Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data

Rakibul M Islam, Robin J Bell, Sally Green, Matthew J Page, Susan R Davis

Summary

Background The benefits and risks of testosterone treatment for women with diminished sexual wellbeing remain controversial. We did a systematic review and meta-analysis to assess potential benefits and risks of testosterone for women.

Methods We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science for blinded, randomised controlled trials of testosterone treatment of at least 12 weeks' duration completed between Jan 1, 1990, and Dec 10, 2018. We also searched drug registration applications to the European Medicine Agency and the US Food and Drug Administration to identify any unpublished data. Primary outcomes were the effects of testosterone on sexual function, cardiometabolic variables, cognitive measures, and musculoskeletal health. This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42018104073.

Findings Our search strategy retrieved 46 reports of 36 randomised controlled trials comprising 8480 participants. Our meta-analysis showed that, compared with placebo or a comparator (eg, oestrogen, with or without progestogen), testosterone significantly increased sexual function, including satisfactory sexual event frequency (mean difference 0·85, 95% CI 0·52 to 1·18), sexual desire (standardised mean difference 0·36, 95% CI 0·22 to 0·50), pleasure (mean difference 6·86, 95% CI 5·19 to 8·52), arousal (standardised mean difference 0·28, 95% CI 0·21 to 0·35), orgasm (standardised mean difference 0·25, 95% CI 0·18 to 0·32), responsiveness (standardised mean difference 0·28, 95% CI 0·21 to 0·35), and self-image (mean difference 5·64, 95% CI 4·03 to 7·26), and reduced sexual concerns (mean difference 8·99, 95% CI 6·90 to 11·08) and distress (standardised mean difference –0·27, 95% CI –0·36 to –0·17) in postmenopausal women. A significant rise in the amount of LDL-cholesterol, and reductions in the amounts of total cholesterol, HDL-cholesterol, and triglycerides, were seen with testosterone administered orally, but not when administered non-orally (eg, by transdermal patch or cream). An overall increase in weight was recorded with testosterone treatment. No effects of testosterone were reported for body composition, musculoskeletal variables, or cognitive measures, although the number of women who contributed data for these outcomes was small. Testosterone was associated with a significantly greater likelihood of reporting acne and hair growth, but no serious adverse events were recorded.

Interpretation Testosterone is effective for postmenopausal women with low sexual desire causing distress, with administration via non-oral routes (eg, transdermal application) preferred because of a neutral lipid profile. The effects of testosterone on individual wellbeing and musculoskeletal and cognitive health, as well as long-term safety, warrant further investigation.

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Introduction

No international consensus exists to guide use of testosterone in women. Nonetheless, clinicians have treated women with various forms of testosterone for decades, primarily for diminished sexual wellbeing.[1] Previous systematic reviews of testosterone treatment for women have indicated favourable effects on sexual function,[2,3] but these analyses have included scant data for safety or adverse effects. We did a systematic review and meta-analysis of randomised controlled trials that reported the effects of systemic testosterone treatment compared with placebo or a comparator (eg, oestrogen, with or without progestogen) on sexual function, cardiometabolic variables, cognitive measures, and musculoskeletal health, including previous unpublished data.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[4] We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science using Ovid software. The full search strategy and keywords used have been published elsewhere.[5]

Research in context

Evidence before this study

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science for randomised controlled trials of testosterone in women published between Jan 1, 1990, and Dec 10, 2018, and drug registration applications to the European Medicine Agency and the US Food and Drug Administration in the same period. The search was restricted to the English language and the search terms were as published in PROSPERO (CRD42018104073). Older systematic reviews indicate testosterone therapy has favourable effects on female sexual function. The most recent systematic review, published in 2017, was restricted to use of transdermal testosterone. Unpublished trials and those that did not provide sufficient data were not included in previous reviews.

Added value of this study

Our systematic review and meta-analysis includes data for all modes of testosterone administration (oral and non-oral) and complete data from randomised controlled trials not included in earlier reviews or that remain unpublished. Our meta-analysis shows that testosterone supplementation improves sexual function in naturally and surgically postmenopausal women, whether or not they are using concurrent oestrogen. The findings of our study reaffirm that only non-oral testosterone should be prescribed because of the adverse lipoprotein effects of oral testosterone. Data are insufficient to draw conclusions about the effects of testosterone on musculoskeletal, cognitive, and mental health and long-term safety and use in premenopausal women.

Implications of all the available evidence

Non-oral testosterone treatment is effective for postmenopausal women presenting with low sexual desire that causes them personal concern. Available data do not support use of testosterone in premenopausal women, and testosterone should not be used to treat depression or bone loss or to prevent cognitive decline. To safely prescribe testosterone for low sexual desire, formulations for women are needed because, at present, only male formulations resulting in testosterone concentrations several fold greater than appropriate for women, and compounded testosterone, are available.

We also searched drug registration applications to the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA).

The final search results were restricted to studies completed between Jan 1, 1990, and Dec 10, 2018. Inclusion criteria for studies were that they should be randomised clinical trials, have a duration of systemic testosterone treatment of at least 12 weeks, be at least single blind (ie, participants and assessors had to be unaware of the intervention or interventions), and have a placebo or comparator arm (eg, oestrogen, with or without progestogen). Participants could be aged 18–75 years and be premenopausal or postmenopausal. No restriction was placed on type of menopause (natural or surgical), use of concurrent hormone treatment (oestrogen with or without progestogen), or publication language. Studies of intravaginal testosterone were excluded.

Studies were selected in a two-stage process. First, titles and abstracts from the electronic searches were scrutinised by two independent reviewers (RMI and RJB). Second, if the abstract met inclusion criteria we obtained full reports and final decisions were made about study inclusion. Disagreement between reviewers about inclusion or exclusion of a particular report was resolved by discussion between the review team (RMI, RJB, and SRD). Corresponding authors of reports selected for inclusion were contacted for further details if data were incomplete or unclear. Amgen (Thousand Oaks, CA, USA) approved the inclusion of data pertaining to randomised controlled trials of a testosterone patch from documents submitted to the EMA[6] and the FDA.[7] These documents provided details and outcomes of two unpublished randomised controlled trials that were done under the FDA's Investigational New Drug programme, as well as precise sample sizes and SEs not included in published papers. In two instances, data were only available as combined studies and, hence, were included in this manner.

Procedures

Two reviewers (RMI and RJB) independently extracted data for participants' characteristics, interventions, and study outcomes. A pro-forma—designed by the review team—was used and included study characteristics for author and year, study location and setting, menopausal status, age, sample size, type of treatments used, mode of administration, dose administered, duration of treatment, and outcomes measured.

A transdermal patch releasing 300 µg of testosterone per day achieved amounts of free testosterone in blood in the upper end of the premenopausal range.[8] Therefore, only outcomes for the 300 µg releasing patch were used for any studies that included lower or higher dose patches. For any studies that assessed other modes of testosterone delivery, outcomes for the dose that resulted in amounts of testosterone in blood closest to those seen with the 300 µg patch were used.

The Cochrane risk-of-bias tool[9] was used to assess random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and

other biases. Risk of bias was assessed by two of us (RMI and RJB) independently, except for seven trials in which SRD was a co-author, in which case the risk of bias was assessed by MJP. Disagreements were resolved by consensus or by consultation with a third individual (SRD or SG).

Outcomes

The primary outcomes included the effects of testosterone on sexual function (ie, sexual events, total sexual function scores, and scores for sexual desire, arousal, orgasm, pleasure, concerns, responsiveness, sexual self-image, and sexual distress), cardiometabolic variables (ie, weight, BMI, waist-to-hip ratio, systolic and diastolic blood pressure, measures of glucose intolerance, high-sensitivity C-reactive protein, and lipids), cognitive performance and cognitive fatigue, and musculoskeletal health (ie, bone mineral density, body composition, and muscle strength). Secondary outcomes included serious adverse events, androgenic effects, breast effects, mood and wellbeing, and study withdrawal.

Statistical analysis

Studies were grouped according to the mode of testosterone administration (oral or non-oral), menopausal status (postmenopausal or premenopausal), type of menopause (natural or surgical), mode of concurrent oestrogen delivery (oral or non-oral), outcome measured, and trial duration (12 months or >12 months if data were available). For studies that used the same assessment method and provided continuous data we reported mean difference, and for those that used different methods we reported the standardised mean difference, using the inverse-variance method. For dichotomous data, we used the number of events in the control and intervention groups of every study to calculate the Mantel-Haenszel risk ratio (RR). Outcomes from individual studies were pooled using a random-effects model, because this approach assumes that there could be clinical and methodological heterogeneity that might affect the findings. All pooled analyses were reported with 95% CIs. The DerSimonian and Laird method of moments estimator was used to estimate the between-study variance, and 95% CIs were calculated using the Wald type method.[10] Heterogeneity of exposure effects was assessed using the I^2 statistic. Prediction intervals were calculated for sexual outcomes with high I^2 values (I^2>50%), which indicated variability in the treatment effect was attributable to study heterogeneity not chance.[11] The χ^2 test for heterogeneity was also done. We judged a p value less than 0·05 significant. Subgroup analyses were done to assess the potential contribution of differences in menopausal status and mode of testosterone administration. When more than ten studies were included in an outcome analysis, contour enhanced funnel plots were created to investigate small study effects, which can result from reporting biases, methodological or clinical heterogeneity, or other factors.[12] When data were only available as graphs in published papers, we used DigitizeIt software version 2.3[13] to extract the required data from the graphs. Furthermore, we imputed missing SDs of means for some studies using SEs, 95% CIs, or p values. We adhered to published guidance of the Cochrane handbook[14] throughout. We used the *metan* command in Stata version 15 (StataCorp, College Station, TX, USA) to do random effects meta-analyses.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

A PRISMA flowchart of study selection is presented in figure 1. The overall search resulted in 6491 citations. 2651 duplicate studies were excluded; a further 3769 studies were excluded on review of title and abstract, and 25 reports did not meet inclusion criteria. Thus, 46 publications from 36 randomised controlled trials

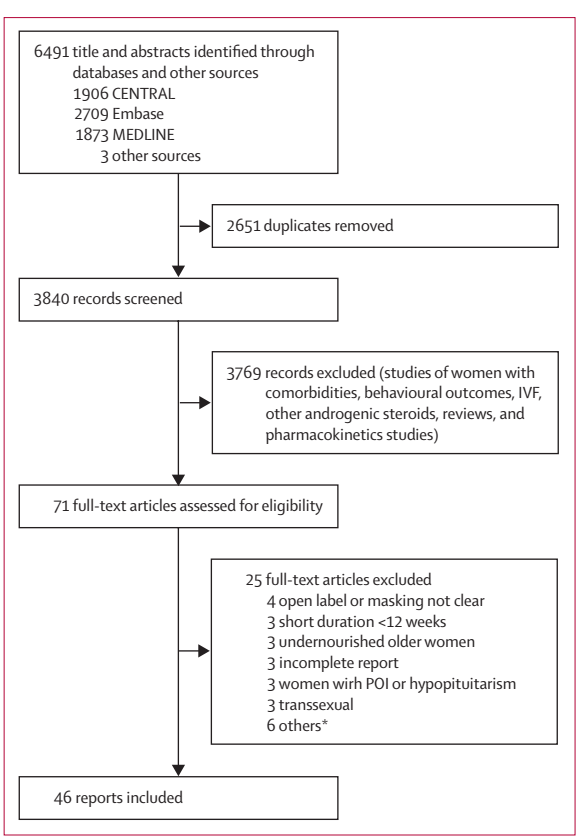

Figure 1: **Selection of studies for inclusion**
CENTRAL=Cochrane Central Register of Controlled Trials. POI=primary ovarian insufficiency. IVF=in-vitro fertilisation. *Studies were excluded because they were either a review, protocol, non-randomised controlled trial, or had no appropriate comparators.

	Country	Setting	Study population	Primary outcomes of study	Age range or mean age (years)	Women randomised (n)	Study duration	Route of administration	Interventions
Barrett-Connor et al (1999)[15]	USA	Multicentre	Surgical menopause	Bone mineral density and lipids	21–65	311	2 years	Oral	Conjugated equine oestrogen 0·625 mg or 1·25 mg daily; conjugated equine oestrogen 0·625 mg plus methyltestosterone 1·25 mg daily; or conjugated equine oestrogen 1·25 mg plus methyltestosterone 2·5 mg daily
Basaria et al (2002)[16]	USA	Single centre	Surgical menopause and natural menopause on oestrogen therapy	Plasma viscosity and fibrinogen	42–77	40	16 weeks	Oral	Esterified oestrogen 1·25 mg daily with or without methyltestosterone 2·5 mg daily
Braunstein et al (2005)[17]	USA	Multicentre	Surgical menopause with low sexual desire	Sexual function	24–70	447	24 weeks	Patch	Conjugated equine oestrogen daily plus transdermal testosterone patch 150 µg, 300 µg, or 450 µg twice weekly; or placebo
Buster et al (2005)[18]	Australia, Canada, and USA	Multicentre	Surgical menopause with low sexual desire	Sexual function	≥20	533	24 weeks	Patch	Conjugated equine oestrogen plus testosterone patch 300 µg twice weekly; or placebo
Davis et al (1995,[22] 2000)[24*†]	Australia	Single centre	Surgical menopause and natural menopause	Sexual function	51·3 (oestradiol), 57·0 (testosterone)	34	2 years	Implant	Oestradiol 50 mg every 3 months with or without testosterone 50 mg every 3 months
Davis et al (2006)[23]	Australia and Europe	Multicentre	Surgical menopause with low sexual desire	Sexual function	20–70	77	24 weeks	Patch	Testosterone patch 300 µg daily; or placebo
Davis et al (2008a)[19]	Australia	Multicentre	Premenopausal women with low sexual desire	Sexual function	35–46	261	16 weeks	Spray	Testosterone spray 56 µL, 90 µL, or 180 µL (50 µg/µL) daily; or placebo
Davis et al (2008b,[8] 2009)[20†]	Multinational	Multicentre	Surgical menopause and natural menopause with low sexual desire	Sexual function	20–70	814	52 weeks	Patch	Testosterone patch 150 µg or 300 µg daily; or placebo
Davis et al (2014)[21]	Australia	Single centre	Natural menopause	Cognition	55–65	89	26 weeks	Gel	Transdermal testosterone gel 300 µg daily; or placebo
de Paula et al (2007)[25]	Brazil	Single centre	Natural menopause with sexual dysfunction	Sexual function	49–63	85	4 months	Oral	HRT plus either methyltestosterone 2·5 mg daily or placebo
Dias et al (2006)[26]	Brazil	Multicentre	Natural menopause with depression	Depression	53·7	72	24 weeks	Oral	Oestradiol 0·625 mg, medroxyprogesterone acetate 2·5 mg, and methyltestosterone 2·5 mg daily; oestradiol 0·625 mg, medroxyprogesterone 2·5 mg, and placebo daily; methyltestosterone 2·5 mg and two placebos daily; or three placebos daily
Dobs et al (2002)[27]	USA	Single centre	Surgical menopause and natural menopause	Body composition	41–76	40	16 weeks	Oral	Esterified oestrogen 1·25 mg daily with or without methyltestosterone 2·5 mg
El-Hage et al (2007)[28]	Australia	Single centre	Surgical menopause with low sexual function	Sexual function	54·0	36	12 weeks	Cream	Testosterone 10 mg cream daily; or placebo
Floter et al (2002,[30] 2004,[31] 2005)[29] and Kocoska-Maras et al (2009)[42†]	Sweden	Single centre	Surgical menopause	Sexual function	45–60	50	24 weeks	Oral	Oestradiol valerate 2 mg with or without testosterone undecanoate 40 mg daily
Fooladi et al (2014)[32]	Australia	Single centre	Women on SSRI or SNRI therapy and low sexual desire	Sexual function	35–55	44	12 weeks	Patch	Transdermal testosterone patch 300 µg daily; or placebo
Goldstat et al (2003)[33]	Australia	Single centre	Premenopausal women with low sexual desire	Sexual function	30–45	49	12 weeks	Cream	Testosterone 10 mg cream daily; or placebo
Gruber et al (1998)[34]	Austria	Single centre	Surgical menopause, no HRT	Body composition	51·4	39	6 months	Gel	2·5 g androstanolone twice daily; or placebo
Hickok et al (1993)[35]	USA	Single centre	Natural menopause	Lipids and menopausal symptoms	40–60	26	6 months	Oral	Esterified oestrogen 0·625 mg with or without methyltestosterone 1·25 mg daily

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	Country	Setting	Study population	Primary outcomes of study	Age range or mean age (years)	Women randomised (n)	Study duration	Route of administration	Interventions
(Continued from previous page)									
Hofling et al (2007a,[36] 2007b)[37]†	Sweden	Single centre	Natural menopause	Breast density and cell proliferation	45–65	99	6 months	Patch	Conjugated equine oestrogen 2 mg and norethisterone acetate 1 mg plus testosterone 300 µg twice weekly; or conjugated equine oestrogen 2 mg and norethisterone acetate 1 mg plus placebo
Huang et al (2014a,[38] 2014b,[40] 2015a,[39] 2015b)[41]†	USA	Two centres	Surgical menopause and natural menopause with total testosterone <31 ng/dL or free testosterone <3·5 pg/mL	Sexual function	21–60	71	24 weeks	Intramuscular injection	Testosterone enanthate 3 mg, 6·25 mg, 12·5 mg, or 25 mg weekly; or placebo
Leao et al (2006)[43]	Brazil	Two centres	Surgical menopause	Cardiometabolic biomarkers	42–62	37	12 months	Oral	Oestradiol 1 mg plus either methyltestosterone 1·25 mg daily or placebo
Liu et al (2011)[44]	USA	Not clear	Natural menopause with 50 hot flushes per week	Vasomotor symptoms	Not clear	1248	12 weeks	Oral	Esterified oestrogen 0·15 mg, 0·30 mg, or 0·45 mg daily; esterified oestrogen 0·15 mg plus methyltestosterone 0·15 mg or 0·30 mg daily; esterified oestrogen 0·30 mg plus methyltestosterone 0·30 mg or 0·60 mg daily; methyltestosterone 0·60 mg daily; or placebo
Lobo et al (2003)[45]	USA	Multicentre	Surgical menopause and natural menopause with low sexual desire	Sexual function	45–65	218	16 weeks	Oral	Esterified oestrogen 0·625 mg with or without methyltestosterone 1·25 mg daily
Miller et al (2000)[46]	USA	Single centre	Surgical menopause and natural menopause	Bone mineral density and bone turnover markers	53·5 (oestradiol), 54·6 (testosterone)	66	12 weeks	Sublingual	Patients with hysterectomy: micronised oestradiol 0·5 mg with or without micronised testosterone 1·25 mg twice daily; patients with intact uterus: micronised oestradiol 0·5 mg plus micronised progesterone 100 mg with or without micronised testosterone 1·25 mg twice daily
Moller et al (2010,[47] 2013)[48]†	Sweden	Single centre	Surgical menopause	Cognitive fatigue	45–60	50	24 weeks	Oral	Oestradiol valerate 2 mg plus either testosterone undecanoate 40 mg or placebo daily
Nathorst-Boos et al (2006)[49]	Sweden	Single centre	Natural menopause, on HRT with low sexual desire	Sexual function	50–65	60	3 months	Oral and transdermal	Testosterone 10 mg daily; or placebo
Panay et al (2010)[50]	Australia, Canada, Germany, and UK	Multicentre	Natural menopause with low sexual desire	Sexual function	40–70	272	6 months	Patch	Transdermal testosterone patch 300 µg twice weekly; or placebo
Penteado et al (2009)[51]	Brazil	Single centre	Natural menopause with sexual complaints	Sexual function	42–60	60	12 months	Oral	Conjugated equine oestrogen 0·625 mg and medroxyprogesterone acetate 2·5 mg plus either methyltestosterone 2·0 mg or placebo daily
Shifren et al (2000)[52]	USA	Multicentre	Surgical menopause with low sexual function	Sexual function	31–56	75	12 weeks	Oral and patch	Conjugated equine oestrogen 0·625 mg with or without testosterone 150 mg or 300 mg daily
Shifren et al (2006)[53]	Australia, Canada, and USA	Multicentre	Natural menopause with low sexual desire	Sexual function	40–70	549	24 weeks	Patch	Testosterone patch 300 µg twice weekly; or placebo
Simon et al (1999)[55]	USA	Multicentre	Natural menopause with menopausal symptoms	Somatic menopausal symptoms	53·7	93	12 weeks	Oral	Esterified oestrogen 0·625 mg or 1·25 mg daily; or esterified oestrogen 0·625 mg plus methyltestosterone 1·25 mg daily; or esterified oestrogen 1·25 mg plus methyltestosterone 2·5 mg daily; or placebo
Simon et al (2005)[54]	Australia, Canada, and USA	Multicentre	Surgical menopause with low sexual desire	Sexual function	20–70	562	24 weeks	Patch	Transdermal or oral oestrogen with transdermal testosterone patch or placebo
Watts et al (1995)[56]	USA	Multicentre	Surgical menopause	Bone mineral density and lipids	21–60	66	2 years	Oral	Esterified oestrogen 1·25 mg with or without methyltestosterone 2·5 mg daily
Wisniewski et al (2002)[57]	USA	Single centre	Surgical menopause and natural menopause	Cognitive function	46–77	26	4 months	Oral	Esterified oestrogen 1·25 mg with or without methyltestosterone 2·5 mg daily

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	Country	Setting	Study population	Primary outcomes of study	Age range or mean age (years)	Women randomised (n)	Study duration	Route of administration	Interventions
(Continued from previous page)									
Unpublished trial 2002005 (2004)[7]	Australia, Canada, and USA	Multicentre	Natural menopause	Sexual function	40–70	610	52 weeks	Patch	Transdermal testosterone patch 300 µg daily; or placebo
Unpublished trial 2007004 (2011)[58]	USA	Multicentre	Natural menopause	Endometrial safety	45–70	1271	52 weeks	Patch	Transdermal testosterone patch 300 µg daily; or placebo

HRT=hormone replacement therapy. SSRI=selective serotonin reuptake inhibitor. SNRI=serotonin noradrenalin reuptake inhibitor. *Single-blind trial. †Same trial but yielded multiple publications with different outcomes.

Table: **Characteristics of included trials**

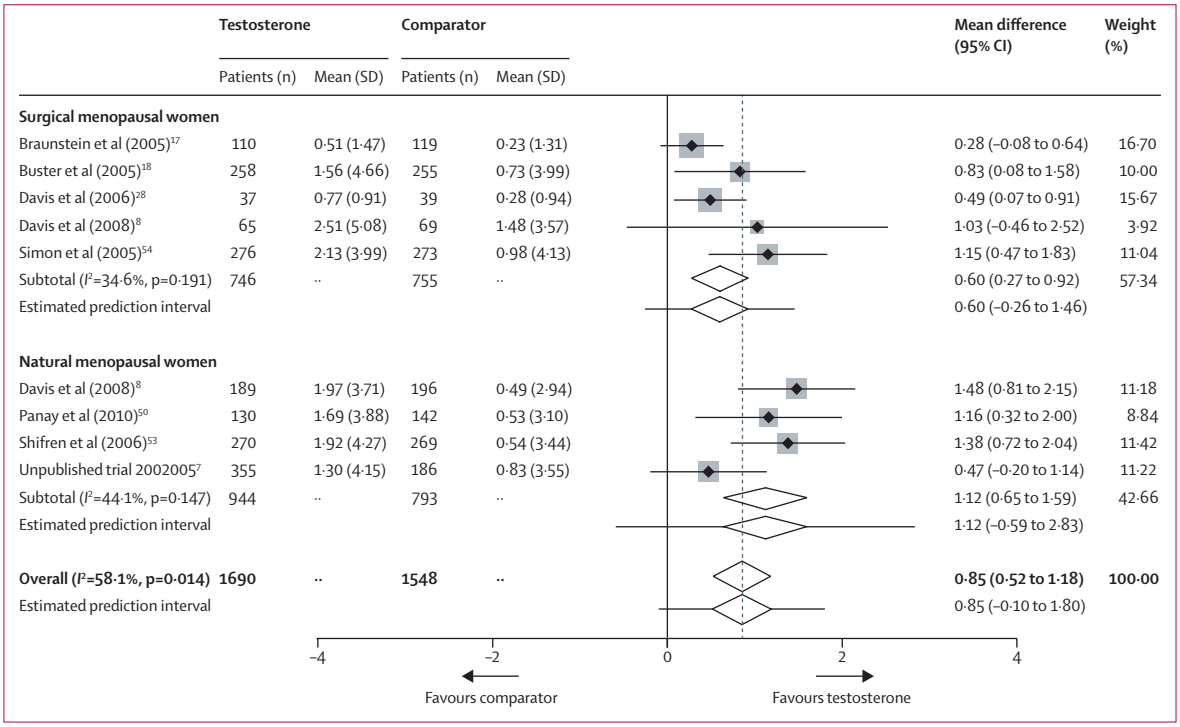

Figure 2: **Effect of testosterone versus comparator on satisfying sexual events, by menopausal status**
Data are change in number of satisfactory sexual events per month. Grey square indicates the weight of the study. Black diamond represents the mean difference per study and white diamond the mean difference overall. Horizontal lines depict the 95% CI. Vertical dotted line shows overall mean difference.

See Online for appendix

were included in the meta-analysis. 44 reports[8,15–57] were identified by electronic searches and two[7,58] were unpublished trials identified by manual searching. 13 studies specifically recruited women with low sexual function and one study recruited women based on the amount of testosterone in blood (table). Data included in the meta-analysis are from 8480 participants in 43 publications[7,8,15–18,20–31,34–58] of postmenopausal women, two reports[19,33] of premenopausal women, and one study[32] that included both premenopausal and postmenopausal women. Testosterone was administered orally in 15 trials;[7,15,16,25–27,30,35,43–45,47,51,55–58] non-oral administration was by transdermal patch in 13 trials,[8,17–19,23,32,49,50,52–54] transdermal cream in two trials,[28,33] transdermal gel in two trials,[21,34] transdermal spray in one trial,[19] a sublingual formulation in one trial,[46] intramuscular injection in one trial,[38] and subcutaneous implant in one trial.[22]

15 studies[7,8,17,18,23,25,28,30,38,45,50–54] in 3766 postmenopausal women and three studies[19,32,33] in 226 premenopausal women provided data for the effects of testosterone on sexual function (appendix pp 1, 2). Eight studies[7,8,17,18,23,50,53,54] reported on the mean change in satisfying sexual events over 4 weeks; four studies included women who had surgical menopause, three included those in natural menopause, and one included both. In postmenopausal women, compared with placebo or a comparator,

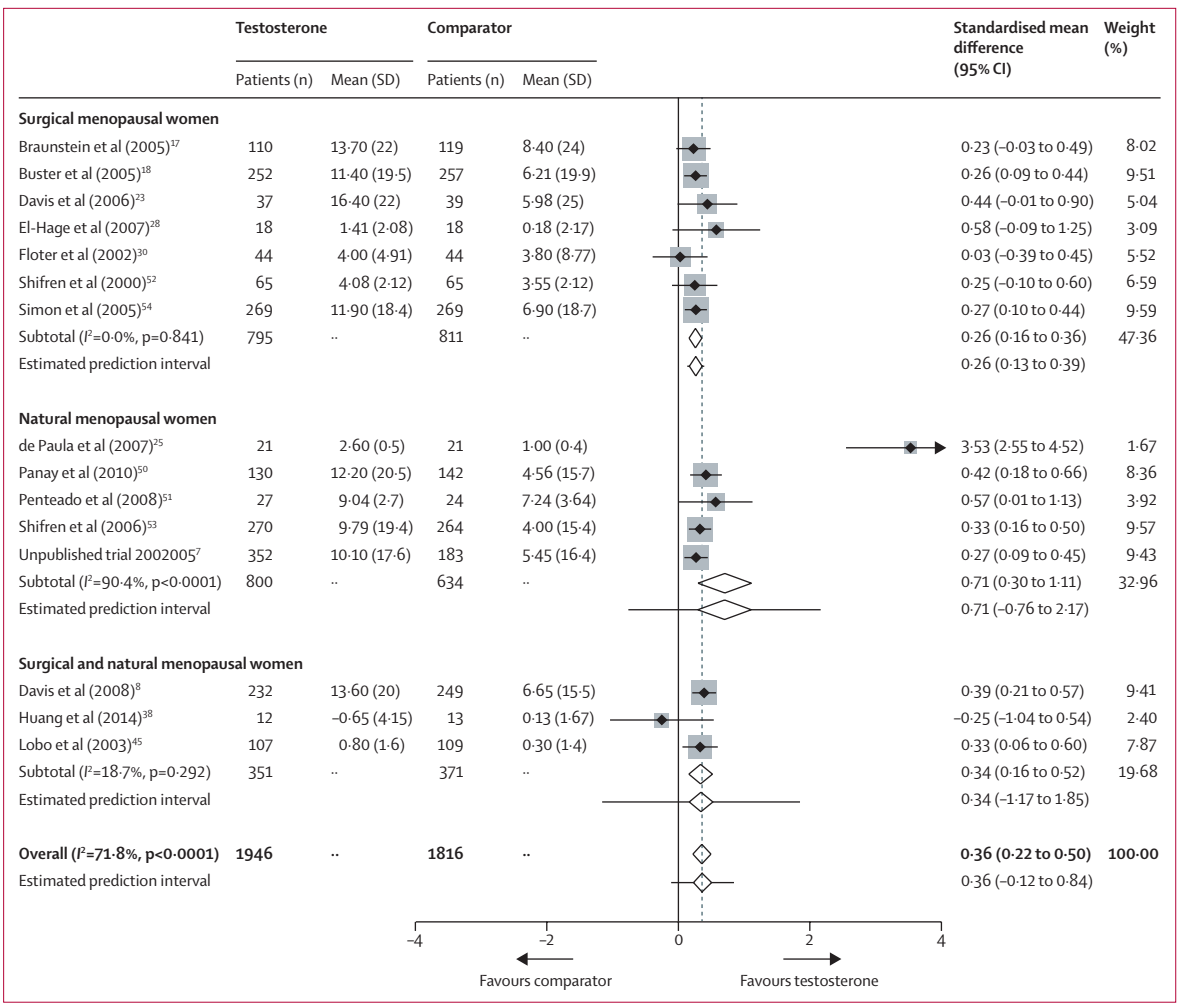

Figure 3: **Effect of testosterone versus comparator on sexual desire, by menopausal status**
Data are change in sexual desire score per month. Grey square indicates the weight of the study. Black diamond represents the standardised mean difference per study and white diamond represents the overall standardised mean difference. Horizontal lines depict the 95% CI. Vertical dotted line shows overall standardised mean difference.

testosterone was associated with a significant increase in the number of satisfying sexual events (mean difference 0·85, 95% CI 0·52 to 1·18; p=0·014; 95% prediction interval –0·10 to 1·80; figure 2). In eight studies, testosterone was associated with a significant rise in the frequency of satisfying sexual events compared with placebo or a comparator, irrespective of the mode of oestrogen delivery (mean difference 0·82, 95% CI 0·50 to 1·15; appendix p 8). In postmenopausal women, compared with placebo or a comparator, testosterone augmented sexual desire (standardised mean difference 0·36, 95% CI 0·22 to 0·50; p<0·0001; 95% prediction interval –0·12 to 0·84; figure 3), arousal (standardised mean difference 0·28, 95% CI 0·21 to 0·35; appendix p 11), orgasm (standardised mean difference 0·25, 95% CI 0·18 to 0·32; appendix p 12), pleasure (mean difference 6·86, 95% CI 5·19 to 8·52; appendix p 14), responsiveness (standardised mean difference 0·28, 95% CI 0·21 to 0·35; appendix p 17), and self-image (mean difference 5·64, 95% CI 4·03 to 7·26; appendix p 18); moreover, testosterone reduced concerns (mean difference 8·99, 95% CI 6·90 to 11·08; appendix p 16). The three small studies that included premenopausal women showed no benefit over placebo or a comparator for the frequency of satisfying sexual events, total sexual function score, or any sexual function domain for which data were available (appendix pp 9, 10, 13, 15). Compared with placebo or a comparator, testosterone was associated with reduced personal sexual distress in all studies of postmenopausal women (standardised mean difference –0·27, 95% CI –0·36 to –0·17; appendix p 21). The one study that provided data for premenopausal women showed a reduction in personal sexual distress (mean difference –14·06, 95% CI –18·16 to –9·96; appendix p 22).

Pooled results of nine studies[15,16,25,27,31,35,43,45,56] in 637 post-menopausal women showed that testosterone given

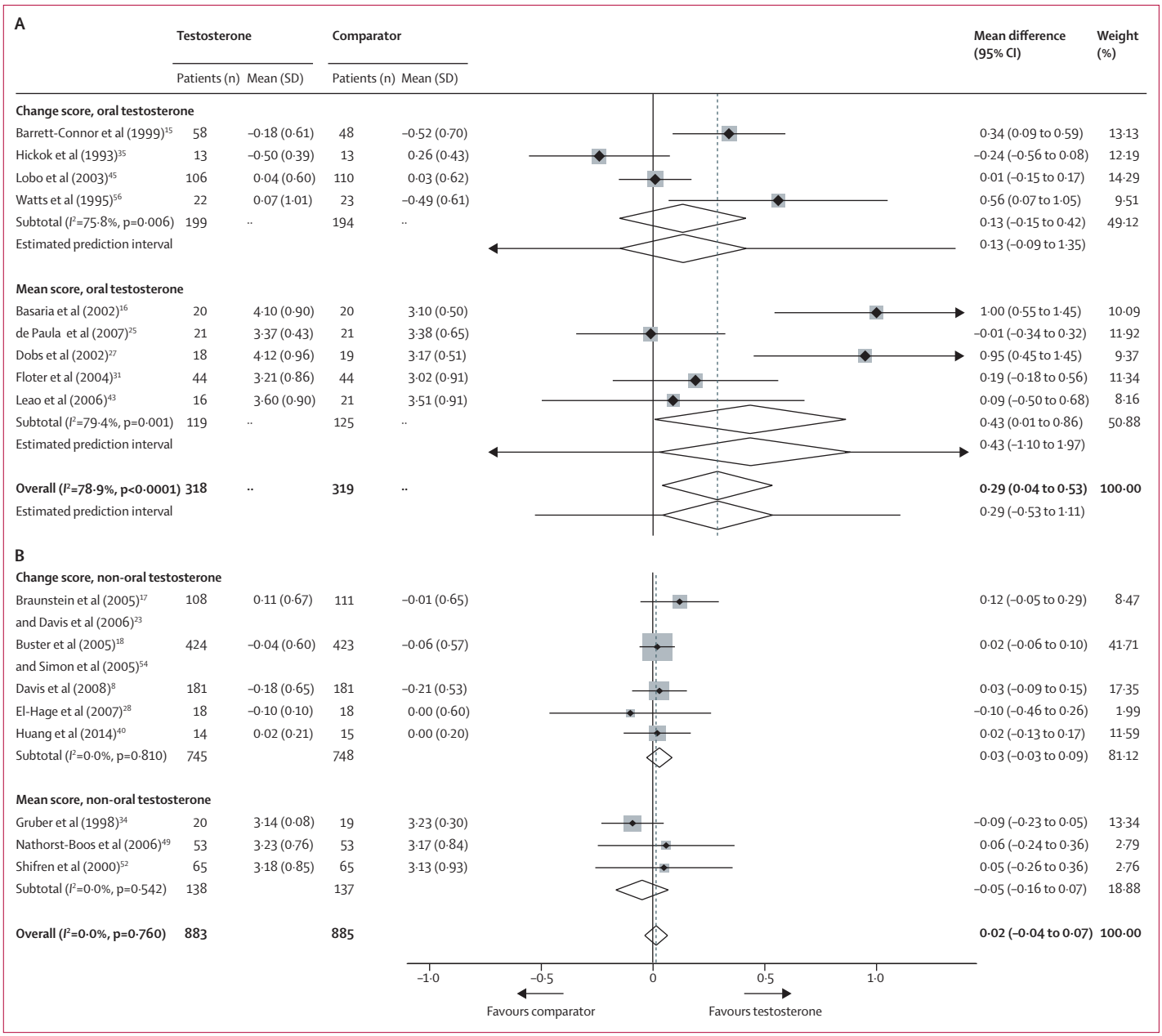

Figure 4: **Effect of testosterone versus comparator on LDL-cholesterol for oral and non-oral testosterone**

Oral testosterone effects are shown in (A) and non-oral testosterone effects in (B). Studies reported outcomes in different ways such that they could not all be combined; some provided the change from baseline to end of study, others only provided the mean score for each treatment group at the end of the study. Data are mmol/L. Grey square indicates the weight of the study. Black diamond represents the mean difference per study and white diamond the mean difference overall. Horizontal lines depict the 95% CI. Vertical dotted line shows overall mean difference.

orally was associated with an increase in LDL-cholesterol (mean difference 0·29, 95% CI 0·04 to 0·53; p<0·0001; 95% prediction interval −0·53 to 1·11; figure 4A) and a reduction in total cholesterol (mean difference −0·32, 95% CI −0·50 to −0·14; appendix p 23) HDL-cholesterol (mean difference −0·40, 95% CI −0·49 to −0·30; appendix p 25), and triglycerides (mean difference −0·30, 95% CI −0·49 to −0·12; appendix p 27) compared with placebo or a comparator. In ten studies[8,17,18,23,28,34,38,49,52,54] of 1774 participants, testosterone administered non-orally was not associated with any significant lipid effects (mean difference 0·02, 95% CI −0·04 to 0·07; p=0·76; figure 4B; appendix pp 24, 26, 28). No effects of testosterone given both orally and non-orally were recorded for amounts of glucose and insulin in blood, blood pressure, or waist-to-hip ratio (appendix pp 29–31).

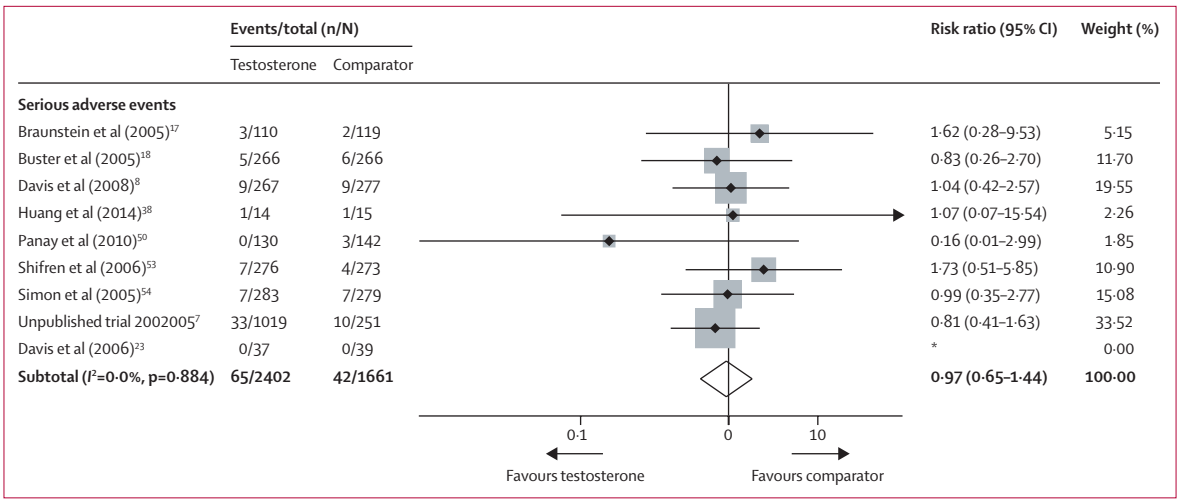

Figure 5: **Effect of testosterone versus comparator on serious adverse events**
Grey square indicates the weight of the study. Black diamond represents the risk ratio per study and white diamond the risk ratio overall. Horizontal lines depict the 95% CI. *Excluded.

Analysis of three studies[25,34,43] in 118 participants that provided data for BMI showed no increase with testosterone (appendix p 32); however, analysis of data for weight from five studies[18,34,43,54,58] in 2032 postmenopausal women indicated that testosterone led to weight gain (mean difference 0·48, 95% CI 0·16 to 0·79; appendix p 32).

Limited data were available for cognitive performance, from three studies of 159 postmenopausal women—two parallel group randomised controlled trials[21,57] and one crossover study.[47] Data showed no effect of testosterone for any of the reported cognitive measures (appendix pp 33–35).

Together, data for 500 postmenopausal women from seven parallel group studies[15,22,24,27,38,46,56] and one crossover study[29] showed no effect of testosterone on bone mineral density, body composition, or muscle strength (appendix pp 36–39).

Analysis of pooled data from four studies[8,28,32,33]—two of 538 postmenopausal women and two of 67 premenopausal women—showed that testosterone treatment did not modify depressive mood, irrespective of menopausal status (appendix p 40). No benefits of testosterone were seen for psychological general wellbeing index scores from five studies[8,21,23,38,52] in 810 postmenopausal women and three studies[19,32,33] in 224 premenopausal women (appendix p 41).

Mammographic breast density did not change with testosterone treatment (data available for 345 postmenopausal women).[7,20,37] One study[7] of Ki67 staining of breast tissue—as an index of breast cell proliferation—did not show an effect of testosterone in 45 postmenopausal women. No other adverse breast health effects of testosterone were identified (breast pain, breast tenderness, breast engorgement, breast mass, or breast cancer; appendix pp 42, 43). Using data from one unpublished study,[58] endometrial thickness did not increase with testosterone treatment in 843 postmenopausal women (appendix p 44).

Pooling data from 11 publications[8,17–19,23,30,45,50,53,54,56] in 3264 participants showed that use of testosterone was associated with a greater likelihood of acne compared with placebo or a comparator (RR 1·46, 95% CI 1·11–1·92; appendix p 45). Data from 11 studies[8,16–18,30,35,50,53,54,56] in 4178 participants showed that testosterone was associated with a greater likelihood of hair growth compared with placebo or a comparator (RR 1·69, 95% CI 1·33–2·14; appendix p 45). No other androgenic effects of testosterone (eg, alopecia, clitoromegaly, or voice change) were recorded compared with placebo or a comparator therapy (appendix p 45).

No serious adverse event was more frequent with testosterone compared with placebo or a comparator (RR 0·97, 95% CI 0·65–1·44; p=0·884; figure 5).[8,17,18,23,38,50,53,54] Specifically, testosterone was not associated with more frequent reporting of cardiovascular events (eg, acute myocardial infarction, stroke, deep vein thrombosis, or cardiovascular deaths; appendix p 46). The overall proportion of patients who withdrew from treatment because of adverse events was similar across treatment groups (appendix p 47).[8,17–19,23,50,53,54]

Among the 36 randomised controlled trials included in the meta-analysis, there was a high risk of attrition bias. Information about random sequence generation and allocation concealment was unclear in about half the trials. A summary of the proportion of trials that were at low, unclear, and high risk of bias for each domain is shown in figure 6. Details of the risk-of-bias assessment for included trials are provided in the appendix (p 48). A funnel plot could only be generated for sexual desire because of the few included studies reporting other outcomes; no small study effect was seen in the funnel plot (appendix p 49).

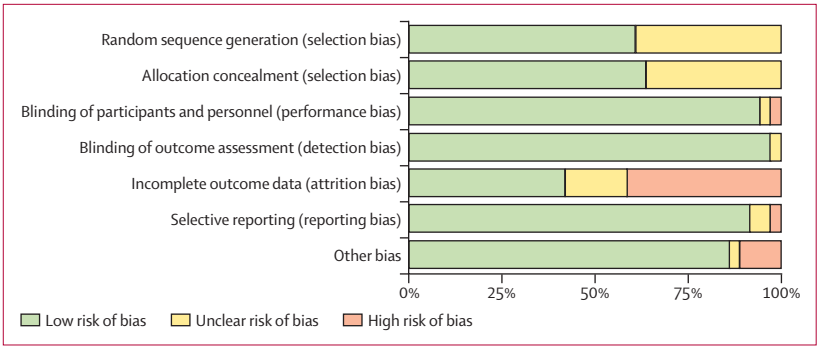

Figure 6: **Review authors' assessments about risk-of-bias of included studies**
Bars show percentages across all included studies.

Discussion

The findings of our systematic review and meta-analysis show beneficial treatment effects of testosterone for postmenopausal women on a comprehensive array of sexual function domains, the frequency of satisfying sexual events, and sexually associated personal distress. For premenopausal women, the only observed benefit was a reduction in sexually associated personal distress in one small study. Although testosterone treatment was associated with an increase in acne and hair growth, these adverse events have not led to participant withdrawal from clinical trials.[8] Thus, mild androgenic effects might be a concern more to clinicians than to patients. Unfavourable cardiometabolic effects were restricted to adverse lipoprotein effects with oral testosterone.

The most frequently used female sexual function questionnaires are the Female Sexual Function Index (FSFI)[59] and the Profile of Female Sexual Function (PFSF).[60] Both provide assessments of desire, arousal, and orgasm, but only the PFSF, which was developed after the FSFI, assesses sexual concerns, responsiveness, and self-image. Diaries for satisfying sexual events and sexual distress scales have only been introduced in the past few years and, thus, none of the studies of oral testosterone provided data for these outcomes. Irrespective of the scales used and outcomes measured, consistent beneficial effects were seen with testosterone treatment for naturally and surgically menopausal women, whether or not they were also using oral or non-oral oestrogen concurrently. The clinical meaningfulness of these effects is much debated, with the relevance of one or two additional satisfying sexual events per month questioned. However, the beneficial effects of testosterone, as shown in our study, extend beyond a simple count of the number of satisfying sexual events per month. Sexually active postmenopausal women dissatisfied with sexual function report, on average, five sexual events per month.[8,61] Increasing the number of occasions on which women experience a satisfying sexual encounter from never, or occasionally, to at least once or twice a month can strikingly improve the personal wellbeing and self-esteem of the affected women, their partners, and their relationships.[62,63] Further confirmation of the importance of these effects of testosterone is with the reduction in sexual concerns, improved sexual self-image, and diminished sexually associated distress reported in the present meta-analysis.

It is noteworthy that most of the studies we included in our systematic review and meta-analysis excluded women with identifiable causes of sexual concerns, such as dyspareunia, depression, or antidepressant use. Testosterone is not a first-line treatment for management of female sexual dysfunction and is only indicated after a full clinical assessment.[64] I^2 values for the pooled outcomes of satisfying sexual events (58%) and sexual desire (69%) indicated moderately high heterogeneity between the included studies. To estimate the potential effects of testosterone on these outcomes in future individual studies, prediction intervals were estimated. For both outcomes, the 95% prediction interval included zero meaning that, although the effect of testosterone for the completed studies was, on average, positive for satisfying sexual events and sexual desire, testosterone might not always be beneficial in an individual setting. For the other sexual outcomes, including sexual distress, the random-effects meta-analysis with 95% prediction intervals provided strong evidence that testosterone will be beneficial for postmenopausal women in future individual studies. This finding would suggest that the effects of testosterone on satisfying sexual events and sexual desire are more complex and affected by factors additional to the effects of testosterone on arousal, orgasm, and other measured outcomes.

The dearth of data pertaining to premenopausal women means no conclusions can be drawn about the efficacy of testosterone treatment for sexual dysfunction in this population. Larger studies in premenopausal women are needed to inform clinical recommendations.

Concern about the cardiometabolic safety of exogenous testosterone has been a barrier to approval of testosterone treatment for women. Findings of the present systematic review and meta-analysis show that oral testosterone adversely affects lipid profiles whereas non-oral treatment (eg, via transdermal patch or cream) has no such adverse effects. Although testosterone has been shown to be a vasodilator,[65] the overall effect on blood pressure was neutral. Overall, testosterone treatment was associated with a small but significant increase in weight, such that patients should be advised of this effect if testosterone treatment is being considered.

Although cognitive and musculoskeletal effects were included as primary outcomes, our study highlights the paucity of adequately powered clinical trials with data for these outcomes. For any conclusions to be made, standardisation of endpoints is needed for future studies, particularly for the assessment of cognitive performance and muscle health.

Claims have been made that testosterone treatment for women—even in supraphysiological doses—is

not masculinising.[66] Our analyses indicate testosterone treatment administered at doses intended to approximate physiological replacement to levels seen in premenopausal women is associated with a greater likelihood of acne and hair growth, but not alopecia, voice deepening, or cliteromegaly, compared with a comparator or placebo. Therefore, women who initiate testosterone treatment must be warned that these side-effects can occur and counselled against applying more than the prescribed dose. Anxiety, irritability, and depression are purported symptoms of testosterone insufficiency in women and testosterone treatment is suggested to be mood stabilising.[66] However, available data—although limited—do not support these conclusions. Without strong evidence of improvement in depressive symptoms and mood, testosterone should not be considered a treatment for depression in postmenopausal women. Our systematic review and meta-analysis indicates that current testosterone use was not associated with an increase in serious adverse events, including adverse endometrial and breast effects.

Our study has several strengths. First, we included data not only from studies identified by a comprehensive search of the published literature but also from completed but unpublished randomised controlled trials from the clinical development programme of the transdermal testosterone patch, identified from EMA and FDA submissions. Second, after contacting corresponding authors and accessing source data, we included several published studies previously excluded from reviews because of insufficient outcome data.[3,67] These strengths make our study the most comprehensive systematic review and meta-analysis of testosterone treatment for women yet undertaken.

Our analysis has several limitations. First, a limitation of the included studies was attrition bias. In several studies, withdrawal and lost to follow-up was enhanced in women randomly allocated placebo compared with those assigned the active treatment. This bias is an issue for studies of several months' duration in which the main outcome is self-reported and the active treatment is effective. In the largest of the included studies,[8] women randomly allocated placebo were more likely to discontinue because of a lack of benefit, resulting in participants who persisted possibly being more likely to be placebo responders. A second limitation was that not all studies that reported sexual function outcomes recruited women with sexual dysfunction, and among those that had sexual dysfunction as an inclusion criterion, the definition of sexual dysfunction was not consistent. Third, we were unable to include the outcomes of two large double-blind randomised controlled trials of a transdermal testosterone gel, in which a therapeutic effect of testosterone on satisfying sexual events was not detected, because the findings have only been reported in abstract form, with insufficient numerical and methodological data to enable inclusion.[68,69] Not only were the overall increases in satisfying sexual events per month in these two studies greater than seen across the transdermal testosterone patch studies, but the placebo groups in these two trials had increases in satisfying sexual events three fold to fourfold greater than seen with placebo in other testosterone patch studies.[8,50,53] This finding suggests there could have been some fundamental differences in either the study populations or the conduct of these studies, compared with other published studies. Finally, the reporting of outcomes for premenopausal women was limited by the paucity of studies. Similarly, findings for several of our a priori outcomes—notably, effects on musculoskeletal health, cognitive performance, mood and wellbeing, breast cancer risk, and cardiovascular disease—are inconclusive. This drawback is attributable to scant published data (these being mostly secondary outcomes for which data were available and analyses underpowered) and use of different outcome measures.[65]

Our comprehensive systematic review provides robust support for a trial of testosterone treatment, using a dose appropriate for women, when clinically indicated in postmenopausal women.[64] The absence of any approved testosterone formulations for women in any country, however, is a major treatment barrier. This shortfall urgently needs to be addressed to eradicate the widespread practice of women being treated with male formulations and compounded products, resulting in testosterone concentrations several fold greater than appropriate for women. Further research is needed to clarify the effects of testosterone treatment in premenopausal women and the effects on musculoskeletal and cognitive health and long-term safety.

Contributors

RMI, RJB, and SRD contributed to study design and preparation of the figures. RMI contributed to the literature search and data extraction. RMI, RJB, SG, and SRD contributed to study selection. RMI, RJB, and MJP contributed to the risk-of-bias analysis and data analysis. All authors contributed to data interpretation and review of the report. RMI and SRD contributed to writing of the report.

Declaration of interests

SRD declares honoraria from Besins Healthcare and Pfizer Australia and has been a consultant to Besins Healthcare, Mayne Pharmaceuticals, Lawley Pharmaceuticals, and Que Oncology. RMI, RJB, SG, and MJP declare no competing interests.

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