Testosterone therapy and traditional cardiovascular disease risk factors among men and women: a systematic review and meta-analysis of randomized controlled trials

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**Introduction**

Observationally, higher serum testosterone is associated with generally healthier values of cardiovascular disease risk factors, such as lower HbA1c, higher HDL-cholesterol, and lower blood pressure. Observational studies are open to uncontrollable confounding by socio-economic factors, health behavior and physiological changes with aging and ill health. As such, it is difficult to know whether these observations mean that testosterone protects against cardiovascular disease or that testosterone is simply a marker of other processes. Reviews and expert advice warn that low testosterone or androgen deprivation therapy may increase cardiovascular disease risk, making self-medicating with over the counter testosterone supplements an attractive option. Currently, testosterone replacement is heavily promoted and increasingly widely used.

The most up-to-date meta-analysis of randomized controlled trials (RCTs) of testosterone therapy amongst men suggests that testosterone increases the risk of a cardiovascular-related event, for reasons which are unclear, although it has recently come to light that the most effective lipid modulating therapy for prevention of CVD, i.e., statins, also lowers testosterone, as do some of the more effective therapies for preventing CVD in diabetes, such as metformin and perhaps pioglitazone. Moreover, the effect of testosterone on traditional CVD risk factors is heterogeneous. RCTs among men suggest testosterone therapy improves glucose metabolism. A meta-analysis of RCTs among men including trials through August 2008 found that testosterone therapy lowered HDL-cholesterol, but had little effect on blood pressure. Since that date many more trials of testosterone therapy have been conducted among both men and women enabling a more comprehensive and precise estimate of the effect of testosterone therapy on each major CVD risk factor, and thus a better understanding of the role of testosterone, and its environmental drivers such as endocrine disruptors, in CVD and its risk factors.

**Review Question**

What is the effect of testosterone therapy on traditional cardiovascular disease risk factors?

**Eligibility criteria**

Studies will be eligible if they meet all the following criteria:

- RCT of testosterone therapy compared with a placebo. Given that many of these trials are in older people with chronic diseases, we will include trials where there is a comparison of testosterone therapy with placebo against the background of other drug use as long as the groups only differ in their use of testosterone.
- Duration of at least 4 weeks to ensure testosterone has had its full effects.
- Participants are adults, because hormone levels are different in children.
- Participants are both men and women, because there is no reason to think the effects of testosterone therapy on cardiovascular disease risk factors would vary by sex.
- Published study or registered trial where we are able to track down the results.
- Any date, because there is no reason to think that the effect of testosterone has changed over the years.
- Any setting, because there is no reason to think that the effect of testosterone varies by setting.
- Provides information explicitly on at least one CVD risk factor by study arm.

We will consider the traditional CVD risk factors in most risk scoring systems, The outcomes considered will include:

1. Systolic and/or diastolic blood pressure
2. LDL- and HDL-cholesterol, and cholesterol
3. Diabetes, or its risk indicators, i.e., fasting glucose, insulin, HbA1c and HOMA-IR

Information Sources
We will search the literature databases PubMed (1950-June 2013), EMBASE (1974-June 2013), Web of Science (1900-June 2013) and the WHO International Clinical Trials Registry for trials of testosterone therapy reporting any of the cardiovascular risk factors given. In addition, we will also search the references of any included study and Web of Science will be used to review citing articles of included studies where available. Where we find one report on a trial that gives one risk factor we will check all other publications on that same trial for reports concerning other risk factors. Where we find duplicate publications from the same trial we will include the most up-to-date relevant information. In cases where relevant trials are identified through the trial registry, but results have not been published in the literature, we will contact the trial investigators to request the results of their study.

Search
The search terms used in each database is presented in Appendix 1. We will search the databases for each CVD risk factor using each risk factors and its synonyms, for example for blood pressure we will use "blood pressure" or "hypertension" or "SBP" or "DBP" and “testosterone" or “androgen” and "placebo-controlled,” “randomized-controlled trial,” and “trial” in title, abstract or any field, because RCTs are not always tagged as such.27 We will similarly search the WHO International Clinical Trials Registry Platform. Validated filters for identifying clinically sound treatment studies will be applied to PubMed and EMBASE searches.

Study selection process
We will use a three-step process for screening studies. Firstly, two investigators will independently review each title and discard any study that can be excluded purely based on title. Secondly, two investigators will independently review the abstracts and exclude any study that can be excluded purely based on abstract. Thirdly, two investigators will independently review the full text reports of CVD risk factors by trial arm. At the first and second screening stages, studies included by either investigator will be included in the following screening stage and disagreements regarding the included studies will be resolved by consensus or if necessary by reference to a third investigator.

We will not exclude studies based on the number of participants, because we want to make full use of the evidence available. We will not exclude by participant characteristics’, because testosterone is used in a wide variety of people, and there is no reason to think that testosterone has different effects by sub-group.

Data extraction
An investigator will extract data from the selected studies, using a standard template. A second investigator will check all the extracted data.

We will not contact authors for confirmation of their published numbers because we assume the authors would have corrected or withdrawn their papers if a major error came to light. We will contact the authors twice for clarification, if necessary. In the event of no response we will make conservative assumptions.

Data items
We will extract the following information for each trial:

- Publication details (author, year of publication, title, journal)
• Study population, including number by study arm, sex, health status, age and setting
• Primary study outcome
• Duration of follow-up
• Number of participants in each arm at start and end (testosterone and placebo groups)
• Type of testosterone
• Mean and standard deviation of CVD risk factors by trial arm at the start and finish of the trial.
• Funding source
• Affiliations and competing interests of investigators
• Trial implementation and reporting, including information on:
  o randomization
  o treatment allocation
  o comparison of groups at baseline
  o trial eligibility criteria
  o ‘blinding’ of outcome assessors, care providers, adverse event assessors and participants
  o Type of analysis: intention to treat, per-protocol or other

Bias assessment for individual studies
We will use the Jadad scoring system\(^28\) to assess the methodological quality of each RCT. Two investigators will independently rate each study and settle any differences by consensus or reference to a third investigator.

Summary Measure
The principal summary measure will be a pooled weighted mean difference of pre- to post-treatment differences for continuous outcomes and a measure of relative risk for dichotomous outcomes.

Synthesis of results
We will obtain the weighted mean difference in each CVD risk factor for testosterone versus placebo using inverse variance weighting with random or fixed effects depending on the heterogeneity between trials. We will obtain a measure of relative risk using a Mantel Hazel estimator. We will use meta-analysis regression with inverse variance weighting to assess whether the effects of testosterone therapy varies by specified sub-group. Heterogeneity will be assessed using the \(I^2\) statistics. \(I^2\) is the proportion of total variation observed between the trials attributable to differences between trials rather than to sampling error (chance), with values less than 30% representing low variation, less than 60% moderate variation, and greater than 60% high variation.

Bias Assessment for all studies
We will use funnel plots to assess publication bias. We will use the trim and fill method to assess the impact of publication bias on the pooled effect.

Subgroup analysis
We will do subgroup analysis primarily by sex and source of funding. Although it is unusual for the effect of the same hormone to vary by sex,\(^29\) we cannot rule it out. A previous meta-analysis of the effects of testosterone therapy on cardiovascular-related events found different associations by source of funding.\(^16\) We will also do sub-group analysis by age, type of testosterone, dose of testosterone and baseline testosterone, if possible.
Statistical analysis

We will use R to do the analysis, using functions, such as ‘metacont’ and ‘metabin’ from the R package ‘meta’, and ‘rma’ from the R package ‘metafor’ (R Development Core Team, Vienna, Austria).
Reference List


10. Sexual dysfunction as the last bastion of urological drug commercialisation within the pharmaceutical industry. *BJU Int* 2011;107:1845-6.


**Appendix 1: Search Strategies**

**PubMed**

(Testosterone [MeSH Terms] OR testosterone* OR androgens[MeSH Terms] OR androgen*) AND ("Blood Pressure"[Mesh] OR "Systolic blood pressure" OR "diastolic blood pressure" OR "blood pressure" OR hypertension OR "Hypertension"[Mesh] OR "cholesterol"[Mesh] OR "Low-density lipoprotein" OR "LDL-cholesterol" OR "High-density lipoprotein" OR "HDL-cholesterol" OR "cholesterol" OR diabetes OR "Diabetes Mellitus"[Mesh] OR "fasting glucose" OR "blood glucose" OR insulin OR "insulin resistance" OR "HOMA-IR" OR "hemoglobin A1c" OR "Hemoglobin"[Mesh] OR "glycated hemoglobin" OR "glycosylated hemoglobin" OR "HbA1c") AND ("randomized controlled trial"[ptyp] OR Randomized OR placebo)

**Embase (OvidSP)**

exp testosterone/ or testosterone$.mp. or exp androgen/ or androgen$.mp. AND "exp systolic blood pressure/" or " systolic blood pressure$.mp." or "exp diastolic blood pressure/" or "diastolic blood pressure$.mp. or " ex blood pressure/" or "exp hypertension/" or "hypertension$.mp." or "exp Low-density lipoprotein/" or "exp LDL-cholesterol/" or "low-density lipoprotein$.mp." or "LDL cholesterol$.mp." "exp High-density lipoprotein/" or "exp HDL-cholesterol/" "high-density lipoprotein$.mp." or "HDL cholesterol$.mp." or "exp cholesterol/" or "cholesterol$.mp." or "exp diabetes/" or "diabetes$.mp." or "exp fasting glucose/" or "fasting glucose$.mp." or "exp blood glucose/" or "blood glucose$.mp. or "exp insulin/" or "insulin$.mp." or "exp insulin resistance/" or "insulin resistance$.mp." or "exp HOMA-IR/" or "homa ir$.mp." or "exp homa A1c/" or "hemoglobin A1c$.mp." or "exp glycated hemoglobin/" or "glycated hemoglobin$.mp." or "exp HbA1c/" or "HbA1c$.mp." AND "random.tw." or placebo.mp" or double-blind.tw."

**Web of Science**

Topic=(testosterone* OR androgen*) AND Topic=("systolic blood pressure" OR "diastolic blood pressure" OR "blood pressure" OR "hypertension" OR "Low-density lipoprotein" OR "LDL-cholesterol" OR "High-density lipoprotein" OR "HDL-cholesterol" OR "cholesterol" OR "diabetes" OR "fasting glucose" OR "blood glucose" OR "insulin" OR "insulin resistance"
OR "HOMA-IR" OR "hemoglobin A1c" OR "glycated hemoglobin" OR glycosylated hemoglobin* OR "HbA1c") AND Topic="(randomized" OR "placebo" OR "double-blind")

WHO International Clinical Trials Registry Platform

Testosterone OR androgen