Symptomatic benefits of testosterone treatment in patient subgroups: a systematic review, individual participant data meta-analysis, and aggregate data meta-analysis

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Summary

Background Testosterone replacement therapy is known to improve sexual function in men younger than 40 years with pathological hypogonadism. However, the extent to which testosterone alleviates sexual dysfunction in older men and men with obesity is unclear, despite the fact that testosterone is being increasingly prescribed to these patient populations. We aimed to evaluate whether subgroups of men with low testosterone derive any symptomatic benefit from testosterone treatment.

Methods We did a systematic review and meta-analysis to evaluate characteristics associated with symptomatic benefit of testosterone treatment versus placebo in men aged 18 years and older with a baseline serum total testosterone concentration of less than 12 nmol/L. We searched major electronic databases (MEDLINE, Embase, Science Citation Index, and the Cochrane Central Register of Controlled Trials) and clinical trial registries for reports published in English between Jan 1, 1992, and Aug 27, 2018. Anonymised individual participant data were requested from the investigators of all identified trials. Primary (cardiovascular) outcomes from this analysis have been published previously. In this report, we present the secondary outcomes of sexual function, quality of life, and psychological outcomes at 12 months. We did a one-stage individual participant data meta-analysis with a random-effects linear regression model, and a two-stage meta-analysis integrating individual participant data with aggregated data from studies that did not provide individual participant data. This study is registered with PROSPERO, CRD42018111005.

Findings 9871 citations were identified through database searches. After exclusion of duplicates and publications not meeting inclusion criteria, 225 full texts were assessed for inclusion, of which 109 publications reporting 35 primary studies (with a total 5601 participants) were included. Of these, 17 trials provided individual participant data (3431 participants; median age 67 years [IQR 60–72]; 3281 [97%] of 3380 aged ≥40 years) Compared with placebo, testosterone treatment increased 15-item International Index of Erectile Function (IIEF-15) total score (mean difference 5·52 [95% CI 3·95–7·10]; τ^2=1·17; n=1412) and IIEF-15 erectile function subscore (2·14 [1·40–2·89]; τ^2=0·64; n=1436), reaching the minimal clinically important difference for mild erectile dysfunction. These effects were not found to be dependent on participant age, obesity, presence of diabetes, or baseline serum total testosterone. However, absolute IIEF-15 scores reached during testosterone treatment were subject to thresholds in patient age and baseline serum total testosterone. Testosterone significantly improved Aging Males' Symptoms score, and some 12-item or 36-item Short Form Survey quality of life subscores compared with placebo, but it did not significantly improve psychological symptoms (measured by Beck Depression Inventory).

Interpretation In men aged 40 years or older with baseline serum testosterone of less than 12 nmol/L, short-to-medium-term testosterone treatment could provide clinically meaningful treatment for mild erectile dysfunction, irrespective of patient age, obesity, or degree of low testosterone. However, due to more severe baseline symptoms, the absolute level of sexual function reached during testosterone treatment might be lower in older men and men with obesity.

Funding National Institute for Health and Care Research Health Technology Assessment Programme.

Introduction

Low testosterone can induce reductions in secondary sexual characteristics and cause sexual dysfunction, decreased lean mass and muscle strength, anaemia, and osteoporosis, among other symptoms.[1] Testosterone replacement therapy can provide symptomatic benefit in

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Research in context

Evidence before this study

Global revenue in sales of testosterone increased from US$150 million, in 2000, to $1·8 billion, in 2011. Testosterone is approved by the US Food and Drug Administration (FDA) for the treatment of men with low testosterone due to testicular or hypothalamic–pituitary disorders (ie, classic hypogonadism) only. However, testosterone has been increasingly prescribed off-label to relieve symptoms attributable to low testosterone in men with a reduced health status due to old age and obesity. The National Institutes of Health Testosterone Trials were designed to evaluate the efficacy of testosterone treatment in men older than 65 years with low testosterone, with or without obesity; improved sexual function was observed (effect size 0·45) but the magnitude of benefit compared with younger men has been questioned by some clinicians. The FDA still states that the benefits of testosterone have not been established in men with age-related low testosterone. Lifestyle interventions (eg, weight loss or exercise) are commonly recommended for symptomatic low testosterone in men with obesity. A scarcity of evidence to stratify the effects of testosterone by patient subgroup has created conflicting guidance, wide variations in clinical practice, and inconsistent treatment for men with symptoms of low testosterone. Comparing the effectiveness of testosterone to improve symptoms in specific patient subgroups, including older men and men with obesity, would improve the prediction of symptomatic benefit in men with low testosterone.

We used individual participant data to evaluate whether subgroups of men with low testosterone had any symptomatic benefit from testosterone treatment versus placebo. Sensitive search strategies identified reports of published, ongoing, and unpublished randomised clinical trials with data on symptoms during at least 3 months of testosterone monotherapy in men with testosterone concentrations of less than 12 nmol/L at baseline. Major electronic databases (MEDLINE, Embase, Science Citation Index, the Cochrane Central Register of Controlled Trials, and clinical trial registries) were searched for reports in English published between Jan 1, 1992, and Aug 27, 2018. A collaborative group of investigators from 35 identified trials collected individual participant data from 17 trials. All available individual participant data measuring sexual function, quality of life, and psychological symptoms were analysed. The risk of bias of trials contributing individual participant data was assessed as generally low.

Added value of this study

We observed that testosterone treatment improves sexual function and quality of life compared with placebo in men with low serum testosterone but without classic hypogonadism. Mean improvements in erectile function during testosterone treatment were similar to minimal clinically important differences previously reported during phosphodiesterase inhibitor treatment for mild erectile dysfunction. However, men older than 65 years and those with obesity with the poorest baseline sexual function were less likely than other men to reach adequate sexual function during testosterone treatment because of a more severe baseline symptom burden.

Implications of all the available evidence

Clinicians and patients should be advised that testosterone is an efficacious short-to-medium-term treatment to improve sexual function and quality of life in all men with low serum testosterone. The current study provides new evidence helping clinicians and men to predict the short-to-medium effectiveness of testosterone in providing clinically meaningful improvements in symptoms of low testosterone and could inform related reimbursement health-care decisions. In middle-aged or older men (≥40 years) with low serum testosterone, age, obesity, and degree of low testosterone cannot predict increments in sexual function and quality of life during testosterone treatment. However, the absolute severity of symptoms during testosterone treatment tends to be greater in older men and men with obesity. A holistic model of health optimisation is required to treat symptoms attributable to low testosterone in men, unless they have classic hypogonadism. The long-term risks and benefits of testosterone treatment for older men and men with obesity require further investigation.

otherwise healthy men younger than 40 years with classic causes of low testosterone, such as Klinefelter syndrome and hypopituitarism. However, testosterone is most often prescribed to men with non-classic (also known as functional) low testosterone associated with low health status, such as older age, obesity, or diabetes, which are also conditions associated with sexual dysfunction, low mood, tiredness, and fatigue, independently of low testosterone.[2] Therefore, how effectively testosterone improves symptoms in older men and those with obesity or diabetes, compared with younger men with classic forms of hypogonadism, is not yet clear. Testosterone sales globally increased by 12 times from US$150 million in 2000 to $1·8 billion in 2011, and most prescriptions are for men older than 50 years.[3] However, uncertainty among clinicians regarding the clinical effectiveness of testosterone among patient subgroups has contributed to discrepant prescribing practices and inconsistent treatment for men with low testosterone.[4,5] Identifying men who are symptomatically responsive to testosterone treatment would improve the consistency of treatment offered for low testosterone.

The Testosterone Efficacy and Safety (TestES) Consortium[6] is a global network of researchers sharing individual participant data to objectively appraise the safety and efficacy of testosterone treatment during randomised clinical trials, according to predetermined methodological approaches. Our primary analysis did not identify an increase in short-to-medium-term risk of cardiovascular outcomes during testosterone treatment.[7]

We have also previously conducted a qualitative review, the findings of which suggested that many symptoms other than sexual dysfunction are important to men with hypogonadism.[8] The current individual participant data analysis appraised all symptomatic efficacy outcomes during testosterone treatment versus placebo in men. We hypothesised that the symptomatic benefits of testosterone treatment might differ by subgroup characteristics, namely age, baseline serum testosterone concentration, BMI, smoking status, and presence of diabetes. The results of this analysis could help clinicians to identify men who are most likely to benefit from testosterone treatment.

Methods

Search strategy and selection criteria

We conducted a systematic review, individual participant data meta-analysis, and aggregate data meta-analysis to evaluate characteristics associated with symptomatic benefit of testosterone in men. The methods have been reported previously[7] and were in accordance with current methodological standards.[9,10] Eligible studies were placebo-controlled randomised clinical trials evaluating the effects of at least 3 months of testosterone treatment in men aged 18 years or older with a baseline total serum testosterone concentration of less than 12 nmol/L (350 ng/dL). The PRISMA checklist for Individual Patient Data systematic reviews is provided in the appendix (pp 1–5). The study protocol is available online.

On Aug 27, 2018, we conducted a search of MEDLINE, Embase, Science Citation Index, and the Cochrane Central Register of Controlled Trials for reports published between Jan 1, 1992, and the date of the search, using sensitive search strategies (appendix pp 6–7). The Cochrane Database of Systematic Reviews, the Database of Abstracts of Review of Effects, the NHS Economic Evaluation database, and the UK National Institute for Health and Care Research Health Technology Assessment database were also searched for evidence syntheses. Conference proceedings of relevant organisations were searched from Jan 1, 2016, to Aug 29, 2018, for hypogonadism, testosterone, randomised studies, and quality of life. All citations identified by these searches were independently assessed by two reviewers (MC and MB or MA-M) and all potentially relevant reports were assessed by one reviewer (MC), with 10% (randomly selected using an online random number generator) independently checked by a second reviewer (MA-M). All selected reports were independently assessed by a clinical expert (CNJ or RQ). Any disagreements during selection were resolved by consensus between at least two authors (MC, MB, MA-M, CNJ, or RQ). Data collection procedures and risk of bias assessments have been reported previously.[7]

Outcomes

The primary (cardiovascular) outcomes of TestES have been reported previously.[7] Secondary outcomes (ie, quality of life, sexual function, and psychological symptoms) are reported here, along with the ranges and direction of scores (appendix pp 8–9). The prioritisation of outcomes and strategy for study selection were developed in collaboration with an advisory panel of two men with hypogonadism recruited from NHS reproductive clinics. Outcomes were assessed at 12 months or at the closest timepoint. Diabetes status (yes *vs* no) was categorised independently by two masked clinical authors (CNJ and RQ) who reviewed individual participant data.

Statistical analysis

Analysis was done on the intention-to-treat principle and at the participant level, following a prespecified statistical analysis plan (appendix pp 10–20). The one-stage approach used a random-effects linear regression model accounting for clustering and allowing baseline adjustment per study, and a separate residual variance using restricted maximum likelihood (an example of the Stata code used is shown in the appendix [p 21]). Effect estimates were presented as mean difference with 95% CI. Heterogeneity was assessed using the estimated between-study variance (τ^2). For the two-stage meta-analysis, individual participant data were first analysed separately using a linear regression model adjusting for baseline values. For studies without individual participant data, effect estimates and SEs were obtained according to methodological recommendations.[11] The second stage pooled the effect estimates using a random effects model with restricted maximum likelihood. For models that did not converge using a restricted maximum likelihood, a random-effects model using DerSimonian and Laird method was used.[12] Heterogeneity was assessed using the I^2 statistic.

A post-hoc subgroup analysis by treatment interaction was performed by including the within-interaction terms in the aforementioned models of diabetes status, smoking status, age, serum total testosterone, free testosterone concentrations, route of testosterone administration (gel, injection, or other), and BMI (<25 kg/m², 25–29·9 kg/m², 30–39·9 kg/m², or ≥40 kg/m²) using a stricter level of significance (two-sided 1% significance level). On the basis of methodological recommendations,[13] continuous covariates were centred on the mean value within each trial and binary covariates were centred on the proportion within each trial. A sensitivity analysis was also conducted in which continuous outcomes were converted to categorical data. The analysis was performed on either the outcomes most often reported in the trials included in our individual participant data analysis, or outcomes with substantial heterogeneity (τ^2). The selected outcomes were the Aging Males' Symptoms scale (AMS) for quality of life (score ranges from 17 to 85, with higher scores indicating severe symptoms consistent with a low testosterone level); the 15-item International Index of Erectile Function (IIEF-15)

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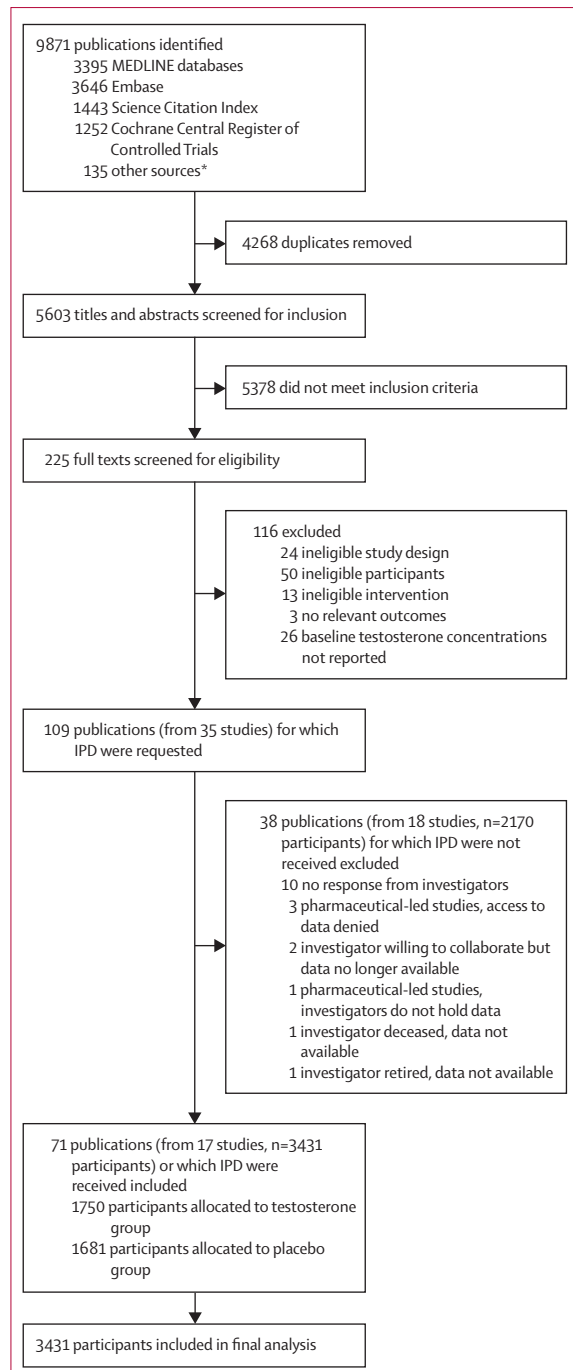c.jayasena@imperial.ac.uk

Figure 1: Study selection diagram
IPD=individual patient data. *Other sources used in the literature search were the Cochrane Database of Systematic Reviews, the Database of Abstracts of Review of Effects, the NHS Economic Evaluation Database, and the UK National Institute for Health and Care Research Health Technology Assessment database.

for sexual function (score ranges from 5 to 75, with higher values indicating better sexual function); and the Beck Depression Inventory (BDI) for psychological symptoms (score ranges from 0 to 63, with higher scores indicating more severe depression). For IIEF-15 and its

subscores, we also performed a post-hoc subgroup analysis exploring treatment-modifying effects of age, total serum testosterone, and BMI.

Post-hoc threshold regression analysis was used to establish whether there were any thresholds for IIEF-15 score at follow-up for age, baseline serum total testosterone (also for IIEF-15 score at baseline), and BMI. According to the number of categories identified, to confirm whether these thresholds were significant, we performed either an ANOVA or a *t* test analysis. Scatter plots are also presented.

No adjustment for multiple secondary outcomes was performed. To allow direct comparison, SF-36 and SF-12 scores were transformed into t-scores.[14] All statistical analyses were done with Stata software (version 16). The study is registered on the PROSPERO database, CRD42018111005.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

9871 publications were identified through database searches (figure 1). After the removal of 4268 duplicates, 5603 titles and abstracts were screened for inclusion. Of these, 5378 did not meet our inclusion criteria and were excluded (appendix p 22). 225 full-text publications were assessed for inclusion, of which 116 were excluded.[7] 109 publications from 35 primary studies (including a total of 5601 participants) were deemed suitable for inclusion, of which we were able to obtain individual participant data for 17 studies from nine countries (3431 participants; see appendix pp 23–28 for study characteristics). The 17 studies that provided individual participant data involved 1750 participants allocated to the testosterone group and 1681 to the placebo group, in a double-blinded manner. The median age was 67 years (IQR 60–72), and 3281 (97·1%) of 3380 participants were aged 40 years or older (table 1). Most participants were White (1803 [87·5%] of 2060) and non-smokers (1594 [88·1%] of 1810; appendix pp 29–30; baseline characteristics by studies that reported IIEF-15, AMS, and 36-Item Short Form Survey [SF-36] outcomes are shown in the appendix [pp 30–35]). Overall, 1719 (50·2%) 3423 of participants had a BMI greater than 30 kg/m². Across studies, the median duration of testosterone treatment was 8 months (IQR 6–12) and the median follow-up was 30 weeks (26–52). The overall risk of bias was assessed as being low for most individual participant data studies and unclear for the majority of studies without individual participant data.

The IIEF-15 questionnaire was the tool most frequently used to measure sexual function during testosterone treatment, with individual participant data from 1412 participants across five studies analysed. Mean

differences (95% CI) for testosterone replacement therapy versus placebo (one-stage analysis) are shown in table 2 and were greatest for IIEF-15 total score, IIEF-15 erectile function subscore, and IIEF-15 intercourse satisfaction subscore; smaller mean differences were observed for subscores of orgasmic function, sexual desire, and overall satisfaction. Testosterone also improved IIEF-15 scores during two-stage analysis (appendix p 36–41). One-stage and two stage meta-analyses for other sexual symptoms are shown in the appendix (pp 42–50).

We investigated whether IIEF-15 score during testosterone treatment versus placebo was associated with subgroup characteristics, after correcting for

	Number of studies providing data type	Testosterone group		Placebo group	
		Number of participants	Median (IQR), %, or mean (SD)	Number of participants	Median (IQR), %, or mean (SD)
Age, years	16	1724	66·5 (59·0–71·9)	1656	67·0 (60·0–72·0)
BMI, kg/m²	17	1746	30·0 (27·0–33·1)	1677	30·0 (26·9–33·3)
Ethnicity	6	..	..	..	..
White	..	915	87·5%	888	87·6%
Asian	..	63	6·0%	62	6·1%
Black or African American	..	16	1·5%	12	1·2%
Other	..	9	0·9%	7	0·7%
Missing or not reported	..	43	4·1%	45	4·4%
Smoking status	10	..	..	..	..
No	..	838	88·9%	756	87·2%
Yes	..	103	10·9%	107	12·3%
Missing	..	2	0·2%	4	0·5%
Diabetes*	12	..	..	..	..
Yes	..	434	27·5%	402	26·9%
No	..	1142	72·5%	1090	73·1%
Biochemistry					
Albumin, g/L	9	817	42·6 (3·2)	783	42·7 (3·1)
Oestradiol, pmol/L	8	782	80·8 (38·6)	710	77·1 (33·6)
Follicle stimulating hormone, IU/L	8	711	14·7 (16·7)	683	14·2 (16·0)
Luteinising hormone, IU/L	8	435	6·0 (5·6)	362	6·3 (5·6)
Total testosterone, nmol/L	16	1387	9·21 (2·85)	1318	9·21 (2·83)
<8·0 nmol/L	..	481	34·7%	462	35·1%
8·0–9·9 nmol/L	..	381	27·5%	346	26·5%
≥10·0 nmol/L	..	525	37·9%	510	39·0%
Sex hormone binding globulin, nmol/L	15	1256	33·8 (16·6)	1190	32·7 (16·2)
Quality of life indicators					
SF-36 or SF-12	5	..	..	..	..
Physical functioning	..	305	50·40 (7·81)	275	50·05 (7·96)
Role limitations due to physical health	..	304	46·04 (13·71)	274	45·58 (14·21)
Pain	..	299	52·46 (9·12)	272	51·23 (8·98)
General health	..	305	49·65 (9·85)	273	49·26 (8·96)
Vitality (energy and fatigue)	..	305	54·80 (9·58)	275	54·34 (9·56)
Social functioning	..	305	51·18 (8·38)	274	51·06 (8·48)
Role limitations due to emotional problems	..	304	44·42 (16·38)	275	43·52 (17·15)
General mental health or emotional wellbeing	..	305	53·06 (8·02)	275	52·52 (8·66)
Physical health composite score	..	298	50·04 (8·73)	269	49·54 (7·83)
Mental health composite score	..	298	50·53 (11·07)	269	50·00 (11·48)
Aging Males' Symptoms scale	..	..	..	..	..
Total	8	549	38·91 (12·36)	519	37·05 (11·42)
Somatic subscale	5	344	8·88 (4·01)	338	8·44 (3·87)
Psychological subscale	5	335	14·91 (5·35)	337	14·53 (4·86)
Sexual subscale	5	346	12·20 (4·19)	336	11·90 (4·27)
					(Table 1 continues on next page)

	Number of studies providing data type	Testosterone group		Placebo group	
		Number of participants	Median (IQR) or mean (SD)	Number of participants	Median (IQR) or mean (SD)
(Continued from previous page)					
Sexual function scores					
IIEF-15 score	5	..	..	..	..
Total	..	800	33·47 (20·65)	818	31·11 (20·84)
Erectile function	..	814	13·12 (10·03)	838	12·02 (10·00)
Orgasmic function	..	820	5·28 (3·91)	841	4·76 (4·02)
Sexual desire	..	819	5·18 (2·12)	839	5·03 (2·12)
Intercourse satisfaction	..	818	5·27 (5·00)	844	4·65 (4·96)
Overall satisfaction	..	808	4·65 (2·48)	826	4·59 (2·52)
IIEF-15 erectile function subscore†	5	..	..	..	..
Severe	..	143	17·6%	133	15·9%
Moderate	..	83	10·2%	75	8·9%
Mild to moderate	..	83	10·2%	68	8·1%
Mild	..	118	14·5%	124	14·8%
No erectile disfunction	..	387	47·5%	438	52·3%
IIEF-5	5	273	14·66 (7·16)	206	14·74 (7·01)
Psychological symptoms					
Beck Depression Inventory	3	158	10·01 (7·99)	113	9·36 (7·57)

IIEF-15=15-item International Index of Erectile Function. IIEF-5=five-item International Index of Erectile Function. SF-12=12-item Short Form Survey. SF-36=36-item Short Form Survey. *Type 1, type 2, and unknown type. †Based on values by Cappelleri and colleagues.[15]

Table 1: Baseline characteristics of participants enrolled in the 17 studies with available individual participant data (n=3431)

baseline IIEF-15 score. No significant associations were observed for age, baseline serum total testosterone, baseline free testosterone, diabetes status, or BMI (figure 2A; appendix pp 51). Furthermore, none of the IIEF-15 subscore increments during testosterone treatment versus placebo were associated with age, serum baseline total testosterone, or BMI (appendix p 52). Smoking status was available for 481 (26·6%) of 1810 men with individual participant data. Testosterone significantly improved IIEF-15 score in non-smokers (p<0·0001), but not in smokers (figure 2A). The effects of testosterone on IIEF-15 score were not significantly affected by route of administration (appendix p 51).

When adjusting for baseline values, IIEF-15 score during testosterone treatment versus placebo was not associated with specific subgroup characteristics (appendix p 52). The threshold analysis is presented in figure 3 and in the appendix (p 53). Significant thresholds in IIEF-15 score during testosterone treatment were identified at the participant ages of 52·0 years, 70·0 years, 72·0 years, and 72·8 years. After combining the similar thresholds of 70·0 years, 72·0 years, and 72·8 years into a single threshold (70·0 years), we observed that participants older than 70·0 years had lower post-treatment sexual function than those aged 70·0 years or younger. In summary, increments in IIEF-15 score during testosterone treatment were not associated with age, but a lower baseline IIEF-15 score meant that older men had lower mean post-treatment IIEF-15 scores as well.

A single threshold of IIEF-15 score reached during testosterone treatment was identified at a baseline total serum testosterone concentration of 9·8 nmol/L; improvements in sexual function during testosterone treatment were greater when baseline serum total testosterone was above this threshold. Pretreatment sexual dysfunction was milder in men with higher baseline serum total testosterone (appendix p 54). In summary, IIEF-15 score increments during testosterone treatment were not associated with serum baseline testosterone, but a lower baseline IIEF-15 score meant that post-treatment IIEF-15 scores were lower in men with a baseline serum total testosterone concentration of less than 9·8 nmol/L.

A single threshold of IIEF-15 score during testosterone treatment was identified at a BMI of 30·6 kg/m²; mean sexual function during testosterone treatment was lower in men with a BMI higher than this threshold. In summary, IIEF-15 score increments during testosterone treatment were not associated with BMI, but men with a BMI greater than 30·6 kg/m² had the lowest mean post-treatment IIEF-15 score.

The AMS was the tool most commonly used to investigate the effects of testosterone on quality of life of participants (table 1). One-stage analysis of individual participant data from 938 participants across seven studies showed that quality of life measured by AMS was better during testosterone treatment versus placebo. Further-more, all AMS subscores of quality of life were better during testosterone treatment versus placebo, and the

	Number of studies providing data type	Testosterone group		Placebo group		Mean difference (95% CI)	τ^2
		Number of participants	Mean (SD)	Number of participants	Mean (SD)		
Sexual function (IIEF-15 score and subscores)							
Total score	5	703	40·67 (21·51)	709	33·77 (22·44)	5·52 (3·95 to 7·10)	1·17
Erectile function score	5	714	15·98 (10·32)	722	13·15 (10·62)	2·14 (1·40 to 2·89)	0·64
Orgasmic function score	5	714	6·11 (3·78)	726	5·08 (4·14)	0·81 (0·48 to 1·14)	0·27
Sexual desire	5	716	6·04 (2·15)	724	5·21 (2·25)	0·80 (0·62 to 0·97)	0·00
Intercourse satisfaction	5	714	6·67 (5·19)	725	5·01 (5·17)	1·33 (0·95 to 1·71)	0·15
Overall satisfaction	5	706	5·70 (2·66)	711	5·10 (2·66)	0·52 (0·29 to 0·74)	0·02
Quality of life indicators							
Aging Males' Symptoms scale							
Total	7	482	32·19 (10·23)	456	34·22 (11·10)	–2·62 (–4·02 to –1·23)	1·52
Somatic subscale	5	315	12·73 (4·21)	307	13·25 (4·58)	–0·64 (–1·18 to –0·09)	0·03
Psychological subscale	5	309	7·71 (3·16)	312	7·99 (3·47)	–0·40 (–0·76 to –0·05)	0·00
Sexual subscale	5	320	10·33 (3·82)	324	11·12 (4·20)	–0·78 (–1·33 to –0·24)	0·07
SF-36 or SF-12 norm-based scores							
Physical functioning	5	277	51·03 (7·49)	262	49·84 (8·25)	0·56 (–0·33 to 1·44)	0·00
Role limitations due to physical health	5	277	45·64 (13·90)	261	45·13 (14·46)	0·72 (–0·70 to 2·14)	0·64
Pain	5	277	52·92 (9·01)	262	51·87 (9·86)	0·05 (–1·17 to 1·27)	0·00
General health	5	277	50·46 (8·70)	262	49·71 (9·31)	0·77 (–1·11 to 2·65)	2·70
Vitality (energy and fatigue)	5	277	56·67 (8·81)	263	54·55 (9·34)	1·78 (–0·43 to 3·99)	4·01
Social functioning	5	274	52·23 (7·34)	262	50·68 (8·64)	1·74 (0·14 to 3·34)	1·51
Role limitations due to emotional problems	5	277	44·46 (15·91)	260	42·92 (17·23)	1·66 (0·57 to 2·76)	0·00
General mental health or emotional wellbeing	5	277	53·88 (7·51)	263	53·14 (9·17)	0·41 (–0·65 to 1·47)	0·00
Physical health composite score	5	274	50·35 (8·08)	258	49·70 (8·47)	0·01 (–1·48 to 1·51)	1·36
Mental health composite score	5	274	51·65 (9·50)	258	50·20 (11·76)	1·95 (0·64 to 3·26)	0·20
Psychological symptoms							
Beck Depression Inventory	3	143	6·99 (6·37)	103	8·49 (7·75)	–1·10 (–2·49 to 0·30)	0·71

Outcomes were analysed using random effects. IIEF-15=15-item International Index of Erectile Function. SF-12=12-item Short Form Survey. SF-36=36-item Short Form Survey.

Table 2: One-stage analysis of sexual function, quality-of-life, and psychological outcomes during testosterone replacement therapy versus placebo

two-stage analysis showed similar results (appendix pp 57–60). After baseline correction, differences in AMS score between participants in the testosterone and placebo groups were not significantly associated with age, baseline total serum testosterone, free testosterone, or BMI (figure 2B; appendix pp 55). Improvements in AMS score during testosterone treatment were not significant in smokers and men with diabetes. The Short Form Survey (SF-36 or 12-item Short Form Survey [SF-12]) was used by five studies (with a total of 539 participants) to investigate the effects of testosterone on health-related quality of life (table 2). One-stage analysis of individual participant data showed significant improvements in three of the ten SF-36 or SF-12 subscores during testosterone treatment versus placebo: social functioning, role limitations due to emotional problems, and mental health composite score. One-stage and two stage meta-analyses for other quality of life outcomes are shown in the appendix (pp 56–65).

One-stage analysis of individual participant data from 246 participants across three studies using the BDI did not show a significant effect of testosterone on psychological symptoms compared with placebo (table 2). No eligible studies reporting aggregate data for BDI were identified. Subgroup analysis did not identify associations between the effects of testosterone on BDI by age, baseline total serum testosterone, serum free testosterone, smoking status, or diabetes status (figure 2C; appendix p 66). One-stage and two stage meta-analyses for other psychological symptom outcomes are shown in the appendix (pp 67–71).

Discussion

The symptomatic benefits experienced by men receiving testosterone replacement therapy have not been previously stratified by patient age or BMI. Uncertainty regarding the effectiveness of testosterone treatment in older men and men with obesity have contributed to
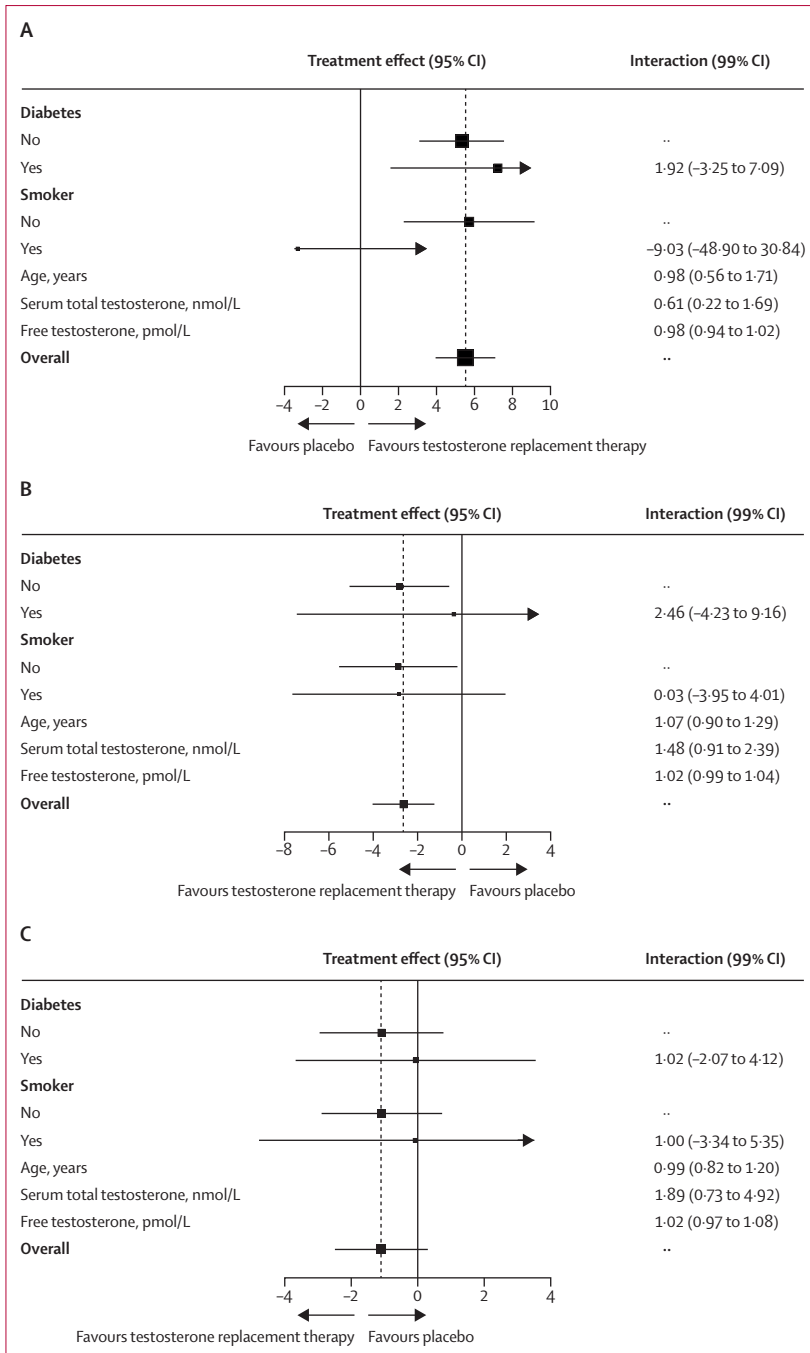
A

B

C

Figure 2: **Post-hoc subgroup analysis for testosterone treatment versus placebo for IIEF-15 score (A), Aging Males' Symptoms scale (B), and Beck Depression Inventory (C)**
Effects by route of administration are shown in the appendix (pp 51, 55). IIEF-15=15-item International Index of Erectile Function.

wide variations in prescribing practices among clinicians.[16] Our analysis of more than 3000 individual men suggests that age, BMI, and diabetes status do not significantly alter the short-to-medium-term effectiveness of testosterone replacement therapy in improving sexual function or quality of life compared with placebo within a

double-blinded randomised clinical trial setting. However, due to more severe baseline symptoms, the absolute level of sexual function reached during testosterone might be lower in older men and men with obesity compared with younger men and those who are not obese.

Individual participant data were successfully obtained from approximately half of the total eligible participants within published trials, but other individual participant data were not retrieved due to data loss, retirement or death of lead investigators, or unwillingness of two pharmaceutical trial sponsors to disclose individual participant data. To assess the impact of studies without individual participant data available, aggregate study-level data were extracted and incorporated alongside individual participant data using two-stage individual participant data random-effect meta-analyses, the results of which suggested that none of the reported outcomes were significantly discrepant between studies with and without individual participant data. However, we cannot exclude the possibility that unreported data in the studies without individual participant data would have changed our findings. The mean testosterone treatment duration within our individual participant data was 8 months, so longer-term effects of testosterone cannot be inferred from our analysis. Since our analysis, two additional randomised trials have been completed. The first, evaluating the independent and combined effects of metformin and testosterone in 106 men with obesity,[17] found that metformin only, testosterone only, and the combination of metformin plus testosterone were more effective than placebo in reducing insulin resistance, although no evidence of additional benefits in erectile function and quality of life were reported. Sexual symptom outcomes from the second, a large randomised clinical trial evaluating the safety of testosterone treatment, have been published, but other efficacy outcomes have yet to be published.[18,19] A search of Clinicaltrials.gov conducted on July 6, 2023, found no additional ongoing trials that meet our inclusion criteria.

Few studies in our analysis had maintenance of a sexual relationship as an inclusion criterion, which is recommended when evaluating male sexual dysfunction;[20] our analysis is therefore limited in its assessment of sexual function by the design of its constituent studies. Placebo-controlled trials for classic forms of low testosterone are considered unethical due to the strong evidence of efficacy of treatment already available. Therefore, most participants within our analysis are likely to have had functional hypogonadism, and our conclusions might not be applicable to the minority of men who are prescribed testosterone for classic hypogonadism. We observed that testosterone treatment increased erectile function (IIEF-15 erectile function subscore) compared with placebo by a mean difference of 2·14 (95% CI 1·40–2·89), which reaches the proposed minimal clinically important difference required for men to have

improvements in mild erectile dysfunction during phosphodiesterase inhibitor treatment (minimal clinically important difference of 2).[21] Therefore, testosterone alone is likely to be sufficient to treat mild erectile dysfunction in men with non-classic low testosterone, but might not be meaningfully beneficial for men with moderate or severe erectile dysfunction, in whom minimal clinically important differences of 5 and 7 have been reported, respectively.[21] However, our study cannot provide insight into whether minimal clinically important differences reported for phosphodiesterase inhibitors are transposable to testosterone treatment. Unlike phosphodiesterase inhibitors, testosterone improves other aspects of sexual function, such as sexual desire. Therefore, the benefits of testosterone on sexual function are likely to be underestimated if only improvements in erectile dysfunction are considered. On-treatment serum testosterone concentrations were not analysed due to the inexistence of an established approach to compare levels among different testosterone formulations used during the included trials. The conclusions of our analysis should be interpreted with caution because factors that were not accounted for, such as variations in clinical prescribing, population heterogeneity, diet, exercise, and exposure to phosphodiesterase inhibitors are also likely to modify the symptom changes felt during testosterone treatment. Our analysis was limited to studies including men with baseline total serum testosterone of less than 12 nmol/L; therefore, our conclusions cannot be extrapolated to men with low free or bioavailable testosterone but serum total testosterone of 12 nmol/L or higher.

Older age increases the risk of sexual dysfunction due to penile vascular or metabolic disease, mood disorders, dementia, and movement disorders.[22] Serum testosterone reduces in an age-dependent and comorbidity-dependent manner,[23] and the National Institutes of Health (NIH) Testosterone Trials demonstrated the short-term efficacy of testosterone to improve sexual function compared with placebo in men older than 65 years. Despite this evidence, the merits of testosterone treatment in older men remain a topic of debate among clinicians.[17] No randomised trials or meta-analyses have compared the effects of testosterone in younger and older men. We were surprised to observe no significant interaction of patient age (≥40 years) with improvement in sexual function, measured with the IIEF-15 questionnaire or any of its subscores, during testosterone replacement therapy versus placebo. These analyses accounted for baseline differences in IIEF-15 scores between men aged younger than 52 years, 52–70 years, and older than 70 years. On average, older men have lower sexual function than younger men; therefore, similar improvements in sexual function in men of all ages would still result in older men having poorer sexual function than younger men. Accordingly, we found that absolute levels of sexual function achieved during testosterone treatment was subject to thresholds of patient age. Taken together, our findings suggest that

testosterone improves all aspects of sexual function in younger and older men, but supports the view that older men are less likely than younger men to achieve optimal sexual function during testosterone treatment.[17] Moreover,
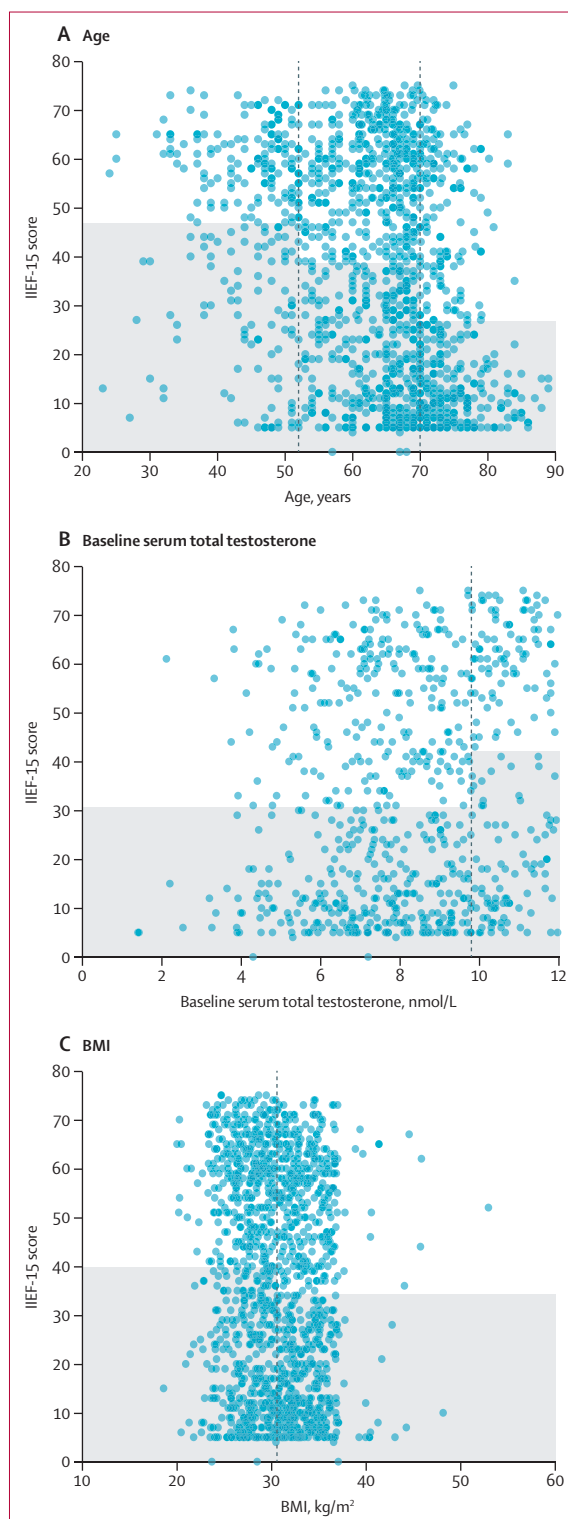

Figure 3: Thresholds for IIEF-15 score during testosterone replacement therapy
Scatter plots of IIEF-15 score during testosterone treatment for participant age (A), baseline total serum testosterone (B), and BMI (C). Vertical dashed lines indicate statistically significant thresholds in the characteristic (age, serum testosterone, or BMI). Grey shading indicates mean IIEF-15 scores of less than the mean. IIEF-15=15-item International Index of Erectile Function.

we are unable to ascertain whether the symptomatic effects of testosterone are sustained in the long term, as has been commented regarding the NIH Testosterone Trials outcomes.[24] Additionally, men younger than 40 years could have greater symptomatic benefits compared with participants included in this analysis.

Lifestyle interventions are the recommended first-line treatment for obesity-induced hypogonadism,[1] but weight loss is sustained in only a minority of individuals beyond 1 year.[25] Accordingly, testosterone is often prescribed to men with obesity, but this practice is controversial. An aggregate meta-regression by Corona and colleagues[26] reported that the mean BMI of participants within individual studies was negatively associated with the mean effects of testosterone on the erectile function subscore of the IIEF-15 questionnaire reported in each study. Our analysis shows that men with obesity (BMI ≥30 kg/m²) benefit from similar improvements in total IIEF-15 score (and each IIEF-15 subscore) during testosterone treatment compared with men with lower BMI. However, we also identified a threshold of BMI (30·6 kg/m²) above which the level of sexual function reached is more likely to be suboptimal due to poorer baseline sexual function. In summary, our analysis suggests that testosterone treatment should be considered as a potentially effective treatment for sexual dysfunction in men with obesity, but men should be counselled that the level of sexual function reached might be lower than in men with a lower BMI.

Diabetes can cause erectile dysfunction through neuropathy and vasculopathy.[27] We were therefore surprised to observe that testosterone was not less effective in improving total IIEF-15 (or any of its subscores) in men with diabetes compared with those without diabetes. In the aggregate meta-regression by Corona and colleagues,[26] the mean effect of testosterone on the IIEF-15 erectile function subscore in all participants was negatively associated with the proportion of participants with diabetes. Unlike the analysis by Corona and colleagues, which was restricted to study-wide characteristics and erectile function, we were able to directly compare total and subscore changes in IIEF-15 of individual men from different studies with and without diabetes. Furthermore, the analysis by Corona and colleagues included eugonadal and hypogonadal men, whereas we selected individuals with baseline total serum testosterone of less than 12 nmol/L. Although diabetes status for each participant was categorised independently by two masked clinical authors, individual studies categorised diabetes status as presence or absence, without reporting objective data (eg, fasting glucose, oral glucose tolerance test or glycated haemoglobin, use of glucose-lowering medications, or evidence of β cell autoimmunity). Therefore, it was not possible to categorise diabetes any further (eg, type 2 *vs* type 1, established diabetes *vs* prediabetes, glycaemic control, or degree of diabetes complications), but such

factors could have affected the response to testosterone treatment. Smoking also impairs erectile function by causing vasculopathy, and smoking cessation improves physiological and self-reported indices of sexual health.[28,29] To our knowledge, the effects of smoking status on testosterone efficacy outcomes have not been investigated previously. Our individual participant data analysis suggested that testosterone improved IIEF-15 scores in non-smokers but not in smokers. Smokers have an increased risk of penile vasculo-occlusive disease, which might reduce the therapeutic response to testosterone.[30] However, our observation is based on a modest sample size and self-reporting smoking status, which might have incorrectly classified some participants.

Most endocrine deficiencies have clearly defined thresholds of circulating hormone concentrations below which therapy becomes recommended.[31,32] However, some hormones (eg, growth hormone and parathyroid hormone)[33,34] have proven therapeutic indications in patients without a demonstrable endocrine deficiency.[33] Many clinical guidelines recommend that circulating total testosterone concentrations be at least below 8–12 nmol/L (231–346 ng/dL) to diagnose and treat low testosterone.[35] However, analyses of the European Male Aging Study[36] and NIH Testosterone Trial[37] suggest that the association between sexual function and circulating testosterone concentration is weak. To help to identify men most likely to benefit from testosterone, we analysed whether baseline testosterone status was associated with altered treatment efficacy within the range of less than 12 nmol/L. Surprisingly, after adjusting for baseline differences in sexual function, we observed no significant interaction between baseline total or free testosterone and the ability of testosterone to improve sexual function compared with placebo. Thus, whereas testosterone is assumed to have physiological effects that help to restore sexual function in young men with organic hypogonadism, we cannot exclude that it also has pharmacological effects on sexual function in men with non-classic forms of low testosterone. This hypothesis is supported by the T4DM study, which reported improvements in sexual function in normogonadal men during testosterone treatment versus placebo.[38] The absolute level of sexual function achieved during testosterone treatment was dependent on baseline serum testosterone above a specific threshold; mean IIEF-15 score during testosterone treatment was 24% higher in men with baseline serum total testosterone of more than 9·8 nmol/L compared with men with lower testosterone concentrations. Our results are explained in part by the observation that men with baseline total serum testosterone concentrations greater than 9·8 nmol/L had milder symptoms (15% higher mean IIEF-15 score) than other men (appendix p 53). Corona and colleagues[26] reported that testosterone improved one IIEF-15 subscore (erectile function) more effectively in randomised trials restricted

to men with baseline serum testosterone concentrations of less than 8 nmol/L compared with less than 12 nmol/L. That analysis is based on 14 pooled mean observations,[26] whereas we analysed more than 1000 individual responses from men with different baseline serum total testosterone concentrations (35% with serum testosterone <8 nmol/L, 27% with 8–9·9 nmol/L, and 38% with 10–11·9 nmol). Collectively, our analysis proposes that, in men with baseline serum testosterone concentrations of less than 12 nmol/L, degree of low testosterone might not be a good predictor of symptomatic benefits with testosterone treatment.

In contrast to sexual function outcomes, few randomised trials have reported significant improvements in quality of life during testosterone treatment in men. An added complication is that multiple validated quality of life tools exist, each focusing on different aspects of quality of life. A 2020 meta-analysis of aggregate data from pooled analyses of different quality of life tools concluded that testosterone modestly improves quality of life.[39] Our individual participant data meta-analysis assessed the impact of testosterone on individual quality of life tools. We observed that testosterone improved all domains of the AMS scale, which is highly sensitive to sexual complaints in men.[40] SF-36 (or SF-12) is a generic quality of life tool allowing broad comparisons with other health interventions.[41] Testosterone treatment significantly improved the SF-36 or SF-12 domains of social functioning, role limitations due to emotional problems, and mental health composite score, but had no significant effect on any other SF-36 or SF-12 domains. In the subgroup analysis, differences between AMS score during testosterone treatment versus placebo were not significantly associated with patient age or serum testosterone after baseline differences were considered. A non-significant interaction between AMS scire and baseline serum total testosterone was observed. Smokers and men with diabetes had non-significant improvements in AMS, but this finding might simply reflect low statistical power. Alternatively, smoking and diabetes, which are known to reduce quality of life, might have blunted improvements in quality of life during testosterone treatment.[42,43]

Although long-term efficacy and safety data regarding testosterone replacement therapy are not yet available, this study provides useful new information for clinicians to counsel men without classic hypogonadism about the short-to-medium-term benefits of testosterone treatment. Testosterone should always be initiated within a holistic clinical care model, including assessment for potentially modifiable risk factors, such as obesity and smoking.

Contributors

Declaration of interests

Data sharing

Acknowledgments

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