all-cause mortality. However, it remains unclear whether these associations reflect causation because of the possibility of residual confounding, given the observational nature of studies included.

In the main analysis considering testosterone in quintiles, the associations of the lowest quintile of testosterone with all-cause mortality, cardiovascular death, and cardiovascular events were attenuated and no longer evident after adjustment for confounders. In the dose response analyses, men with low testosterone (<7.4 nmol/L) were associated with higher risk of all-cause mortality and cardiovascular death albeit without a clear dose response. These findings are somewhat inconsistent with a recent large trial, which found no cardiovascular or mortality benefits of testosterone replacement therapy for older men (mean age 63.3 years) with low testosterone (median: 7.87 nmol/L).[2] As such, unmeasured confounding and survival bias could potentially explain the observed associations. Poor health often leads to reduced testosterone and could be an issue in studies with older participants.[3]

Triangulation of evidence from study designs with different assumptions can help clarify the causal role of testosterone in cardiovascular disease risk. Mendelian randomization studies, a design more robust to residual confounding due to the use of genetic variants randomly allocated at conception, showed possible harms for cardiovascular diseases and survival rather than a potentially protective effect.[4, 5]

Given the discrepancies between observational studies, randomized controlled trials, and Mendelian randomization, it remains to be determined whether low testosterone is merely a marker of poor health (for risk prediction) or a genuine cause of cardiovascular disease and mortality (for intervention). Further interrogation using these epidemiologic designs is necessary to clarify causation from correlation. This will help inform appropriate clinical management for men with low testosterone.

References

1. Yeap BB, Marriott RJ, Dwivedi G, et al. Associations of Testosterone and Related Hormones With All-Cause and Cardiovascular Mortality and Incident Cardiovascular Disease in Men : Individual Participant Data Meta-analyses. *Ann Intern Med* 2024 doi: 10.7326/M23-2781 [published Online First: 2024/05/13]

2. Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular Safety of Testosterone-Replacement Therapy. *N Engl J Med* 2023;389(2):107-17. doi: 10.1056/NEJMoa2215025 [published Online First: 20230616]

3. Marriott RJ, Murray K, Adams RJ, et al. Factors Associated With Circulating Sex Hormones in Men : Individual Participant Data Meta-analyses. *Ann Intern Med* 2023;176(9):1221-34. doi: 10.7326/M23-0342 [published Online First: 2023/08/28]

4. Luo S, Au Yeung SL, Zhao JV, et al. Association of genetically predicted testosterone with thromboembolism, heart failure, and myocardial infarction: mendelian randomisation study in UK Biobank. *BMJ* 2019;364:l476. doi: 10.1136/bmj.l476 [published Online First: 20190306]

5. Schooling CM, Zhao JV. Investigating the association of testosterone with survival in men and women using a Mendelian randomization study in the UK Biobank. *Sci Rep* 2021;11(1):14039. doi: 10.1038/s41598-021-93360-z [published Online First: 20210707]

Disclosures:

SLAY received honoraria from SomaLogic for scientific presentations on proteomic studies that was unrelated to this letter. The authors declared no other conflict of interest.

Bu B. Yeap (1), Gary A. Wittert (2), Frederick C.W. Wu (3), Dirk Vanderschueren (4), Eric S. Orwoll (5) • (1) University of Western Australia, Australia; (2) University of Adelaide, Australia; (3) University of Manchester, UK

University of Western Australia, Australia, (2) University of Adelaide, Australia, (3) University of Manchester, UK, (4) KU Leuven, Belgium, (5) Oregon Health and Science University, USA. • 11 June 2024

Authors' response to comments

We thank Dr Selinger and Drs Au Yeung and colleagues for their interest in this work. In our individual participant data meta-analysis of men ranging from younger to older ages, we found that below a threshold of testosterone (measured using mass spectrometry) of 7.4 nmol/L (213 ng/dL), the risk of all-cause mortality increased. Below a threshold of 5.3 nmol/L (153 ng/dL) the risk of cardiovascular death increased. These analyses were adjusted for age, body mass index, and other potential confounders and cardiovascular risk factors (1). We acknowledge that not all potential confounders were included and causality cannot be established from observational data. Our article does not advocate for the use of testosterone to influence mortality risk, and there are established guidelines for the clinical assessment and management of hypogonadal men (2,3). While the results of large, randomised trials such as TRAVERSE or T4DM are important (4,5), those trials had specific eligibility criteria, leaving scope for future studies. Our findings provide new insight into thresholds of testosterone associated with poorer health outcomes, and those we might expect to find in healthy men (2,3).

References

1. Yeap BB, Marriott RJ, Dwivedi G, et al. Associations of testosterone and related hormones with all-cause and cardiovascular mortality, and incident cardiovascular disease in men: Individual Participant Data meta-analyses. Ann Intern Med. 2024 May 14. doi: 10.7326/M23-2781.

2. Yeap BB, Grossmann M, McLachlan RI, et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. Med J Aust. 2016; 205: 173-78.

3. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018; 103: 1715-44.

4. Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular safety of testosterone-replacement therapy. N Engl J Med. 2023; 389: 107-117. 5. Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled phase 3b trial. Lancet Diabetes Endocrinol. 2021; 9: 32-45.

Yu-Hsiang Lin, Kuo-Jen Lin, Jau-Yuan Chen, Horng-Heng Juang, Chun-Te Wu • (1)Chang Gung Memorial Hospital-Linkou (2) Chang Gung University • 13 June 2024

Revisiting the Interplay of Testosterone, Nocturia, and Cardiovascular Health

After reviewing the study by Yeap et al.(1), which evaluated the effects of sex hormones on health outcomes in aging men, we, as urologists, are particularly intrigued by the link between

health outcomes in aging men, we, as urologists, are particularly intrigued by the link between testosterone levels and mortality from all causes and cardiovascular disease (CVD). This significant correlation is insightful for urological practice, particularly in the management of benign prostatic hyperplasia (BPH) and nocturia. Yeap et al.'s comprehensive study, encompassing data up to March 2024 and meta-analyses from nine studies with over 255,830 participant-years, conclusively showed that lower levels of testosterone and dihydrotestosterone (DHT) correlate with higher mortality rates due to all causes and CVD. It also highlighted that reduced levels of sex hormone-binding globulin (SHBG) could help lower mortality risks(1).

These findings gain additional context when considered alongside the known complications of BPH, including nocturia. Notably, Bursztyn et al.(2) identified nocturia as a significant risk factor for decreased survival over a 12-year period in patients previously diagnosed with coronary heart disease. The interplay of nocturia and CHD appears to exacerbate mortality risks, thus underlining the multifaceted role of nocturia beyond mere discomfort(2).

Moreover, the implications of sleep disruption from nocturia extend into hormonal regulation, as Leproult et al.(3) found that sleep deprivation itself could lead to decreased testosterone levels. This cascading effect of sleep interruption potentially disrupts the circadian rhythm and subsequently the hypothalamic-pituitary-gonadal (HPG) axis, crucial for maintaining normal levels of male hormones(4).

This connection is further complicated by the aging process, during which testosterone levels naturally decline, as well as the potential initiation of a vicious cycle involving the HPG axis and antidiuretic hormone (ADH) due to nocturia as discussed by Lin et al.(5). These interactions suggest a possibly unified pathophysiological pathway involving sleep disturbances, hormonal imbalances, and cardiovascular health.

Given these intricate relationships, it may be beneficial to explore strategies to reduce nocturia as a means to potentially mitigate lower testosterone levels. Beyond monitoring testosterone, addressing nocturnal polyuria and ADH deficiency should also be considered vital components of managing patients caught in this deleterious cycle.

In conclusion, while the study by Yeap et al.(1) provides significant insights into the hormonal underpinnings of mortality in aging men, it also compels us to consider broader implications for clinical practice, particularly in the fields of urology and cardiology. A multidimensional approach to treatment that includes careful management of nocturia may improve both quality of life and survival outcomes.

References:

1. Yeap BB, Marriott RJ, Dwivedi G, Adams RJ, Antonio L, Ballantyne CM, et al. Associations of Testosterone and Related Hormones With All-Cause and Cardiovascular Mortality and Incident Cardiovascular Disease in Men : Individual Participant Data Meta-analyses. Ann Intern Med. 2024. Epub 20240514. doi:10.7326/M23-2781. PubMed PMID: 38739921

2024. Epub 20240514. doi: 10.7326/M23-2781. PubMed PMID: 38739921.

2. Bursztyn M, Jacob J, Stessman J. Usefulness of Nocturia as a Mortality Risk Factor for Coronary Heart Disease Among Persons Born in 1920 or 1921. Am J Cardiol. 2006;98(10):1311-5.

3. Leproult R, Van Cauter E. Effect of 1 week of sleep restriction on testosterone levels in young healthy men. JAMA. 2011;305(21):2173-4. doi: 10.1001/jama.2011.710. PubMed PMID: 21632481; PubMed Central PMCID: PMC4445839.

4. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005;437(7063):1257-63. doi: 10.1038/nature04284. PubMed PMID: 16251950.

5. Lin YH, Wu CT, Juang HH. Exploring the complex interplay: BPH, nocturia, and aging male health. World J Urol. 2024;42(1):105. Epub 20240226. doi: 10.1007/s00345-024-04849-x. PubMed PMID: 38407677.