BMJ open

Endogenous testosterone level and testosterone supplementation therapy in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003127
Article Type:	Research
Date Submitted by the Author:	26-Apr-2013
Complete List of Authors:	Atlantis, Evan; University of Western Sydney, Family and Community Health Research Group School of Nursing and Midwifery Fahey, Paul Cochrane, Belinda Wittert, Gary Smith, Sheree; University of Western Sydney, Family and Community Health Research, School of Nursing and Midwifery
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	Sex steroids & HRT < DIABETES & ENDOCRINOLOGY, Thoracic medicine < INTERNAL MEDICINE, Diabetes & endocrinology < INTERNAL MEDICINE, Chronic airways disease < THORACIC MEDICINE, EPIDEMIOLOGY

Article title: Endogenous testosterone level and testosterone supplementation therapy in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis

[1]Evan Atlantis, PhD; e-mail: e.atlantis@uws.edu.au

[2]Paul Fahey, MMedStat; e-mail: p.fahey@uws.edu.au

[1,3,4]Belinda Cochrane, MD; e-mail: belindacochrane@bigpond.com

[5]Gary Wittert, MD; e-mail: gary.wittert@adelaide.edu.au

[1,6]Sheree Smith, PhD; e-mail: sheree.smith@uws.edu.au

[1]School of Nursing and Midwifery, University of Western Sydney, Campbelltown Campus, New South Wales, Australia

[2]School of Science and Health, University of Western Sydney, Campbelltown Campus, New South Wales, Australia

[3]School of Medicine, University of Western Sydney, Campbelltown Campus, New South Wales, Australia

[4]Staff Specialist Respiratory and Sleep Physician, Campbelltown Hospital, New South Wales, Australia

[5]School of Medicine, University of Adelaide, Adelaide, South Australia, Australia

[6]Centre for Pharmacology and Therapeutics, Division of Experimental Medicine, Imperial College, South Kensington, London

This research was performed at the University of Western Sydney.

Keywords: Gonadal steroid hormones; pulmonary disease, chronic obstructive; lung diseases, obstructive; exercise therapy; exercise test; quality of life

Text word count: 3520

Abstract word count: 300

For submission to: BMJ open

Date: 26 April 2013

Corresponding Author: Evan Atlantis, PhD

Senior Research Fellow

Family and Community Health Research Group

School of Nursing and Midwifery | University of Western Sydney

Building 17, Room 17.1.14, Campbelltown Campus,

Locked Bag 1797, Penrith NSW 2751 AUSTRALIA

Phone: + 61 2 4620 3263

Fax: + 61 2 4620 3199

Email: e.atlantis@uws.edu.au

ABSTRACT

Objective: Low testosterone level may be a reversible risk factor for functional disability and deterioration in patients with COPD. We sought to systematically assess endogenous testosterone levels and effect of testosterone therapy on exercise capacity and health-related quality of life (HRQoL) outcomes in COPD patients, to inform guidelines and practice.

Design: Systematic review and meta-analysis.

Data sources: We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, and PsychINFO and reference lists of retrieved articles published before May 2012.

Inclusion criteria: Observational studies on endogenous testosterone levels in people with chronic lung disease compared with controls, or randomised controlled trials (RCTs) on testosterone therapy for exercise capacity and/or HRQoL outcomes in COPD patients were eligible.

Data extraction and analysis: Data on the mean difference in endogenous total testosterone (TT) values, and the mean difference in exercise capacity and HRQoL values were extracted and pooled using random effects meta-analysis.

Results: Nine observational studies in 2918 men with COPD reported consistently lower levels of total testosterone (TT) compared with controls (weighted mean difference was -3.21nmol/L [95% CI: -5.18, -1.23]). Six RCTs in 287 participants yielded five studies on peak muscle strength and peak cardiorespiratory fitness (CRF) outcomes (peak oxygen uptake [VO2] and workload), and three studies on HRQoL outcomes. Testosterone therapies significantly improved peak muscle strength (standardised mean difference [SMD] was 0.31 [95% CI: 0.05, 0.56]) and peak workload (SMD was 0.27 [95% CI: 0.01, 0.52]) compared with control conditions (all but one used placebo), but not peak VO2 (SMD was 0.21 [95% CI: -0.15, 0.56]) or HRQoL (SMD was -0.03 [95% CI: -0.32, 0.25]).

Conclusions: Men with COPD have clinically relevant lower than normal TT levels. Insufficient evidence from short-term studies in predominately male COPD patients suggest that testosterone therapy improves exercise capacity outcomes, namely peak muscle strength and peak workload.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently ranked the fifth leading cause of global disability (health loss)[1]. Health status or health-related quality of life (HRQoL) is a clinically important measurement of disability among patients with COPD for prognostic studies and trials[2-4]. Exercise capacity, one of the main determinants of HRQoL, is significantly impaired in COPD patients[3, 5]. Dyspnea and fatigue due to skeletal muscle dysfunction, among other physiological abnormalities, are cardinal symptoms that limit exercise capacity in COPD patients[6]. This is partly due to decreases in muscle strength and mass (often called "cachexia"), since they are characteristic features of skeletal muscle dysfunction contributing to exercise intolerance and consequential deterioration in HRQoL[5, 6]. Conversely, pulmonary rehabilitation including exercise (namely resistance training) leads to clinically relevant improvements in muscle strength and HRQoL[7, 8], indicating that skeletal muscle dysfunction should be a primary therapeutic target for intervention in patients with COPD.

Since testosterone level has been shown to be positively associated with muscle strength and cardiorespiratory fitness (CRF) accounting for physical activity and muscle mass[9, 10], a low testosterone level may be an independent risk factor for functional disability and deterioration in COPD. For example, levels of testosterone and other androgenic hormones were decreased in both male and female COPD patients compared with controls in a few studies[11-13]. Potential mechanisms for this endocrine dysfunction likely involve hypoxaemia, hypercapnia, systemic inflammation and use of glucocorticoids[14].

Thus, it is important to reliably establish whether the mean endogenous testosterone level is decreased in patients with COPD, because this condition is reversible with testosterone supplementation therapy. Indeed, a small but promising body of randomized controlled trial (RCT) evidence suggests that testosterone therapy improves exercise capacity and HRQoL

without increasing serious adverse events[15-17]. While it is difficult to explain this apparent therapeutic benefit, increased cardiac output[18], haemoglobin and haematocrit[19], baroreflex sensitivity[20], and exercise tolerance due to improvements in peak oxygen uptake (peak VO2) and muscle strength[20] are all plausible mechanisms.

Our initial analysis of the available published literature indicates an absence of a systematic review of relevant studies on endogenous testosterone levels and testosterone therapy in patients with COPD. We therefore sought to systematically review previous research to assess the mean endogenous testosterone level in people with chronic lung disease compared with controls, and the effects of testosterone therapies on exercise capacity and HRQoL outcomes in COPD patients, to inform guidelines and practice.

METHODS

Search strategy

We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, and PsychINFO electronic databases for articles published before May 2012. Search syntaxes were developed in consultation with an experienced university research librarian taking into account a broad range of terms and phrases used in definitions of testosterone and COPD (full electronic search strategies for PubMed, Scopus and Cochrane Library databases in appendix pages 1, 2). Reference lists of potentially eligible articles were searched by hand to identify additional studies missed by our search strategy.

Study selection

One reviewer (EA) identified potentially relevant studies for inclusion by screening titles and/or abstracts of all citations identified with our database searches. A second screening was performed on the full text of these articles. Observational studies in adult populations that

reported endogenous testosterone levels in men and/or women (separately) with chronic lung disease (cases) compared with controls, or RCTs that reported the effects of testosterone treatment on exercise capacity and HRQoL outcomes in COPD patients were eligible. There were no language restrictions for articles.

Data extraction

Data extraction and quality assessment of included studies were performed and/or verified independently by three reviewers (EA, BC and SS). Discrepancies were resolved through discussion. Authors of relevant studies were contacted, where possible, for data that could not be extracted from the published articles.

Quality assessment

For methodology and quality assessment, quality checklists were developed to identify potential sources of bias (tables in appendix pages 3, 4). Quality items for observational studies reviewed were (each worth 1 numerical point): (1) COPD or chronic lung disease was reported to have been clinically diagnosed or categorized according to the WHO International Statistical Classification of Diseases and Related Health Problems (ICD) system, (2) endogenous testosterone level was measured by radioimmunoassay (RIA) or liquid chromatography-tandem mass spectrometry (LC-MS/MS), (3) the study population was representative of the clinical setting or community (i.e., demographic characteristics of cases and hospital controls were typical and community cases or controls were randomly selected), and (4) there was adequate adjustment or exclusion or matching for covariates known to be associated with COPD and hypogonadism in men (each worth 0.2 numerical point): (a) age, (b) socio-economic or partner status, (c) central or general obesity, (d) smoking status, (e) alcohol intake, (f) physical activity, (g) depression or anxiety (or medications), (h) metabolic

syndrome or cardiovascular disease (or medications), (i) systemic inflammation (or glucocorticoids), and (j) sleep apnea (or treatments).

Quality items for RCT studies reviewed were (each worth 1.0 numerical point): (1) study eligibility criteria were adequately described, (2) randomization methodology was adequate (i.e., evidence suggesting "random" method was used to generate and implement random allocation sequence), (3) allocation concealment was adequate (i.e., evidence to suggest that a robust method was used for concealing the sequence of treatment allocation (e.g., independent IT or telephone service or sealed opaque envelopes only opened in front of the participant), (4) between-group prognostic indicators were balanced (i.e., evidence showing that groups were similar at the outset for these prognostic indicators), (5) care providers were blinded to treatment allocation, (6) between-group drop-out rates were balanced, (7) intention to treat analysis was included, and (8) adverse events were reported.

Our quality checklist scales were designed based on criteria for assessment of observational studies[21] and RCTs[21, 22] and allowed summed scores to range from 0 to 5 points and 0 to 8 points, respectively, reflecting lowest to highest quality. Studies were considered 'better quality' if they received a score of 3 or higher for observational studies and of 5 or higher for RCTs, since that meant that they had most of our quality items.

Primary outcomes

The primary outcomes were the mean difference in endogenous total testosterone (TT) values between the case and control groups for observational studies (the most frequently reported testosterone outcome in relevant studies), and the mean difference in exercise capacity and HRQoL values after intervention (post-treatment) between the treatment and control groups for RCTs. Where necessary for observational studies, we estimated the mean and variance from the median, range, and sample size[23]. Where necessary for RCTs, the

post-treatment means were derived from the within group changes and the control group standard deviation carried forward from the baseline values[24]. Exercise capacity outcomes included any assessment of CRF and peripheral skeletal muscle strength. Where multiple CRF outcomes were reported, first we chose peak VO2 measures, and then prioritized peak workload (power output) laboratory assessments of CRF over field tests. Where multiple muscle strength outcomes were reported, we prioritized peak isometric over peak dynamic measures; and knee extension over other joint movements. HRQoL outcomes included any patient-reported assessment of health status or functional disability. Where multiple HRQoL outcomes/scales were reported, first we chose summed score scales, and then prioritized subscales that measure "fatigue" symptoms, and the most frequently reported HRQoL outcome in the other studies reviewed.

Data synthesis

Three reviewers (EA, BC and SS) independently collated and/or verified extracted data to present a descriptive synthesis of important study characteristics and a quantitative synthesis of effect estimates.

Secondary outcomes

The secondary outcomes were data about adverse events reported in the RCTs for a descriptive synthesis.

Statistical methods

We pooled and weighted studies first using random effects meta-analysis models, and second using fixed effects models for verification[25]. Where necessary, we standardised laboratory values for endogenous TT levels between observational studies using the

International System of Units (SI Units), expressed in nanomoles per litre (nmol/L). These studies were then pooled to estimate the weighted mean difference (WMD), including the 95% confidence interval (95% CI), between cases and controls. Median and mean values were assumed to be equivalent estimates of central tendency for meta-analysis.

In examining the effects of testosterone treatment on exercise capacity and HRQoL outcomes, the standardised mean difference (SMD) from each RCT were pooled to produce an overall estimate of effect, and associated 95%CI, between treatment and control groups. For each meta-analysis model, the degree of heterogeneity in SMDs was assessed by visual inspection, the *I*-squared statistic (*I*-squared values > 40 %) and the χ^2-test of goodness of fit[26]. Where evidence of heterogeneity was observed, we checked data extracted from individual outlier studies, qualitatively investigated reasons for their different results, and explored the effects of study exclusion in sensitivity analyses.

We also used sensitivity analysis to investigate the robustness of the meta-analyses models. We variously excluded RCTs in men and women, placebo only (rather than placebo with exercise) controlled trials, longer duration trials (≥ 12 weeks), and studies of lower quality (score < 3.0 for observational studies; score < 5.0 for RCTs). And we repeated the meta-analysis models using different CRF outcomes. Publication bias, which reflects the tendency for smaller studies to be published in the literature only when findings are positive, was assessed visually using funnel plots[27]. All calculations were performed in Stata version 12 (StataCorp, College Station, TX, USA) using the 'metan'and 'metafunnel' commands. A two-tailed *P*-value < 0.05 was considered statistically significant throughout the analyses.

RESULTS

Figure 1 presents a flowchart summarising identification of potentially relevant studies, and those included and excluded (appendix page 8). Our search strategy identified 906

citations after duplicates were removed. Of these, 865 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria, leaving 41 citations for a second full text screening. Hand searching the reference lists of these articles identified two additional potentially relevant citations. After further assessment of these 43 citations, 28 were excluded for reasons listed in figure 1, leaving 15 for final inclusion in the systematic review. Most studies were excluded for inadequate predictor or outcome variables, or not having a control group (list of excluded citations; appendix pages 5-7).

Descriptive data synthesis

Table 1 presents study characteristics of nine observational studies included for review, which were published between 1981 and 2011. Studies were conducted in Scotland[28, 29], Sweden[30], the United States[31], Taiwan[32], Greece[12], Turkey[13], Norway[33] and Belgium[34]. The degree of severity of airflow limitation in COPD cases ranged from mild to very severe, assessed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[35] in four studies[12, 13, 32, 34], and by various spirometry criteria in four[28, 29, 31, 33] out of the five remaining studies. Control participants were recruited from primary care settings in six studies[12, 28, 29, 31, 32, 34]. The sample sizes ranged from 16 to 213, resulting in a total of 2918 participants across studies. Mean age of the samples ranged from 50 to 71 years. All of the observational studies were conducted in men. Mean quality scores ranged from 2.2 to 4.0, and four studies received a score of 3.0 or higher[12, 13, 31, 33].

<< Table 1 >>

Table 2 presents study characteristics of six RCTs included for review, which were published between 2003 and 2011. Studies were conducted in the United States[36], The Netherlands[37], Brazil[38], France[16], Canada[39] and Norway[40]. Major inclusion criteria were stable COPD or chronic respiratory failure in all studies, various spirometry criteria in all but one study[16], low TT in only one study[36], and low body mass index in only two studies[16, 38]. Major exclusion criteria were a range of chronic conditions in all studies, prostatic conditions in four studies[16, 36, 38, 39], and elevated haemoglobin in one study[36]. The sample sizes ranged from 16 to 122, resulting in a total of 287 participants across studies. Mean age of the samples ranged from 66 to 69 years. All but two studies[16, 39] were conducted in men only. Baseline mean TT levels ranged from 9.6 to 21.6nmol/L for men, and 0.42 to 0.45nmol/L for women as reported in one study[16]. Testosterone therapies used were oral testosterone undecanoate in one study[16], oral stanozolol after a baseline intramuscular injection of testosterone in another study[38], and intramuscular injections (testosterone enanthate[36, 40] and nandrolone decanoate[37]) in all remaining studies. Four studies investigated the combined effects of testosterone therapy with resistance training (RT)[36] or pulmonary rehabilitation (PR)[16, 38, 39]. All but one study[16] used placebo control conditions. Trial durations ranged from eight to 27 weeks. Primary outcomes were peak muscle strength in five studies (from four citations[16, 36, 37, 39]), peak VO2 in five studies (from four citations[36-39]), peak workload in five studies (from four citations[16, 36, 37, 39]), six minute walking test (6MWT) in four studies[16, 38-40], and HRQoL in three studies[16, 37, 39]. Mean quality scores ranged from 4.5 to 6.0, and all but one study[39] received a score of 5.0 or higher.

<< Table 2 >>

Quantitative data synthesis

Effect of COPD exposure on endogenous TT level

Figure 2 presents the WMD in endogenous TT level between the case and control groups for observational studies (appendix page 9). Men with COPD had significantly lower levels of TT compared with controls (pooled WMD was -3.21nmol/L [-5.18, -1.23]). There was a high degree heterogeneity between studies (*I*-squared=81.9%, *P*<0.001) that was mostly a result of variation in degree of deference rather than an unfavourable direction towards the null. The sensitivity analyses presented in table 3 shows that the pooled WMD was substantially changed after exclusion of lower quality studies (increased to -3.68 [-7.00, -0.36]) and one large sample size study[33] (increased to -3.56 [-5.63, -1.49]), and in a model using unadjusted rather than adjusted values in one study[33] (decreased to -2.95 [-4.63, -1.27]). In addition, a funnel plot was produced and showed only slight evidence of publication bias, since the WMD in TT was small (-0.60[32] and -1.10nmol/L[33]) for two of the largest studies (figure 3; appendix page 10).

<< Table 3 >>

Effect of testosterone therapy on exercise capacity and HRQoL outcomes

Figure 4 presents the SMD in peak muscle strength outcomes after testosterone therapy between the treatment and control groups for RCTs (appendix page 11). Testosterone therapies significantly improved standardised peak muscle strength outcomes compared with control conditions (pooled SMD was 0.31 [0.05, 0.56]), and there was little evidence of statistical heterogeneity between studies (*I*-squared=0.0%, *P*=0.839). The sensitivity analyses presented in table 4 shows that the pooled SMD was similar after exclusion of one lower quality study [39] (-0.31 [0.04, 0.57]), but was substantially changed after exclusion of two

placebo only controlled studies (no longer statistically significant 0.30 [-0.01, 0.62]), and the two studies in men and women that were also the two longer duration studies[16, 39] (decreased to 0.21 [-0.18, 0.60]). In addition, a funnel plot was produced and showed only slight evidence of publication bias, since the SMD in peak muscle strength outcomes was consistent in all but one treatment arm in one study[36] (figure 5; appendix page 12).

<< Table 4 >>

Figure 6 presents the SMD in peak VO2 outcomes after testosterone therapy between the treatment and control groups for RCTs (appendix page 13). Testosterone therapies consistently failed to show significant improvements in standardised peak VO2 outcomes compared with control conditions (pooled SMD was 0.21 [-0.15, 0.56]; *I*-squared=4.8%, *P*=0.379). The sensitivity analyses presented in table 5 shows that this null effect was similar after exclusion of one lower quality study[39] (0.13 [-0.27, 0.54]), two placebo only controlled studies (0.03 [-0.60, 0.66]), one study in men and women[39] (0.13 [-0.27, 0.54]), and two longer duration studies[38, 39] (0.27 [-0.12, 0.67]), and in the model using 6MWT outcomes (0.10 [-0.34, 0.53]). Conversely, testosterone therapies significantly improved CRF in the model using peak workload rather than peak VO2 outcomes (pooled SMD was 0.27 [0.01, 0.52]), and there was little evidence of statistical heterogeneity between studies (*I*-squared=0.0%, *P*=0.741).

<< Table 5 >>

Figure 7 presents the SMD in peak HRQoL outcomes after testosterone therapy between the treatment and control groups for RCTs (appendix page 14). Testosterone therapies

consistently failed to show better standardised HRQoL outcomes compared with control conditions (pooled SMD was -0.03 [-0.32, 0.25]; *I*-squared=0.0%, *P*=0.934). The sensitivity analyses showed that this null effect was comparable in the fixed effect model (-0.03 [-0.32, 0.25]) and after exclusion of one lower quality study[39] (-0.04 [-0.34, 0.25]).

Adverse events

Two RCTs showed that testosterone therapy was associated with more serious adverse events compared with the control group. One study reported an increased number of exacerbations during short-term, but not long-term, follow-up[16], and another study reported that two of three COPD patients with respiratory failure in the treatment group had died[37]. Conversely, one study reported that more patients died of respiratory failure in the control group[38]. Four studies showed that testosterone therapies decreased gonadotrophin levels compared with controls, as can be expected[16, 36, 38, 40]. Compared with controls, testosterone therapy was associated with a decrease in sex hormone-binding globulin level in two studies[16, 40], and a decrease in oestradiol level in men only in another study[16]. Finally, few studies showed that testosterone therapy was associated with relative increases in haemoglobin or haematocrit[16, 36, 37]; creatinine, aspartate aminotransferase and lactate dehydrogenase values[37].

DISCUSSION

Summary of evidence

We have established that men with COPD have significantly lower levels of endogenous TT compared with controls (weighted mean difference was -3.21nmol/L [-5.18, -1.23]). The size of the mean difference in TT level, which ranks men with COPD in the second quartile (below average) compared with age-matched population norms[9], is likely to be clinically

relevant. For instance, comparable or greater differences in TT levels between cases and controls have been reported in studies on risk of type 2 diabetes (WMD was -2.66nmol/L [-3.45, -1.86])[41], metabolic syndrome (WMD was -2.64nmol/L [-2.95, -2.32])[42], and clinically significant depression (median difference was -1.21nmol/L, $P<0.001$ for Mann-Whitney test)[43]. These comorbidities have been shown to adversely affect COPD prognosis[44-46], and would further complicate COPD management. As the effect of COPD exposure on TT level increased in size after exclusion of lower quality studies and one large sample size study, future higher quality studies will likely strengthen rather than weaken this evidence base. Collectively, our results and the existing literature indicate that testosterone deficiency should be considered in men with COPD.

Based on limited short-term RCT evidence in predominately male COPD patients, our results suggest that testosterone therapy significantly improves several exercise capacity outcomes. The size of the effect of testosterone therapy that can be expected in practice is small to moderate, but comparable to exercise or pulmonary rehabilitation therapies alone[7, 8]. The effect of testosterone therapy on standardised muscle strength outcomes remained robust after exclusion of one lower quality study, but weakened after exclusion of two placebo only studies. This supports the hypothesis that testosterone therapy with exercise is more effective than testosterone therapy alone for functional improvements[47]. In addition, our results suggest that the mechanism for improvement in CRF assessed by peak workload is likely explained by better exercise tolerance due to testosterone-induced increases in muscle strength rather than changes in VO2.

Limitations

Several limitations require careful consideration. Since only a small number of studies conducted in specific populations were included, the findings of this review may not be

relevant to other countries and key groups, requiring further research. In particular, most of the RCTs were conducted in COPD patients without cardiovascular disease and/or diabetes or endocrine disease, which are highly prevalent in this population group[45]. Second, because only a few RTCs targeted COPD patients who would have theoretically benefited most from testosterone therapy such as those with low testosterone or body weight[16, 36, 38], our estimated effect size for improvement in standardised exercise capacity may have been underestimated. Finally, reviewer-level limitations include incomplete retrieval of information for several of the 28 citations excluded, and the existence of other relevant studies not identified with our search strategy resulting in selection bias. However, the results and conclusions reported in most of the excluded studies were in line with those reported here, selection bias was unlikely.

Nevertheless, our systematic analysis of the existing literature revealed that there is an absence of sufficient RCT evidence to draw firm conclusions about the long-term benefits and risks of testosterone therapies for exercise capacity and HRQoL outcomes in male or female COPD patients, or about the pharmacological dosing for specific testosterone therapies needed for effectiveness. Reliable information on the efficacy and safety, as well as cost-effectiveness, of specific testosterone therapies is required to inform clinical practice guidelines for COPD. In addition, future high quality epidemiological research is needed to determine which subgroups of COPD patients are most vulnerable to testosterone deficiency, and to reliably establish whether women with COPD likewise present with significantly lower levels of TT than controls.

Conclusions

Men with COPD have clinically relevant lower than normal endogenous TT levels, and we believe that our meta-analytic results are sufficiently reliable to recommend that clinicians

should consider testosterone deficiency in these patients. Although our results also suggest that testosterone therapy improves several exercise capacity outcomes, there is an absence of sufficient RCT evidence to draw firm conclusions about the long-term benefits and risks of testosterone therapy for exercise capacity and HRQoL outcomes in male or female COPD patients.

ACKNOWLEDGMENTS

Authorship order is according to percentage contribution. EA is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. EA conceived and designed the review, identified studies for inclusion, extracted and interpreted data, and drafted the article. PF analysed and interpreted data, and revised the article. BC and SS extracted and interpreted data, and revised the article. GW interpreted data, and revised the article. All authors approved the final completed article. We are grateful to Mr Geoffrey Lattimore for his work on developing and conducting the electronic database searches.

COMPETING INTERESTS

EA has entered financial agreements to speak at events for Eli Lilly Australia Pty Ltd (Lilly). BC has received speaking fees and/or conference support from GSK, Novartis and Boehringer Ingelheim. GW has received speaking fees and research support from Bayer; is on International and National advisory boards for and has received research support from Lilly; and has received consulting fees and research support from Lawley pharmaceuticals.

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TABLE 1: Characteristics of observational studies reviewed

Study identification	Country	Participants		Sample size	Sex	Mean age (years)	Mean (SD) or median* (range) total testosterone, nmol/L				Covariate considerations (adjusted/excluded/matched)	Quality score (out of 5)
		Cases, assessment	Controls				Cases		Controls			
Bratel et al, 2000[30]	Sweden	COPD with severe airway obstruction and daytime hypoxaemia, not reported	Age-matched "healthy" participants	32	M	69	14.3	6.9	17.9	6.9	Age	1.2
Gow et al, 1987[28]	Scotland	COPD, spirometry FEV1 <40% and FVC <65% predicted	Inpatients ready for discharge	26	M	70	10.7	3.0-19.5	11.0	1.8-21.9	Age, thyroid disease, oral corticosteroids	2.9
Iqbal et al, 1999[31]	United States	Chronic lung disease, predominantly spirometry FEV1/FVC <80% predicted	Primary care clinic patients without history of chronic lung disease or corticosteroid treatments	85	M	62	11.1	9.8	14.0	8.6	Age, ethnicity, BMI, physical activity, smoking status, caffeine and alcohol consumption, thyroid and rheumatologic conditions, medications including glucocorticoids, testosterone, and for osteoporosis	4.0
Hsu et al, 2006[32]	Taiwan	Chronic bronchitis and COPD, GOLD criteria stage 1-4	Outpatients with stable urolithiasis or prostatitis	213	M	71	14.7	7.7	15.3	6.4	Age, chronic diseases including treated benign prostate hyperplasia, other chronic lung disease, exacerbation	2.9
Kaparianos et al, 2011[12]	Greece	COPD, GOLD criteria mean FEV1 54%, mean FEV1/FVC 59%	Outpatient smokers	125	M	61	11.2	4.4	18.4	4.5	Age, ethnicity, BMI, smoking, chronic diseases, endothelin-1 pro-inflammatory allele, other chronic lung diseases, medications including β2-adrenergic agonists, corticosteroids, follicle stimulating hormone, erythrocyte sedimentation rate	3.5
Karadag et al, 2007[13]	Turkey	COPD, GOLD criteria stage 2-3	Age-matched participants	125	M	63	13.2	5.5	16.6	5.5	Age, sexual partner status, BMI, medications that interfere with sex hormones, chronic diseases, treated urogenital disease, aged ≥75 years, regular systemic corticosteroids, oestradiol, tumor necrosis factor-alpha	3.0
Semple et al, 1981[29]	Scotland	COPD, spirometry FEV1 and FEV1/FVC <70%	Age-matched inpatients	16	M	50	13.1	4.4	20.3	5.4	Age	2.7
Svartberg et al, 2007[33]	Norway	Representative population with COPD, spirometry FEV1 <50% predicted with FEV1/FVC <70% predicted	Representative population with spirometry FEV1 ≥50% predicted	2197	M	66	12.7	5.3	14.0	5.5	Age, waist circumference, smoking status	3.6
Van Vliet et al,	Belgium	COPD, GOLD criteria stage 1-4	Outpatients with normal	99	M	65	9.0*	6.8-12.9	12.3*	8.8-16.2	Age, BMI, calculated low free	2.9

2005[34]	lung function	testosterone, sex hormone binding globulin

Abbreviations: COPD, chronic obstructive pulmonary disease; M, men; GOLD, Global Initiative for Chronic Obstructive Lung Disease; BTS, British Thoracic Society; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; BMI, body mass index; Matched, considered if between-group difference in characteristic was not likely statistically significant (P<0.05);

TABLE 2: Characteristics of randomised controlled trials reviewed adjacent.....continued →

Study identification	Country	Sample size	Population		Sex (M/W)	Mean age (years)	Baseline mean total testosterone, nmol/L	
			Major inclusion criteria	Major exclusion criteria			Treated	Controls
Casaburi et al, 2004[36]	United States	47	Stable COPD, spirometry FEV1 ≤60% predicted and FEV1/VC ≤60%; total testosterone ≤13.9nmol/L	CVD, low or high bodyweight, prostatic indications, haemoglobin ≥16g/dL, orthopaedic impairments	M	67	(a) 10.5; (b) 14.1	(a) 10.5; (b) 9.6
Creutzberg et al, 2003[37]	The Netherlands	56	Stable COPD, ATS criteria, spirometry FEV1 <70% predicted and increase in FEV1 <10% post bronchodilation	Obesity, malignancies, CVD, gastro-intestinal inflammatory disorders, type 1 diabetes, oxygen dependency at rest	M	66	13.4	14.6
Ferreira et al, 1998[38]	Brazil	17	Ambulatory and stable COPD, spirometry maximal inspiratory pressure <60% predicted and BMI <20kg/m^2	CVD, prostatic indications	M	69	14.4	17.2
Pison et al, 2011[16]	France	122	Stable CRF, >18 years, PaO2 ≤8kPa, long-term oxygen therapy and/or home mechanical ventilation >three months, BMI ≤21kg/m^2 or fat-free mass index <25th percentile	Pulmonary hypertension, sleep apnoea, prostatic indications, neuromuscular diseases, cystic fibrosis, conditions compromising six month survival, hormone-dependent cancer, women of childbearing age, elevated aminotransferase	M/W	66	M 12.7; W 0.45	M 13.6; W 0.42
Sharma et al, 2008[39]	Canada	16	Stable COPD, GOLD criteria stage 3-4, spirometry FEV1 <50% predicted and FEV1/FVC <0.7	History of asthma, obesity, malignancy, CVD, prostatic indications, renal, hepatic, gastrointestinal or endocrine disease, recent surgery ≤two months	M/W	68	M NR	W NR
Svartberg et al, 2004[40]	Norway	29	Stable COPD, moderate to severe, spirometry FEV1 <60% predicted	Asthma, malignancies, CVD, hepatic or endocrine disease	M	66	21.6	20.5

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular diseases; CRF, chronic respiratory failure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ATS, American Thoracic Society; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; M, men; W, women; IM, intramuscular injection; RT, resistance training; PR, pulmonary rehabilitation; 1RM, one repetition maximum; VO2, volume of oxygen uptake; HRQoL, health-related quality of life; 6MWT, six minute walking test; CRQ, chronic respiratory questionnaire; NR, not reported

→ adjacent.....continued

Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 8)
(a) Testosterone enanthate, 100mg per week IM; (b) Testosterone enanthate, 100mg per week IM with RT	(a) Placebo; (b) Placebo with RT	10	Muscle strength (leg press, 1RM kg); Cardiorespiratory fitness (bicycle, peak VO2L/min and peak workload Watts)	5.0
Nandrolone decanoate, 50mg per two weeks IM	Placebo	8	Muscle strength (knee extension, peak isometric force Newtons); Cardiorespiratory fitness (bicycle, peak workload Watts and peak VO2ml/min); HRQoL (SGRQ total score)	6.0
Testosterone, 250mg IM at baseline and oral stanozolol, 12mg per day with PR	Placebo with PR nine to 27 weeks	27	Cardiorespiratory fitness (bicycle, peak VO2% predicted; 6MWT, distance metres)	5.0
Oral testosterone undecanoate, M 80mg/W 40mg twice daily with PR	Home education on self-management of COPD-related stress and anxiety	13	Muscle strength (knee extension, peak isometric force Newtons); Cardiorespiratory fitness (6MWT, distance metres; bicycle, peak workload Watts); HRQoL (CRQ total score)	5.0
Nandrolone decanoate, M 50mg/W 25mg per two weeks IM with PR	Placebo with PR	16	Muscle strength (knee extension, peak isometric force units NR); Cardiorespiratory fitness (bicycle, peak VO2% predicted and peak workload Watts; 6MWT, distance metres); HRQoL (CRQ fatigue subscore)	4.5
Testosterone enanthate, 250mg per four weeks IM	Placebo	26	Cardiorespiratory fitness (6MWT, distance metres)	5.5

TABLE 3: Sensitivity analysis of observational studies on COPD exposure → total testosterone outcome meta-analysis

	N studies	*N* sample	Total testosterone WMD	(95% confidence interval)	*P*-value for heterogeneity
Fixed effects model	9	2918	-3.00	(-3.75, -2.26)	<0.001
Exclusion of five lower quality studies (score <3.0)	4	2532	-3.68	(-7.00, -0.36)	<0.001
Model using unadjusted rather than adjusted values in one study	9	2918	-2.95	(-4.63, -1.27)	<0.001
Exclusion of a large sample size study	8	721	-3.56	(-5.63, -1.49)	<0.001

Abbreviations: N, number; WMD, weighted mean difference

TABLE 4: Sensitivity analysis of randomised controlled trials on testosterone treatment → muscle strength outcomes meta-analysis

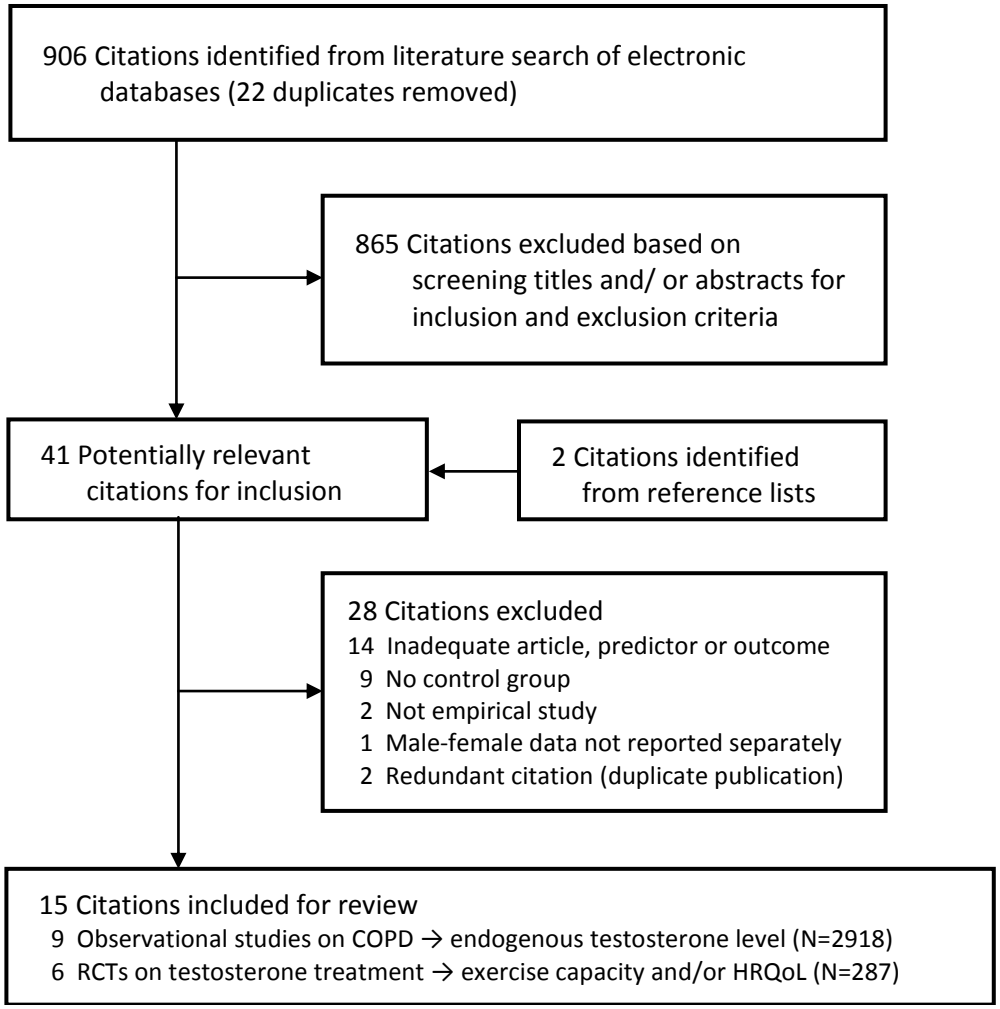
	N studies	*N* sample	SMD	(95% confidence interval)	*P*-value for heterogeneity
Fixed effects model	5	241	0.31	(0.05, 0.56)	0.839
Exclusion of one lower quality study (score <5.0)	4	225	0.31	(0.04, 0.57)	0.699
Exclusion of two placebo only control studies	3	161	0.30	(-0.01, 0.62)	0.491
Exclusion of two studies in men and women	3	103	0.21	(-0.18, 0.60)	0.611
Exclusion of two longer duration studies (≥12 weeks)	3	103	0.21	(-0.18, 0.60)	0.611

Abbreviations: N, number; SMD, standardised mean difference

TABLE 5: Sensitivity analysis of randomised controlled trials on testosterone treatment → cardiorespiratory fitness outcomes meta-analysis

	N studies	*N* sample	SMD	(95% confidence interval)	*P*-value for heterogeneity
Fixed effects model	5	136	0.21	(-0.13, 0.56)	0.379
Exclusion of one lower quality study (score <5.0)	4	120	0.13	(-0.27, 0.54)	0.315
Exclusion of two placebo only control studies	3	56	0.03	(-0.60, 0.66)	0.269
Exclusion of one study in men and women	4	120	0.13	(-0.27, 0.54)	0.315
Exclusion of two longer duration study (≥ 12 weeks)	3	103	0.27	(-0.12, 0.67)	0.553
Model using peak workload rather than peak VO2 outcomes	5	241	0.27	(0.01, 0.52)	0.741
Model using 6MWT rather than peak VO2 outcomes	4	184	0.10	(-0.34, 0.53)	0.210

Abbreviations: N, number; SMD, standardised mean difference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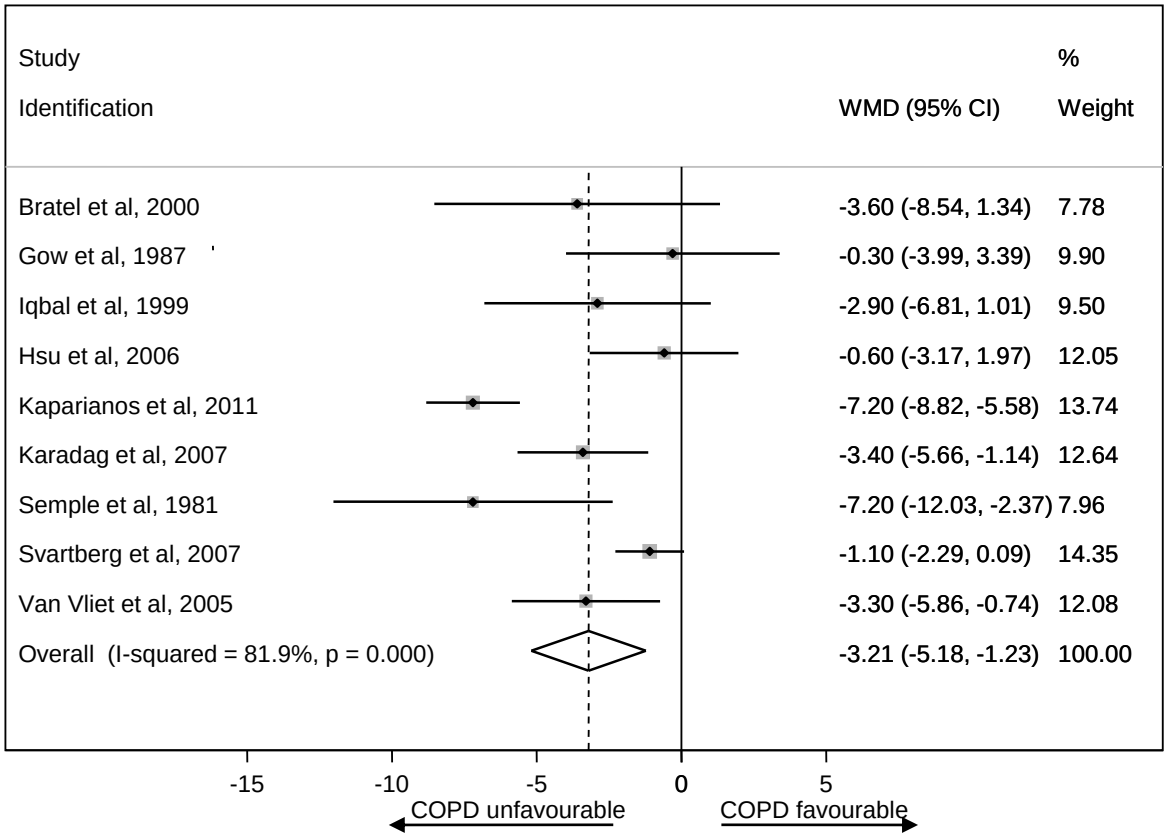
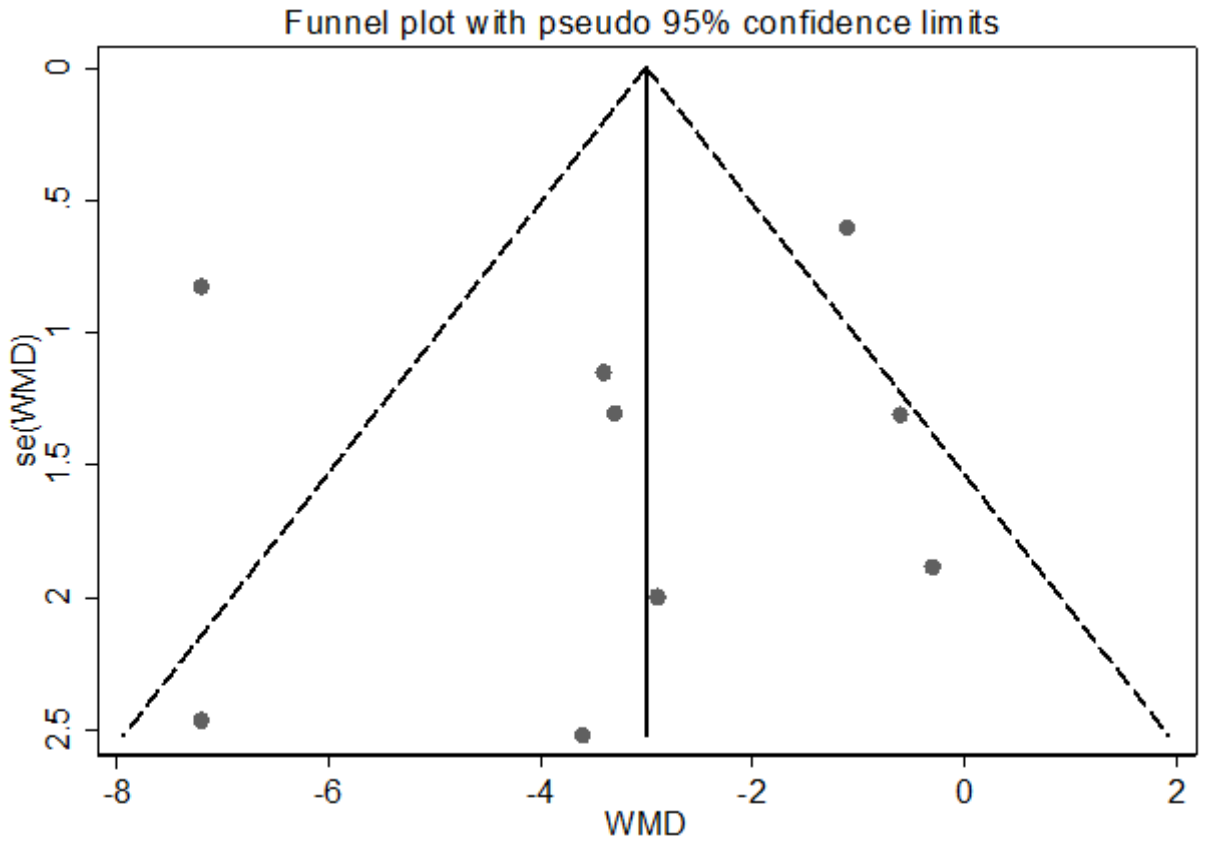
41 Potentially relevant citations for inclusion
2 Citations identified from reference lists
28 Citations excluded
14 Inadequate article, predictor or outcome
9 No control group
2 Not empirical study
1 Male-female data not reported separately
2 Redundant citation (duplicate publication)
15 Citations included for review
9 Observational studies on COPD → endogenous testosterone level (N=2918)
6 RCTs on testosterone treatment → exercise capacity and/or HRQoL (N=287)


Study
Identification
WMD (95% CI)
%
Weight
Bratel et al, 2000
-3.60 (-8.54, 1.34)
7.78
Gow et al, 1987
-0.30 (-3.99, 3.39)
9.90
Iqbal et al, 1999
-2.90 (-6.81, 1.01)
9.50
Hsu et al, 2006
-0.60 (-3.17, 1.97)
12.05
Kaparianos et al, 2011
-7.20 (-8.82, -5.58)
13.74
Karadag et al, 2007
-3.40 (-5.66, -1.14)
12.64
Semple et al, 1981
-7.20 (-12.03, -2.37)
7.96
Svartberg et al, 2007
-1.10 (-2.29, 0.09)
14.35
Van Vliet et al, 2005
-3.30 (-5.86, -0.74)
12.08
Overall (I-squared = 81.9%, p = 0.000)
-3.21 (-5.18, -1.23)
100.00
-15
-10
-5
0
5
COPD unfavourable
COPD favourable


Funnel plot with pseudo 95% confidence limits
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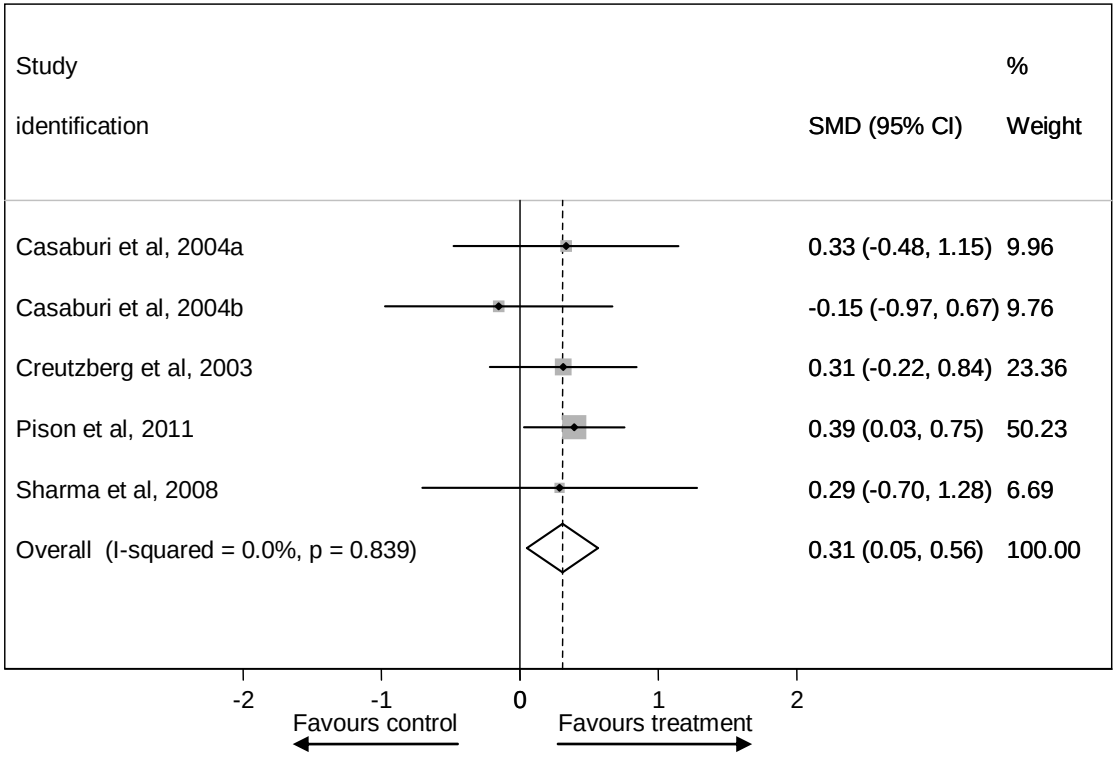
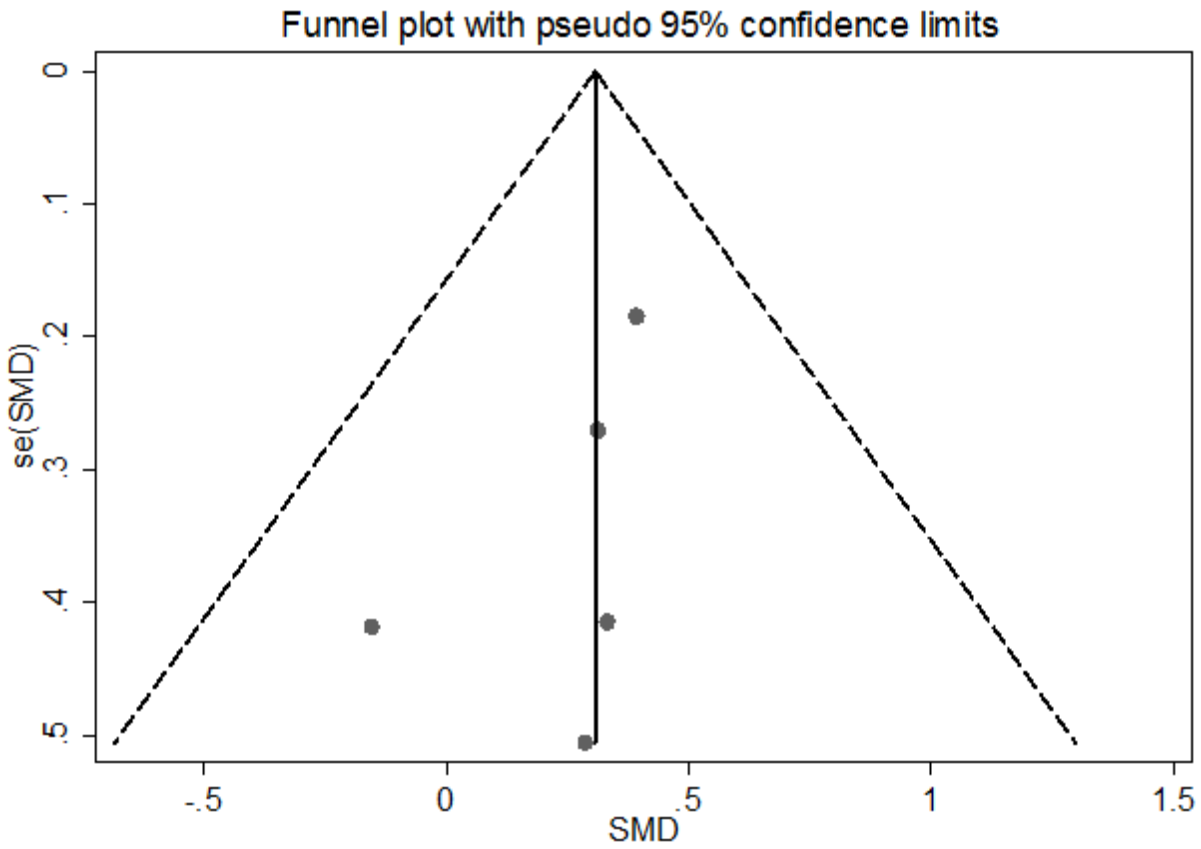
1
1.5
2
2.5
-8
-6
-4
-2
0
2
WMD


Study
identification
%
Weight
SMD (95% CI)
Casaburi et al, 2004a
0.33 (-0.48, 1.15)
9.96
Casaburi et al, 2004b
-0.15 (-0.97, 0.67)
9.76
Creutzberg et al, 2003
0.31 (-0.22, 0.84)
23.36
Pison et al, 2011
0.39 (0.03, 0.75)
50.23
Sharma et al, 2008
0.29 (-0.70, 1.28)
6.69
Overall (I-squared = 0.0%, p = 0.839)
0.31 (0.05, 0.56)
100.00
-2
-1
0
1
2
Favours control
Favours treatment


Funnel plot with pseudo 95% confidence limits
se(SMD)
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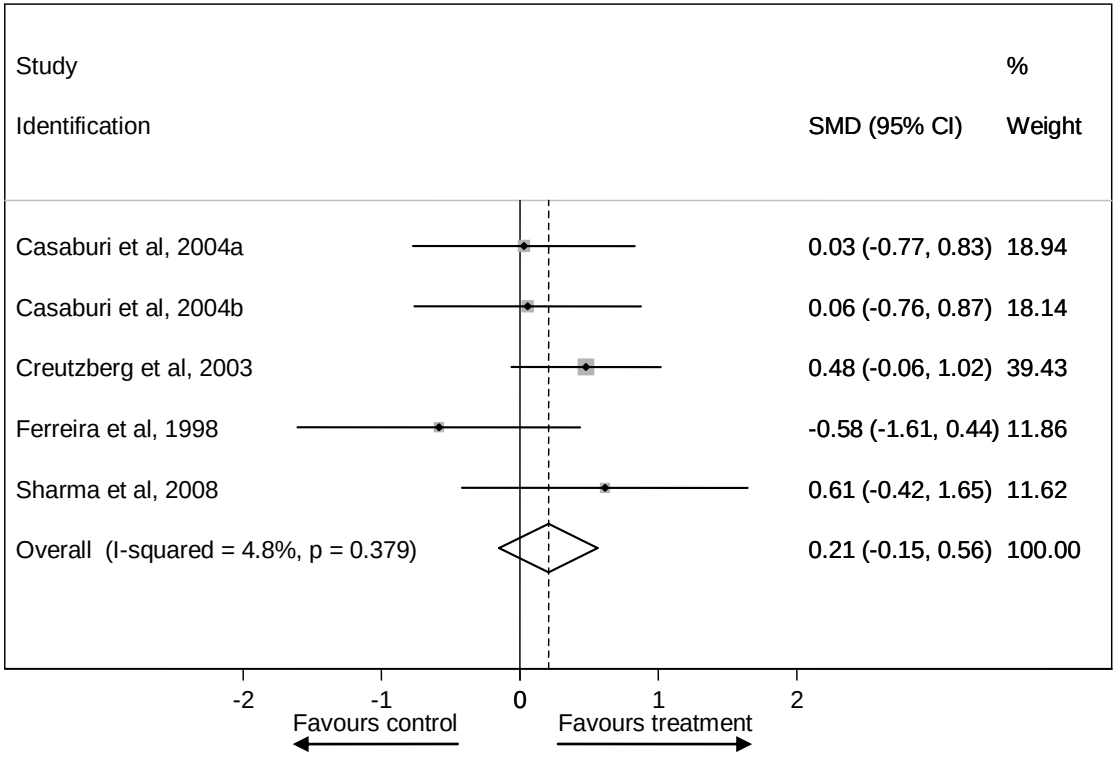
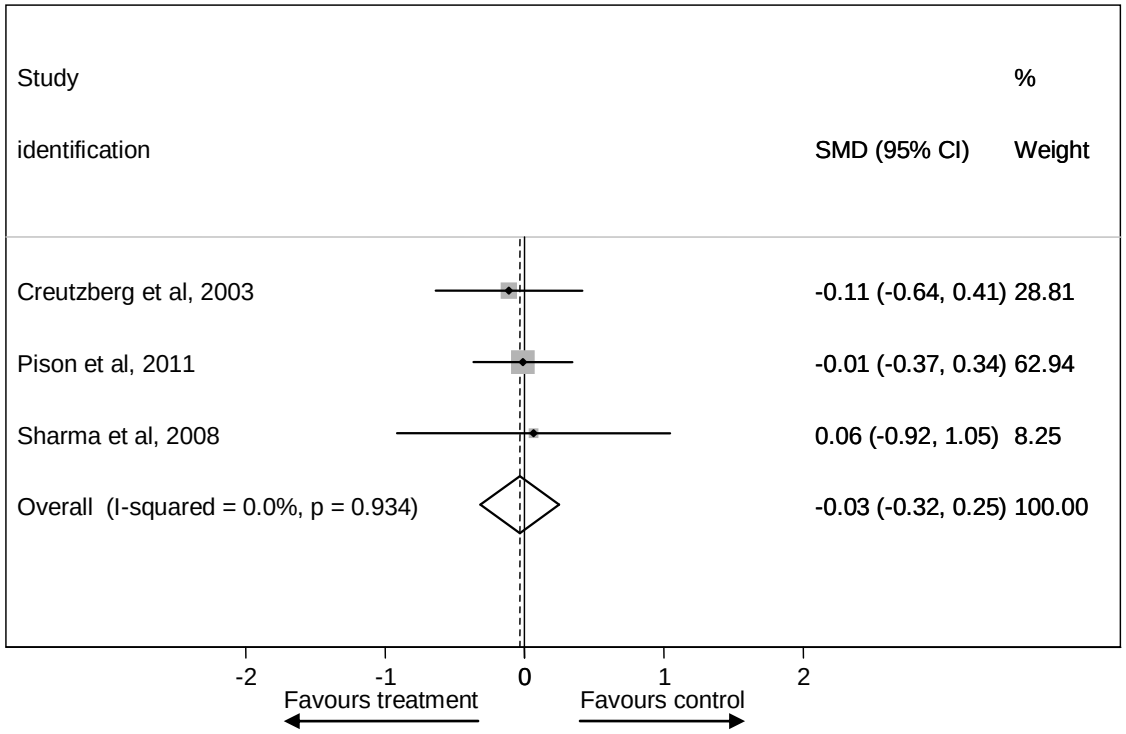
.1
.2
.3
.4
.5
-.5
0
.5
1
1.5
SMD


Study
Identification
%
SMD (95% CI)
Weight
Casaburi et al, 2004a
0.03 (-0.77, 0.83)
18.94
Casaburi et al, 2004b
0.06 (-0.76, 0.87)
18.14
Creutzberg et al, 2003
0.48 (-0.06, 1.02)
39.43
Ferreira et al, 1998
-0.58 (-1.61, 0.44)
11.86
Sharma et al, 2008
0.61 (-0.42, 1.65)
11.62
Overall (I-squared = 4.8%, p = 0.379)
0.21 (-0.15, 0.56)
100.00
-2
-1
0
1
2
Favours control
Favours treatment


Study
identification
%
SMD (95% CI)
Weight
Creutzberg et al, 2003
-0.11 (-0.64, 0.41) 28.81
Pison et al, 2011
-0.01 (-0.37, 0.34) 62.94
Sharma et al, 2008
0.06 (-0.92, 1.05) 8.25
Overall (I-squared = 0.0%, p = 0.934)
-0.03 (-0.32, 0.25) 100.00
-2
-1
0
1
2
Favours treatment
Favours control

APPENDIX

PubMed search syntax

(Gonadal Steroid Hormones[mh] OR Sex Steroid*[tw] OR Sex Hormone*[tw] OR Steroid Hormone*[tw] OR Gonadal Steroid*[tw] OR Androgens[mh] OR Testosterone[tw]) AND (Pulmonary Emphysema[mh] OR Emphysema*[tw] OR Pulmonary Disease, Chronic Obstructive[mh] OR COPD[tw] OR Chronic Obstructive Pulmonary Disease[tw] OR COAD[tw] OR Chronic Obstructive Airway Disease[tw] OR Chronic Obstructive Lung Disease[tw] OR Airflow Obstruction*[tw] OR Lung Diseases, Obstructive[mh] OR Obstructive Lung[tw] OR Obstructive Pulmonary[tw] OR Bronchitis[mh] OR Bronchitis[tw]) NOT (Asthma[mh] OR Asthma*[tw])

Scopus search syntax

((TITLE-ABS-KEY(steroid hormone*) OR TITLE-ABS-KEY(sex steroid*) OR TITLE-ABS-KEY(sex hormone*) OR TITLE-ABS-KEY(steroid hormone*) OR TITLE-ABS-KEY(androgen*) OR TITLE-ABS-KEY(testosterone)) AND (TITLE-ABS-KEY(pulmonary emphysema) OR TITLE-ABS-KEY(emphysema*) OR TITLE-ABS-KEY(pulmonary disease, chronic obstructive) OR TITLE-ABS-KEY(copd) OR TITLE-ABS-KEY(chronic obstructive pulmonary disease) OR TITLE-ABS-KEY(coad) OR TITLE-ABS-KEY(chronic obstructive airway disease) OR TITLE-ABS-KEY(chronic obstructive lung disease) OR TITLE-ABS-KEY(airflow obstruction*) OR TITLE-ABS-KEY(lung diseases, obstructive) OR TITLE-ABS-KEY(obstructivelung) OR TITLE-ABS-KEY(obstructive pulmonary) OR TITLE-ABS-KEY(bronchitis))) AND NOT (TITLE-ABS-KEY(asthma))

Cochrane Library search syntax

Hits Edit Delete #1 (Gonadal Steroid Hormones[mh] OR Sex Steroid*[tw] OR Sex Hormone*[tw] OR Steroid Hormone*[tw] OR Gonadal Steroid*[tw] OR Androgens[mh] OR Testosterone[tw]) AND (Pulmonary Emphysema[mh] OR Emphysema*[tw] OR Pulmonary Disease, Chronic Obstructive[mh] OR COPD[tw] OR Chronic Obstructive Pulmonary Disease[tw] OR COAD[tw] OR Chronic Obstructive Airway Disease[tw] OR Chronic Obstructive Lung Disease[tw] OR Airflow Obstruction*[tw] OR Lung Diseases, Obstructive[mh] OR Obstructive Lung[tw] OR Obstructive Pulmonary[tw] OR Bronchitis[mh] OR Bronchitis[tw]) NOT (Asthma[mh] OR Asthma*[tw]):ti,ab,kw

3

Quality item checklist for observational studies reviewed (each worth 1 numerical point)

Study identification	COPD assessment adequate?	Testosterone assay adequate?	Generalizability? (study population representative of clinical setting or community)	Covariate considerations adequate? (each worth 0.2 points): (1) age, (2) socio-economic or partner status, (3) central or general obesity, (4) smoking status, (5) alcohol intake, (6) physical activity, (7) depression or anxiety (or medications), (8) metabolic syndrome or cardiovascular disease (or medications), (9) systemic inflammation (or glucocorticoids), (10) sleep apnoea (or treatments)	Total quality score (out of 5)
Bratel et al, 2000	0	1	0	0.2	1.2
Gow et al, 1987	1.0	1.0	0.5	0.4	2.9
Iqbal et al, 1999	1.0	1.0	1.0	1.0	4.0
Hsu et al, 2006	1.0	1.0	0.5	0.4	2.9
Kaparianos et al, 2011	1.0	1.0	0.5	1.0	3.5
Karadag et al, 2007	1.0	1.0	0.0	1.0	3.0
Semple et al, 1981	1.0	1.0	0.5	0.2	2.7
Svartberg et al, 2007	1.0	1.0	1.0	0.6	3.6
Van Vliet et al, 2005	1.0	1.0	0.5	0.4	2.9

Quality item checklist for randomised controlled trials reviewed (each worth 1 numerical point)

Study identification	Description of eligibility criteria adequate?	Randomization adequate? (each worth 0.5 points): (1) evidence suggesting "random" allocation; (2) evidence suggesting method used to generate random allocation sequence	Allocation concealment adequate?	Between-group prognostic indicators balanced? (each worth 0.5 points): (1) COPD severity; (2) total testosterone level	Care providers blinded?	Between-group drop-outs balanced?	Intention to treat analysis included?	Adverse events reported?	Total quality score (out of 8)
Casaburi et al, 2004	1.0	0.5	0.0	0.5	1.0	1.0	0.0	1.0	5.0
Creutzberg et al, 2003	1.0	1.0	1.0	1.0	1.0	0.0	0.0	1.0	6.0
Ferreira et al, 1998	1.0	0.5	0.0	1.0	1.0	1.0	0.0	1.0	5.0
Pison et al, 2011	1.0	1.0	1.0	1.0	0.0	0.0	0.0	1.0	5.0
Sharma et al, 2008	1.0	0.5	0.0	0.0	1.0	1.0	0.0	1.0	4.5
Svartberg et al, 2004	1.0	0.5	0.0	1.0	1.0	1.0	0.0	1.0	5.5

EXCLUDED CITATIONS

1 Banks WA, Cooper JA. Hypoxia and hypercarbia of chronic lung disease: minimal effects on anterior pituitary function. South Med J 1990; 83:290-293

2 Bratel T, Wennlund A, Carlström K. Pituitary reactivity, androgens and catecholamines in obstructive sleep apnoea. Effects of continuous positive airway pressure treatment (CPAP). Respiratory medicine 1999; 93:1-7

3 Casaburi R, Cosentino G, Bhasin S, et al. A randomised trial of strength training and testosterone supplementation in men with chronic obstructive pulmonary disease. European Respiratory Journal, 2001; 173s

4 Chavoshan B, Fournier M, Lewis MI, et al. Testosterone and resistance training effects on muscle nitric oxide synthase isoforms in COPD men. Respir Med 2012; 106:269-275

5 Collins EG, Halabi S, Langston M, et al. Sexual dysfunction in men with COPD: impact on quality of life and survival. Lung 2012; 190:545-556

6 D'A.Semple P, Beastall GH, Watson WS, et al. Hypothalamic-pituitary dysfunction in respiratory hypoxia. Thorax 1981; 36:605-609

7 Debigare R, Marquis K, Cote CH, et al. Catabolic/anabolic balance and muscle wasting in patients with COPD. Chest 2003; 124:83-89

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Endogenous testosterone level and testosterone supplementation therapy in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003127.R1
Article Type:	Research
Date Submitted by the Author:	31-May-2013
Complete List of Authors:	Atlantis, Evan; University of Western Sydney, Family and Community Health Research Group School of Nursing and Midwifery Fahey, Paul Cochrane, Belinda Wittert, Gary Smith, Sheree; University of Western Sydney, Family and Community Health Research, School of Nursing and Midwifery
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	Sex steroids & HRT < DIABETES & ENDOCRINOLOGY, Thoracic medicine < INTERNAL MEDICINE, Diabetes & endocrinology < INTERNAL MEDICINE, Chronic airways disease < THORACIC MEDICINE, EPIDEMIOLOGY

Article title: Endogenous testosterone level and testosterone supplementation therapy in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis

[1,5]Evan Atlantis, PhD; e-mail: e.atlantis@uws.edu.au

[2]Paul Fahey, MMedStat; e-mail: p.fahey@uws.edu.au

[1,3,4]Belinda Cochrane, MD; e-mail: belindacochrane@bigpond.com

[5]Gary Wittert, MD; e-mail: gary.wittert@adelaide.edu.au

[1,6]Sheree Smith, PhD; e-mail: sheree.smith@uws.edu.au

[1]School of Nursing and Midwifery, University of Western Sydney, Campbelltown Campus, New South Wales, Australia

[2]School of Science and Health, University of Western Sydney, Campbelltown Campus, New South Wales, Australia

[3]School of Medicine, University of Western Sydney, Campbelltown Campus, New South Wales, Australia

[4]Staff Specialist Respiratory and Sleep Physician, Campbelltown Hospital, New South Wales, Australia

[5]School of Medicine, University of Adelaide, Adelaide, South Australia, Australia

[6]Centre for Pharmacology and Therapeutics, Division of Experimental Medicine, Imperial College, South Kensington, London

This research was performed at the University of Western Sydney.

Keywords: Gonadal steroid hormones; pulmonary disease, chronic obstructive; lung diseases, obstructive; exercise therapy; exercise test; quality of life

Text word count: 3617

Abstract word count: 300

For submission to: BMJ open

Date: 31 May 2013

Corresponding Author: Evan Atlantis, PhD

Senior Research Fellow

Family and Community Health Research Group

School of Nursing and Midwifery | University of Western Sydney

Building 17, Room 17.1.14, Campbelltown Campus,

Locked Bag 1797, Penrith NSW 2751 AUSTRALIA

Phone: + 61 2 4620 3263

Fax: + 61 2 4620 3199

Email: e.atlantis@uws.edu.au

ABSTRACT

Objective: Low testosterone level may be a reversible risk factor for functional disability and deterioration in patients with COPD. We sought to systematically assess endogenous testosterone levels and effect of testosterone therapy on exercise capacity and health-related quality of life (HRQoL) outcomes in COPD patients, to inform guidelines and practice.

Design: Systematic review and meta-analysis.

Data sources: We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, and PsychINFO and reference lists of retrieved articles published before May 2012.

Inclusion criteria: Observational studies on endogenous testosterone levels in people with chronic lung disease compared with controls, or randomised controlled trials (RCTs) on testosterone therapy for exercise capacity and/or HRQoL outcomes in COPD patients were eligible.

Data extraction and analysis: Data on the mean difference in endogenous total testosterone (TT) values, and the mean difference in exercise capacity and HRQoL values were extracted and pooled using random effects meta-analysis.

Results: Nine observational studies in 2918 men with COPD reported consistently lower levels of total testosterone (TT) compared with controls (weighted mean difference was -3.21nmol/L [95% CI: -5.18, -1.23]). Six RCTs in 287 participants yielded five studies on peak muscle strength and peak cardiorespiratory fitness outcomes (peak oxygen uptake [VO2] and workload), and three studies on HRQoL outcomes. Testosterone therapies significantly improved peak muscle strength (standardised mean difference [SMD] was 0.31 [95% CI: 0.05, 0.56]) and peak workload (SMD was 0.27 [95% CI: 0.01, 0.52]) compared with control conditions (all but one used placebo), but not peak VO2 (SMD was 0.21 [95% CI: -0.15, 0.56]) or HRQoL (SMD was -0.03 [95% CI: -0.32, 0.25]).

Conclusions: Men with COPD have clinically relevant lower than normal TT levels. Insufficient evidence from short-term studies in predominately male COPD patients suggest that testosterone therapy improves exercise capacity outcomes, namely peak muscle strength and peak workload.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently ranked the fifth leading cause of global disability (health loss)[1]. Health status or health-related quality of life (HRQoL) is a clinically important measurement of disability among patients with COPD for prognostic studies and trials[2-4]. Exercise capacity, one of the main determinants of HRQoL, is significantly impaired in COPD patients[3, 5]. Dyspnea and fatigue due to skeletal muscle dysfunction, among other physiological abnormalities, are cardinal symptoms that limit exercise capacity in COPD patients[6]. This is partly due to decreases in muscle strength and mass (often called "cachexia"), since they are characteristic features of skeletal muscle dysfunction contributing to exercise intolerance and consequential deterioration in HRQoL[5, 6]. Conversely, pulmonary rehabilitation including exercise (namely resistance training) leads to clinically relevant improvements in muscle strength and HRQoL[7, 8], indicating that skeletal muscle dysfunction should be a primary therapeutic target for intervention in patients with COPD.

Since testosterone level has been shown to be positively associated with muscle strength and cardiorespiratory fitness accounting for physical activity and muscle mass[9, 10], a low testosterone level may be an independent risk factor for functional disability and deterioration in COPD. For example, levels of testosterone and other androgenic hormones were decreased in both male and female COPD patients compared with controls in a few studies[11-13]. Potential mechanisms for this endocrine dysfunction likely involve hypoxaemia, hypercapnia, systemic inflammation and use of glucocorticoids[14].

Thus, it is important to reliably establish whether the mean endogenous testosterone level is decreased in patients with COPD, because this condition is reversible with testosterone supplementation therapy. Indeed, a small but promising body of randomized controlled trial (RCT) evidence suggests that testosterone therapy improves exercise capacity and HRQoL

without increasing serious adverse events[15-17]. While it is difficult to explain this apparent therapeutic benefit, increased cardiac output[18], haemoglobin and haematocrit[19], baroreflex sensitivity[20], and exercise tolerance due to improvements in peak oxygen uptake (peak VO2) and muscle strength[20] are all plausible mechanisms.

However, our initial analysis of the available published literature indicates an absence of a systematic review of relevant studies on endogenous testosterone levels and testosterone therapy in patients with COPD. We therefore sought to systematically review previous research to assess the mean endogenous testosterone level in people with chronic lung disease compared with controls, and the effects of testosterone therapies on exercise capacity and HRQoL outcomes in COPD patients, to inform guidelines and practice.

METHODS

Search strategy

We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, and PsychINFO electronic databases for articles published before May 2012. Search syntaxes were developed in consultation with an experienced university research librarian taking into account a broad range of terms and phrases used in definitions of testosterone and COPD (full electronic search strategies for PubMed, Scopus and Cochrane Library databases in appendix pages 1, 2). Reference lists of potentially eligible articles were searched by hand to identify additional studies missed by our search strategy.

Study selection

One reviewer (EA) identified potentially relevant studies for inclusion by screening titles and/or abstracts of all citations identified with our database searches. A second screening was performed on the full text of these articles. Observational studies in adult populations that

reported endogenous testosterone levels in men and/or women (separately) with chronic lung disease (cases) compared with controls, or RCTs that reported the effects of testosterone treatment on exercise capacity and HRQoL outcomes in COPD patients were eligible. There were no language restrictions for articles.

Data extraction

Data extraction and quality assessment of included studies were performed and/or verified independently by three reviewers (EA, BC and SS). Discrepancies were resolved through discussion. Authors of relevant studies were contacted, where possible, for data that could not be extracted from the published articles.

Quality assessment

For methodology and quality assessment, quality checklists were developed to identify potential sources of bias (tables in appendix pages 3, 4). Quality items for observational studies reviewed were (each worth 1 numerical point): (1) COPD or chronic lung disease was reported to have been clinically diagnosed or categorized according to the WHO International Statistical Classification of Diseases and Related Health Problems (ICD) system, (2) endogenous testosterone level was measured by radioimmunoassay (RIA) or liquid chromatography-tandem mass spectrometry (LC-MS/MS), (3) the study population was representative of the clinical setting or community (i.e., demographic characteristics of cases and hospital controls were typical and community cases or controls were randomly selected), and (4) there was adequate adjustment or exclusion or matching for covariates known to be associated with COPD and hypogonadism in men (each worth 0.2 numerical point): (a) age, (b) socio-economic or partner status, (c) central or general obesity, (d) smoking status, (e) alcohol intake, (f) physical activity, (g) depression or anxiety (or medications), (h) metabolic

syndrome or cardiovascular disease (or medications), (i) systemic inflammation (or glucocorticoids), and (j) sleep apnea (or treatments).

Quality items for RCT studies reviewed were (each worth 1.0 numerical point): (1) study eligibility criteria were adequately described, (2) randomization methodology was adequate (i.e., evidence suggesting "random" method was used to generate and implement random allocation sequence), (3) allocation concealment was adequate (i.e., evidence to suggest that a robust method was used for concealing the sequence of treatment allocation (e.g., independent IT or telephone service or sealed opaque envelopes only opened in front of the participant), (4) between-group prognostic indicators were balanced (i.e., evidence showing that groups were similar at the outset for these prognostic indicators), (5) care providers were blinded to treatment allocation, (6) between-group drop-out rates were balanced, (7) intention to treat analysis was included, and (8) adverse events were reported.

Our quality checklist scales were designed based on criteria for assessment of observational studies[21] and RCTs[21, 22] and allowed summed scores to range from 0 to 5 points and 0 to 8 points, respectively, reflecting lowest to highest quality. Studies were considered 'better quality' if they received a score of 3 or higher for observational studies and of 5 or higher for RCTs, since that meant that they had most of our quality items.

Primary outcomes

The primary outcomes were the mean difference in endogenous total testosterone (TT) values between the case and control groups for observational studies (the most frequently reported testosterone outcome in relevant studies), and the mean difference in exercise capacity and HRQoL values after intervention (post-treatment) between the treatment and control groups for RCTs. Where necessary for observational studies, we estimated the mean and variance from the median, range, and sample size using methods which have been shown

to be reasonably robust in non-extreme circumstances[23]. Where necessary for RCTs, the post-treatment means were derived from the within group changes and the control group standard deviation carried forward from the baseline values[24]. Standardised mean differences were calculated using Glass's Delta method. Exercise capacity outcomes included any assessment of cardiorespiratory fitness and peripheral skeletal muscle strength. Where multiple cardiorespiratory fitness outcomes were reported, first we chose peak VO2 measures, and then prioritized peak workload (power output) laboratory assessments of cardiorespiratory fitness over field tests. Where multiple muscle strength outcomes were reported, we prioritized peak isometric over peak dynamic measures; and knee extension over other joint movements. HRQoL outcomes included any patient-reported assessment of health status or functional disability. Where multiple HRQoL outcomes/scales were reported, first we chose summed score scales, and then prioritized subscales that measure "fatigue" symptoms, and the most frequently reported HRQoL outcome in the other studies reviewed.

Data synthesis

Three reviewers (EA, BC and SS) independently collated and/or verified extracted data to present a descriptive synthesis of important study characteristics and a quantitative synthesis of effect estimates.

Secondary outcomes

The secondary outcomes were data about adverse events reported in the RCTs for a descriptive synthesis.

Statistical methods

We pooled and weighted studies first using random effects meta-analysis models, and second using fixed effects models for verification[25]. Where necessary, we standardised laboratory values for endogenous TT levels between observational studies using the International System of Units (SI Units), expressed in nanomoles per litre (nmol/L). These studies were then pooled to estimate the inverse variance weighted mean difference (WMD), including the DerSimonian and Laird 95% confidence interval (95% CI), between cases and controls. Where papers presented medians without means, we estimated the missing mean as being equal to the median for meta-analysis[23].

In examining the effects of testosterone treatment on exercise capacity and HRQoL outcomes, the standardised mean difference (SMD) from each RCT were pooled to produce an overall estimate of effect, and associated 95%CI, between treatment and control groups. For each meta-analysis model, the degree of heterogeneity in SMDs was assessed by visual inspection, the *I*-squared statistic (moderate being < 50%[26]) and the χ^2-test of goodness of fit[27]. Where evidence of heterogeneity was observed, we checked data extracted from individual outlier studies, qualitatively investigated reasons for their different results, and explored the effects of study exclusion in sensitivity analyses.

We also used sensitivity analysis to investigate the robustness of the meta-analyses models. We variously excluded RCTs in men and women, placebo only (rather than placebo with exercise) controlled trials, longer duration trials (≥ 12 weeks), and studies of lower quality (score < 3.0 for observational studies; score < 5.0 for RCTs). And we repeated the meta-analysis models using different cardiorespiratory fitness outcomes. Publication bias, which reflects the tendency for smaller studies to be published in the literature only when findings are positive, was assessed visually using funnel plots[28]. All calculations were performed in Stata version 12 (StataCorp, College Station, TX, USA) using the 'metan'and

'metafunnel' commands. A two-tailed *P*-value < 0.05 was considered statistically significant throughout the analyses.

RESULTS

Figure 1 presents a flowchart summarising identification of potentially relevant studies, and those included and excluded (appendix page 8). Our search strategy identified 906 citations after duplicates were removed. Of these, 865 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria, leaving 41 citations for a second full text screening. Hand searching the reference lists of these articles identified two additional potentially relevant citations. After further assessment of these 43 citations, 28 were excluded for reasons listed in figure 1, leaving 15 for final inclusion in the systematic review. Most studies were excluded for inadequate predictor or outcome variables, or not having a control group (list of excluded citations; appendix pages 5-7).

Descriptive data synthesis

Table 1 presents study characteristics of nine observational studies included for review, which were published between 1981 and 2011. Studies were conducted in Scotland[29, 30], Sweden[31], the United States[32], Taiwan[33], Greece[12], Turkey[13], Norway[34] and Belgium[35]. The degree of severity of airflow limitation in COPD cases ranged from mild to very severe, assessed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[36] in four studies[12, 13, 33, 35], and by various spirometry criteria in four[29, 30, 32, 34] out of the five remaining studies. Control participants were recruited from primary care settings in six studies[12, 29, 30, 32, 33, 35]. The sample sizes ranged from 16 to 213, resulting in a total of 2918 participants across studies. Mean age of the samples ranged from 50 to 71 years. All of the observational studies were conducted in men.

Mean quality scores ranged from 2.2 to 4.0, and four studies received a score of 3.0 or higher[12, 13, 32, 34].

<< Table 1 >>

Table 2 presents study characteristics of six RCTs included for review, which were published between 2003 and 2011. Studies were conducted in the United States[37], The Netherlands[38], Brazil[39], France[16], Canada[40] and Norway[41]. Major inclusion criteria were stable COPD or chronic respiratory failure in all studies, various spirometry criteria in all but one study[16], low TT in only one study[37], and low body mass index in only two studies[16, 39]. Major exclusion criteria were a range of chronic conditions in all studies, prostatic conditions in four studies[16, 37, 39, 40], and elevated haemoglobin in one study[37]. The sample sizes ranged from 16 to 122, resulting in a total of 287 participants across studies. Mean age of the samples ranged from 66 to 69 years. All but two studies[16, 40] were conducted in men only. Baseline mean TT levels ranged from 9.6 to 21.6nmol/L for men, and 0.42 to 0.45nmol/L for women as reported in one study[16]. Testosterone therapies used were oral testosterone undecanoate in one study[16], oral stanozolol after a baseline intramuscular injection of testosterone in another study[39], and intramuscular injections (testosterone enanthate[37, 41] and nandrolone decanoate[38]) in all remaining studies. Four studies investigated the combined effects of testosterone therapy with resistance training (RT)[37] or pulmonary rehabilitation (PR)[16, 39, 40]. All but one study[16] used placebo control conditions. Trial durations ranged from eight to 27 weeks. Primary outcomes were peak muscle strength in five studies (from four citations[16, 37, 38, 40]), peak VO2 in five studies (from four citations[37-40]), peak workload in five studies (from four citations[16, 37, 38, 40]), six minute walking test (6MWT) in four studies[16, 39-41], and HRQoL in three

studies[16, 38, 40]. Mean quality scores ranged from 4.5 to 6.0, and all but one study[40] received a score of 5.0 or higher.

<< Table 2 >>

Quantitative data synthesis

Effect of COPD exposure on endogenous TT level

Figure 2 presents the WMD in endogenous TT level between the case and control groups for observational studies (appendix page 9). Men with COPD had significantly lower levels of TT compared with controls (pooled WMD was -3.21nmol/L [-5.18, -1.23]). There was a high degree heterogeneity between studies (I-squared=81.9%, P<0.001) that was mostly a result of variation in degree of deference rather than an unfavourable direction towards the null. The sensitivity analyses presented in table 3 shows that the pooled WMD was substantially changed after exclusion of lower quality studies (increased to -3.68 [-7.00, -0.36]) and one large sample size study[34] (increased to -3.56 [-5.63, -1.49]). Finally, for the one study[33] which provided both unadjusted mean differences and mean differences adjusted for age, waist circumference and smoking status, a model using unadjusted rather than adjusted values decreased the pooled WMD to -2.95 (-4.63, -1.27). In addition, a funnel plot was produced and showed only slight evidence of publication bias, since the WMD in TT was small (-0.60[33] and -1.10nmol/L[34]) for two of the largest studies (figure 3; appendix page 10).

<< Table 3 >>

Effect of testosterone therapy on exercise capacity and HRQoL outcomes

Figure 4 presents the SMD in peak muscle strength outcomes after testosterone therapy between the treatment and control groups for RCTs (appendix page 11). Testosterone therapies significantly improved standardised peak muscle strength outcomes compared with control conditions (pooled SMD was 0.31 [0.05, 0.56]), and there was little evidence of statistical heterogeneity between studies (*I*-squared=0.0%, *P*=0.839). The sensitivity analyses presented in table 4 shows that the pooled SMD was similar after exclusion of one lower quality study [40] (0.31 [0.04, 0.57]), but was substantially changed after exclusion of two placebo only controlled studies (no longer statistically significant 0.30 [-0.01, 0.62]), and the two studies in men and women that were also the two longer duration studies[16, 40] (decreased to 0.21 [-0.18, 0.60]). In addition, a funnel plot was produced and showed only slight evidence of publication bias, since the SMD in peak muscle strength outcomes was consistent in all but one treatment arm in one study[37] (figure 5; appendix page 12).

<< Table 4 >>

Figure 6 presents the SMD in peak VO2 outcomes after testosterone therapy between the treatment and control groups for RCTs (appendix page 13). Testosterone therapies consistently failed to show significant improvements in standardised peak VO2 outcomes compared with control conditions (pooled SMD was 0.21 [-0.15, 0.56]; *I*-squared=4.8%, *P*=0.379). The sensitivity analyses presented in table 5 shows that this null effect was similar after exclusion of one lower quality study[40] (0.13 [-0.27, 0.54]), two placebo only controlled studies (0.03 [-0.60, 0.66]), one study in men and women[40] (0.13 [-0.27, 0.54]), and two longer duration studies[39, 40] (0.27 [-0.12, 0.67]), and in the model using 6MWT outcomes (0.10 [-0.34, 0.53]). Conversely, testosterone therapies significantly improved cardiorespiratory fitness in the model using peak workload rather than peak VO2 outcomes

(pooled SMD was 0.27 [0.01, 0.52]), and there was little evidence of statistical heterogeneity between studies (*I*-squared=0.0%, *P*=0.741).

<< Table 5 >>

Figure 7 presents the SMD in peak HRQoL outcomes after testosterone therapy between the treatment and control groups for RCTs (appendix page 14). Testosterone therapies consistently failed to show better standardised HRQoL outcomes compared with control conditions (pooled SMD was -0.03 [-0.32, 0.25]; *I*-squared=0.0%, *P*=0.934). The sensitivity analyses showed that this null effect was comparable in the fixed effect model (-0.03 [-0.32, 0.25]) and after exclusion of one lower quality study[40] (-0.04 [-0.34, 0.25]).

Adverse events

Two RCTs showed that testosterone therapy was associated with more serious adverse events compared with the control group. One study reported an increased number of exacerbations during short-term, but not long-term, follow-up[16], and another study reported that two of three COPD patients with respiratory failure in the treatment group had died[38]. Conversely, one study reported that more patients died of respiratory failure in the control group[39]. Four studies showed that testosterone therapies decreased gonadotrophin levels compared with controls, as can be expected[16, 37, 39, 41]. Compared with controls, testosterone therapy was associated with a decrease in sex hormone-binding globulin level in two studies[16, 41], and a decrease in oestradiol level in men in another study[16]. Finally, few studies showed that testosterone therapy was associated with relative increases in haemoglobin or haematocrit[16, 37, 38]; creatinine, aspartate aminotransferase and lactate dehydrogenase values[38].

DISCUSSION

Summary of evidence

We have established that men with COPD have significantly lower levels of endogenous TT compared with controls (weighted mean difference was -3.21nmol/L [-5.18, -1.23]). The size of the mean difference in TT level, which ranks men with COPD in the second quartile (below average) compared with age-matched population norms[9], is likely to be clinically relevant. For instance, comparable or greater differences in TT levels between cases and controls have been reported in studies on risk of type 2 diabetes (WMD was -2.66nmol/L [-3.45, -1.86])[42], metabolic syndrome (WMD was -2.64nmol/L [-2.95, -2.32])[43], and clinically significant depression (median difference was -1.21nmol/L, $P<0.001$ for Mann-Whitney test)[44]. These comorbidities have been shown to adversely affect COPD prognosis[45-47], and would further complicate COPD management. As the effect of COPD exposure on TT level increased in size after exclusion of lower quality studies and one large sample size study, future higher quality studies will likely strengthen rather than weaken this evidence base. Collectively, our results and the existing literature indicate that testosterone deficiency should be considered in men with COPD.

Based on limited short-term RCT evidence in predominately male COPD patients, our results suggest that testosterone therapy significantly improves several exercise capacity outcomes. The size of the effect of testosterone therapy that can be expected in practice is small to moderate, but comparable to exercise or pulmonary rehabilitation therapies alone[7, 8]. The effect of testosterone therapy on standardised muscle strength outcomes remained robust after exclusion of one lower quality study, but weakened after exclusion of two placebo only studies. This supports the hypothesis that testosterone therapy with exercise is more effective than testosterone therapy alone for functional improvements[48]. In addition,

our results suggest that the mechanism for improvement in cardiorespiratory fitness assessed by peak workload is likely explained by better exercise tolerance due to testosterone-induced increases in muscle strength rather than changes in VO2.

Limitations

Several limitations require careful consideration. Since only a small number of studies conducted in specific populations were included, the findings of this review may not be relevant to other countries and key groups, requiring further research. In particular, most of the RCTs were conducted in COPD patients without cardiovascular disease and/or diabetes or endocrine disease, which are highly prevalent in this population group[46]. Second, we replaced missing data points with estimates in some instances, introducing further uncertainty. This includes both estimating the mean from the median and range and carrying forward the pre-intervention standard deviation of control groups where the post-intervention statistic was not available. Third, because only a few RTCs targeted COPD patients who would have theoretically benefited most from testosterone therapy such as those with low testosterone or body weight[16, 37, 39], our estimated effect size for improvement in standardised exercise capacity may have been underestimated. Finally, reviewer-level limitations include incomplete retrieval of information for several of the 28 citations excluded, and the existence of other relevant studies not identified with our search strategy resulting in selection bias. However, the results and conclusions reported in most of the excluded studies were in line with those reported here, selection bias was unlikely.

Nevertheless, our systematic analysis of the existing literature revealed that there is an absence of sufficient RCT evidence to draw firm conclusions about the long-term benefits and risks of testosterone therapies for exercise capacity and HRQoL outcomes in male or female COPD patients, or about the pharmacological dosing for specific testosterone

therapies needed for effectiveness. Reliable information on the efficacy and safety, as well as cost-effectiveness, of specific testosterone therapies is required to inform clinical practice guidelines for COPD. In addition, future high quality epidemiological research is needed to determine which subgroups of COPD patients are most vulnerable to testosterone deficiency, and to reliably establish whether women with COPD likewise present with significantly lower levels of TT than controls.

Conclusions

Men with COPD have clinically relevant lower than normal endogenous TT levels, and we believe that our meta-analytic results are sufficiently reliable to recommend that clinicians should consider testosterone deficiency in these patients. Although our results also suggest that testosterone therapy improves several exercise capacity outcomes, there is an absence of sufficient RCT evidence to draw firm conclusions about the long-term benefits and risks of testosterone therapy for exercise capacity and HRQoL outcomes in male or female COPD patients.

Figure legends

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Figure 6 presents the SMD in peak VO2 outcomes after testosterone therapy between the treatment and control groups for RCTs.

Figure 7 presents the SMD in peak HRQoL outcomes after testosterone therapy between the treatment and control groups for RCTs

ACKNOWLEDGMENTS

Authorship order is according to percentage contribution. EA is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. EA conceived and designed the review, identified studies for inclusion, extracted and interpreted data, and drafted the article. PF analysed and interpreted data, and revised the article. BC and SS extracted and interpreted data, and revised the article. GW interpreted data, and revised the article. All authors approved the final completed article. We are grateful to Mr Geoffrey Lattimore for his work on developing and conducting the electronic database searches.

COMPETING INTERESTS

EA has entered financial agreements to speak at events for Eli Lilly Australia Pty Ltd (Lilly). BC has received speaking fees and/or conference support from GSK, Novartis and Boehringer Ingelheim. GW has received speaking fees and research support from Bayer; is on International and National advisory boards for and has received research support from Lilly; and has received consulting fees and research support from Lawley pharmaceuticals.

CONTRIBUTORSHIP

Authorship order is according to percentage contribution. EA is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. EA conceived and designed the review, identified studies for inclusion, extracted and interpreted data, and drafted the article. PF analysed and interpreted data, and revised the article. BC and SS extracted and interpreted data, and revised the article. GW interpreted data, and revised the article. All authors approved the final completed article. We are grateful to Mr Geoffrey Lattimore for his work on developing and conducting the electronic database searches.

DATA SHARING

No additional data available.

FUNDING

None

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TABLE 1: Characteristics of observational studies reviewed

Study identification	Country	Participants		Sample size	Sex	Mean age (years)	Mean (SD) or median* (range) total testosterone, nmol/L				Covariate considerations (adjusted/excluded/matched)	Quality score (out of 5)
		Cases, assessment	Controls				Cases		Controls			
Bratel et al, 2000[31]	Sweden	COPD with severe airway obstruction and daytime hypoxaemia, not reported	Age-matched "healthy" participants	32	M	69	14.3	6.9	17.9	6.9	Age	1.2
Gow et al, 1987[29]	Scotland	COPD, spirometry FEV1 <40% and FVC <65% predicted	Inpatients ready for discharge	26	M	70	10.7	3.0-19.5	11.0	1.8-21.9	Age, thyroid disease, oral corticosteroids	2.9
Iqbal et al, 1999[32]	United States	Chronic lung disease, predominantly spirometry FEV1/FVC <80% predicted	Primary care clinic patients without history of chronic lung disease or corticosteroid treatments	85	M	62	11.1	9.8	14.0	8.6	Age, ethnicity, BMI, physical activity, smoking status, caffeine and alcohol consumption, thyroid and rheumatologic conditions, medications including glucocorticoids, testosterone, and for osteoporosis	4.0
Hsu et al, 2006[33]	Taiwan	Chronic bronchitis and COPD, GOLD criteria stage 1-4	Outpatients with stable urolithiasis or prostatitis	213	M	71	14.7	7.7	15.3	6.4	Age, chronic diseases including treated benign prostate hyperplasia, other chronic lung disease, exacerbation	2.9
Kaparianos et al, 2011[12]	Greece	COPD, GOLD criteria mean FEV1 54%, mean FEV1/FVC 59%	Outpatient smokers	125	M	61	11.2	4.4	18.4	4.5	Age, ethnicity, BMI, smoking, chronic diseases, endothelin-1 pro-inflammatory allele, other chronic lung diseases, medications including β2-adrenergic agonists, corticosteroids, follicle stimulating hormone, erythrocyte sedimentation rate	3.5
Karadag et al, 2007[13]	Turkey	COPD, GOLD criteria stage 2-3	Age-matched participants	125	M	63	13.2	5.5	16.6	5.5	Age, sexual partner status, BMI, medications that interfere with sex hormones, chronic diseases, treated urogenital disease, aged ≥75 years, regular systemic corticosteroids, oestradiol, tumor necrosis factor-alpha	3.0
Semple et al, 1981[30]	Scotland	COPD, spirometry FEV1 and FEV1/FVC <70%	Age-matched inpatients	16	M	50	13.1	4.4	20.3	5.4	Age	2.7
Svartberg et al, 2007[34]	Norway	Representative population with COPD, spirometry FEV1 <50% predicted with FEV1/FVC <70% predicted	Representative population with spirometry FEV1 ≥50% predicted	2197	M	66	12.7	5.3	14.0	5.5	Age, waist circumference, smoking status	3.6
Van Vliet et al,	Belgium	COPD, GOLD criteria stage 1-4	Outpatients with normal	99	M	65	9.0*	6.8-12.9	12.3*	8.8-16.2	Age, BMI, calculated low free	2.9

2005[35]	lung function	testosterone, sex hormone binding globulin

Abbreviations: COPD, chronic obstructive pulmonary disease; M, men; GOLD, Global Initiative for Chronic Obstructive Lung Disease; BTS, British Thoracic Society; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; BMI, body mass index; Matched, considered if between-group difference in characteristic was not likely statistically significant (P<0.05);

TABLE 2: Characteristics of randomised controlled trials reviewed adjacent.....continued →

Study identification	Country	Sample size	Population		Sex (M/W)	Mean age (years)	Baseline mean total testosterone, nmol/L	
			Major inclusion criteria	Major exclusion criteria			Treated	Controls
Casaburi et al, 2004[37]	United States	47	Stable COPD, spirometry FEV1 ≤60% predicted and FEV1/VC ≤60%; total testosterone ≤13.9nmol/L	CVD, low or high bodyweight, prostatic indications, haemoglobin ≥16g/dL, orthopaedic impairments	M	67	(a) 10.5; (b) 14.1	(a) 10.5; (b) 9.6
Creutzberg et al, 2003[38]	The Netherlands	56	Stable COPD, ATS criteria, spirometry FEV1 <70% predicted and increase in FEV1 <10% post bronchodilation	Obesity, malignancies, CVD, gastro-intestinal inflammatory disorders, type 1 diabetes, oxygen dependency at rest	M	66	13.4	14.6
Ferreira et al, 1998[39]	Brazil	17	Ambulatory and stable COPD, spirometry maximal inspiratory pressure <60% predicted and BMI <20kg/m^2	CVD, prostatic indications	M	69	14.4	17.2
Pison et al, 2011[16]	France	122	Stable CRF, >18 years, PaO2 ≤8kPa, long-term oxygen therapy and/or home mechanical ventilation >three months, BMI ≤21kg/m^2 or fat-free mass index <25th percentile	Pulmonary hypertension, sleep apnoea, prostatic indications, neuromuscular diseases, cystic fibrosis, conditions compromising six month survival, hormone-dependent cancer, women of childbearing age, elevated aminotransferase	M/W	66	M 12.7; W 0.45	M 13.6; W 0.42
Sharma et al, 2008[40]	Canada	16	Stable COPD, GOLD criteria stage 3-4, spirometry FEV1 <50% predicted and FEV1/FVC <0.7	History of asthma, obesity, malignancy, CVD, prostatic indications, renal, hepatic, gastrointestinal or endocrine disease, recent surgery ≤two months	M/W	68	M NR	W NR
Svartberg et al, 2004[41]	Norway	29	Stable COPD, moderate to severe, spirometry FEV1 <60% predicted	Asthma, malignancies, CVD, hepatic or endocrine disease	M	66	21.6	20.5

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular diseases; CRF, chronic respiratory failure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ATS, American Thoracic Society; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; M, men; W, women; IM, intramuscular injection; RT, resistance training; PR, pulmonary rehabilitation; 1RM, one repetition maximum; VO2, volume of oxygen uptake; HRQoL, health-related quality of life; 6MWT, six minute walking test; CRQ, chronic respiratory questionnaire; NR, not reported

→ adjacent.....continued

Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 8)
(a) Testosterone enanthate, 100mg per week IM; (b) Testosterone enanthate, 100mg per week IM with RT	(a) Placebo; (b) Placebo with RT	10	Muscle strength (leg press, 1RM kg); Cardiorespiratory fitness (bicycle, peak VO2L/min and peak workload Watts)	5.0
Nandrolone decanoate, 50mg per two weeks IM	Placebo	8	Muscle strength (knee extension, peak isometric force Newtons); Cardiorespiratory fitness (bicycle, peak workload Watts and peak VO2ml/min); HRQoL (SGRQ total score)	6.0
Testosterone, 250mg IM at baseline and oral stanozolol, 12mg per day with PR	Placebo with PR nine to 27 weeks	27	Cardiorespiratory fitness (bicycle, peak VO2% predicted; 6MWT, distance metres)	5.0
Oral testosterone undecanoate, M 80mg/W 40mg twice daily with PR	Home education on self-management of COPD-related stress and anxiety	13	Muscle strength (knee extension, peak isometric force Newtons); Cardiorespiratory fitness (6MWT, distance metres; bicycle, peak workload Watts); HRQoL (CRQ total score)	5.0
Nandrolone decanoate, M 50mg/W 25mg per two weeks IM with PR	Placebo with PR	16	Muscle strength (knee extension, peak isometric force units NR); Cardiorespiratory fitness (bicycle, peak VO2% predicted and peak workload Watts; 6MWT, distance metres); HRQoL (CRQ fatigue subscore)	4.5
Testosterone enanthate, 250mg per four weeks IM	Placebo	26	Cardiorespiratory fitness (6MWT, distance metres)	5.5

TABLE 3: Sensitivity analysis of observational studies on COPD exposure → total testosterone outcome meta-analysis

	N studies	*N* sample	Total testosterone WMD	(95% confidence interval)	*P*-value for heterogeneity
Fixed effects model	9	2918	-3.00	(-3.75, -2.26)	<0.001
Exclusion of five lower quality studies (score <3.0)	4	2532	-3.68	(-7.00, -0.36)	<0.001
Model using unadjusted rather than adjusted values in one study	9	2918	-2.95	(-4.63, -1.27)	<0.001
Exclusion of a large sample size study	8	721	-3.56	(-5.63, -1.49)	<0.001

Abbreviations: N, number; WMD, weighted mean difference

TABLE 4: Sensitivity analysis of randomised controlled trials on testosterone treatment → muscle strength outcomes meta-analysis

	N studies	*N* sample	SMD	(95% confidence interval)	*P*-value for heterogeneity
Fixed effects model	5	241	0.31	(0.05, 0.56)	0.839
Exclusion of one lower quality study (score <5.0)	4	225	0.31	(0.04, 0.57)	0.699
Exclusion of two placebo only control studies	3	161	0.30	(-0.01, 0.62)	0.491
Exclusion of two studies in men and women	3	103	0.21	(-0.18, 0.60)	0.611
Exclusion of two longer duration studies (≥12 weeks)	3	103	0.21	(-0.18, 0.60)	0.611

Abbreviations: N, number; SMD, standardised mean difference

TABLE 5: Sensitivity analysis of randomised controlled trials on testosterone treatment → cardiorespiratory fitness outcomes meta-analysis

	N studies	*N* sample	SMD	(95% confidence interval)	*P*-value for heterogeneity
Fixed effects model	5	136	0.21	(-0.13, 0.56)	0.379
Exclusion of one lower quality study (score <5.0)	4	120	0.13	(-0.27, 0.54)	0.315
Exclusion of two placebo only control studies	3	56	0.03	(-0.60, 0.66)	0.269
Exclusion of one study in men and women	4	120	0.13	(-0.27, 0.54)	0.315
Exclusion of two longer duration study (≥ 12 weeks)	3	103	0.27	(-0.12, 0.67)	0.553
Model using peak workload rather than peak VO2 outcomes	5	241	0.27	(0.01, 0.52)	0.741
Model using 6MWT rather than peak VO2 outcomes	4	184	0.10	(-0.34, 0.53)	0.210

Abbreviations: N, number; SMD, standardised mean difference

APPENDIX

PubMed search syntax

(Gonadal Steroid Hormones[mh] OR Sex Steroid*[tw] OR Sex Hormone*[tw] OR Steroid Hormone*[tw] OR Gonadal Steroid*[tw] OR Androgens[mh] OR Testosterone[tw]) AND (Pulmonary Emphysema[mh] OR Emphysema*[tw] OR Pulmonary Disease, Chronic Obstructive[mh] OR COPD[tw] OR Chronic Obstructive Pulmonary Disease[tw] OR COAD[tw] OR Chronic Obstructive Airway Disease[tw] OR Chronic Obstructive Lung Disease[tw] OR Airflow Obstruction*[tw] OR Lung Diseases, Obstructive[mh] OR Obstructive Lung[tw] OR Obstructive Pulmonary[tw] OR Bronchitis[mh] OR Bronchitis[tw]) NOT (Asthma[mh] OR Asthma*[tw])

Scopus search syntax

((TITLE-ABS-KEY(steroid hormone*) OR TITLE-ABS-KEY(sex steroid*) OR TITLE-ABS-KEY(sex hormone*) OR TITLE-ABS-KEY(steroid hormone*) OR TITLE-ABS-KEY(androgen*) OR TITLE-ABS-KEY(testosterone)) AND (TITLE-ABS-KEY(pulmonary emphysema) OR TITLE-ABS-KEY(emphysema*) OR TITLE-ABS-KEY(pulmonary disease, chronic obstructive) OR TITLE-ABS-KEY(copd) OR TITLE-ABS-KEY(chronic obstructive pulmonary disease) OR TITLE-ABS-KEY(coad) OR TITLE-ABS-KEY(chronic obstructive airway disease) OR TITLE-ABS-KEY(chronic obstructive lung disease) OR TITLE-ABS-KEY(airflow obstruction*) OR TITLE-ABS-KEY(lung diseases, obstructive) OR TITLE-ABS-KEY(obstructivelung) OR TITLE-ABS-KEY(obstructive pulmonary) OR TITLE-ABS-KEY(bronchitis))) AND NOT (TITLE-ABS-KEY(asthma))

Cochrane Library search syntax

Hits Edit Delete #1 (Gonadal Steroid Hormones[mh] OR Sex Steroid*[tw] OR Sex Hormone*[tw] OR Steroid Hormone*[tw] OR Gonadal Steroid*[tw] OR Androgens[mh] OR Testosterone[tw]) AND (Pulmonary Emphysema[mh] OR Emphysema*[tw] OR Pulmonary Disease, Chronic Obstructive[mh] OR COPD[tw] OR Chronic Obstructive Pulmonary Disease[tw] OR COAD[tw] OR Chronic Obstructive Airway Disease[tw] OR Chronic Obstructive Lung Disease[tw] OR Airflow Obstruction*[tw] OR Lung Diseases, Obstructive[mh] OR Obstructive Lung[tw] OR Obstructive Pulmonary[tw] OR Bronchitis[mh] OR Bronchitis[tw]) NOT (Asthma[mh] OR Asthma*[tw]):ti,ab,kw

Quality item checklist for observational studies reviewed (each worth 1 numerical point)

Study identification	COPD assessment adequate?	Testosterone assay adequate?	Generalizability? (study population representative of clinical setting or community)	Covariate considerations adequate? (each worth 0.2 points): (1) age, (2) socio-economic or partner status, (3) central or general obesity, (4) smoking status, (5) alcohol intake, (6) physical activity, (7) depression or anxiety (or medications), (8) metabolic syndrome or cardiovascular disease (or medications), (9) systemic inflammation (or glucocorticoids), (10) sleep apnoea (or treatments)	Total quality score (out of 5)
Bratel et al, 2000	0	1	0	0.2	1.2
Gow et al, 1987	1.0	1.0	0.5	0.4	2.9
Iqbal et al, 1999	1.0	1.0	1.0	1.0	4.0
Hsu et al, 2006	1.0	1.0	0.5	0.4	2.9
Kaparianos et al, 2011	1.0	1.0	0.5	1.0	3.5
Karadag et al, 2007	1.0	1.0	0.0	1.0	3.0
Semple et al, 1981	1.0	1.0	0.5	0.2	2.7
Svartberg et al, 2007	1.0	1.0	1.0	0.6	3.6
Van Vliet et al, 2005	1.0	1.0	0.5	0.4	2.9

Quality item checklist for randomised controlled trials reviewed (each worth 1 numerical point)

Study identification	Description of eligibility criteria adequate?	Randomization adequate? (each worth 0.5 points): (1) evidence suggesting "random" allocation; (2) evidence suggesting method used to generate random allocation sequence	Allocation concealment adequate?	Between-group prognostic indicators balanced? (each worth 0.5 points): (1) COPD severity; (2) total testosterone level	Care providers blinded?	Between-group drop-outs balanced?	Intention to treat analysis included?	Adverse events reported?	Total quality score (out of 8)
Casaburi et al, 2004	1.0	0.5	0.0	0.5	1.0	1.0	0.0	1.0	5.0
Creutzberg et al, 2003	1.0	1.0	1.0	1.0	1.0	0.0	0.0	1.0	6.0
Ferreira et al, 1998	1.0	0.5	0.0	1.0	1.0	1.0	0.0	1.0	5.0
Pison et al, 2011	1.0	1.0	1.0	1.0	0.0	0.0	0.0	1.0	5.0
Sharma et al, 2008	1.0	0.5	0.0	0.0	1.0	1.0	0.0	1.0	4.5
Svartberg et al, 2004	1.0	0.5	0.0	1.0	1.0	1.0	0.0	1.0	5.5

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25 Schols AM, Soeters PB, Mostert R, et al. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med 1995; 152:1268-1274

26 Seftel A. Testosterone Treatment Improves Body Composition and Sexual Function in Men With COPD, in a 6-Month Randomized Controlled Trial. J Urol 2005; 173:1278

27 Semple D'A P, Beastall GH, Watson WS, et al. Serum testosterone depression associated with hypoxia in respiratory failure. Clinical Science 1980; 58:105-106

28 Semple d'A P, Watson WS, Beastall GH. Diet, absorption, and hormone studies in relation to body weight in obstructive airways disease. Thorax 1979; 34:783-788

Figure 1 presents flowchart summarising identification of studies included for review.

Figure 2 presents the WMD in endogenous TT level between the case and control groups for observational studies.

Figure 3 presents a funnel plot assessing symmetry of the WMD in TT level between the case and control groups for observational studies.

Figure 4 presents the SMD in peak muscle strength outcomes after testosterone therapy between the treatment and control groups for RCTs.

Figure 5 presents a funnel plot assessing symmetry of the SMD in peak muscle strength outcomes after testosterone treatment between the treatment and control groups for RCTs.

Figure 6 presents the SMD in peak VO2 outcomes after testosterone therapy between the treatment and control groups for RCTs.

Figure 7 presents the SMD in peak HRQoL outcomes after testosterone therapy between the treatment and control groups for RCTs

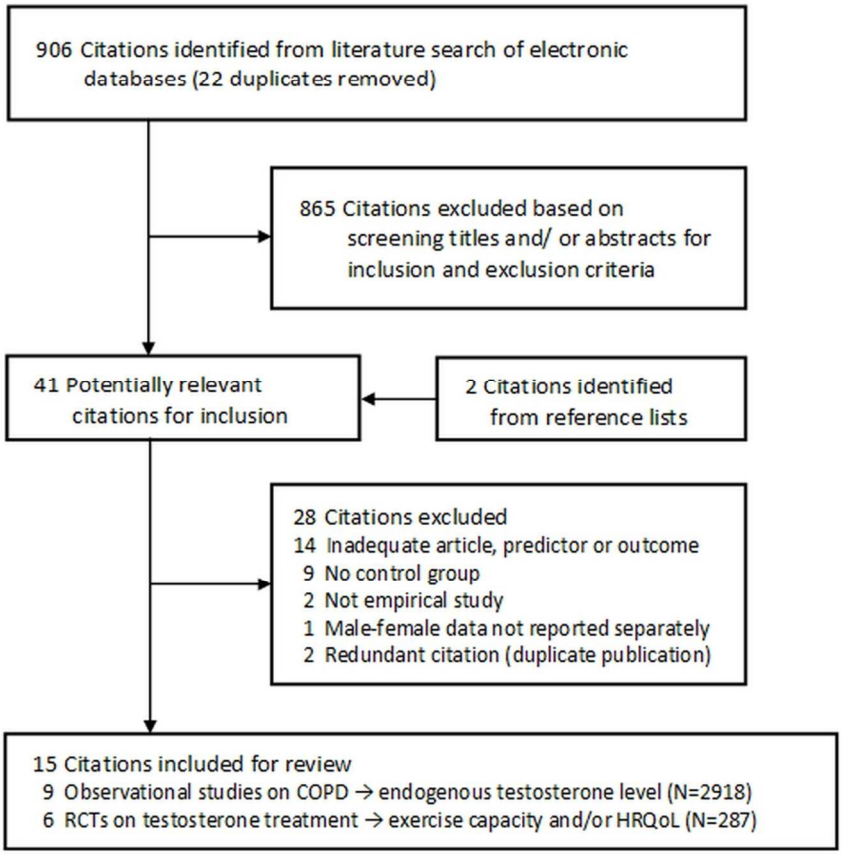
PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3, 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5, 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6, 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	40, 41
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7, 9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8, 9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, 8, 9, 10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9, 10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9, 10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7, 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	33
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	26 to 29
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	42, 43
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	34, 36, 38, 39
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	34, 36, 38, 39
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	35, 37
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	30 to 32
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15 to 16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16 to 17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17 to 18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097



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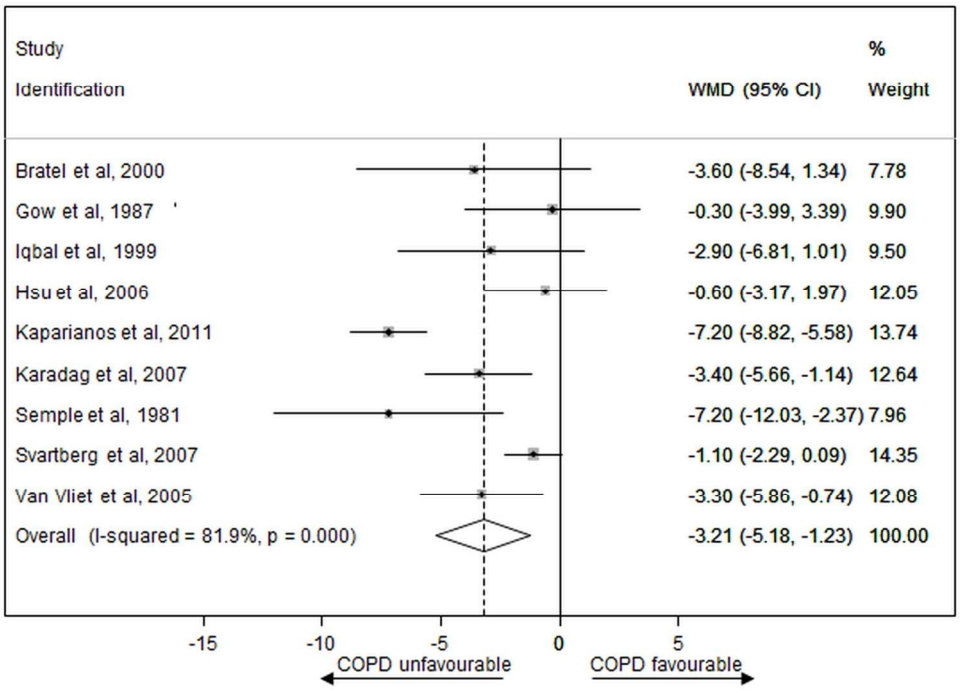

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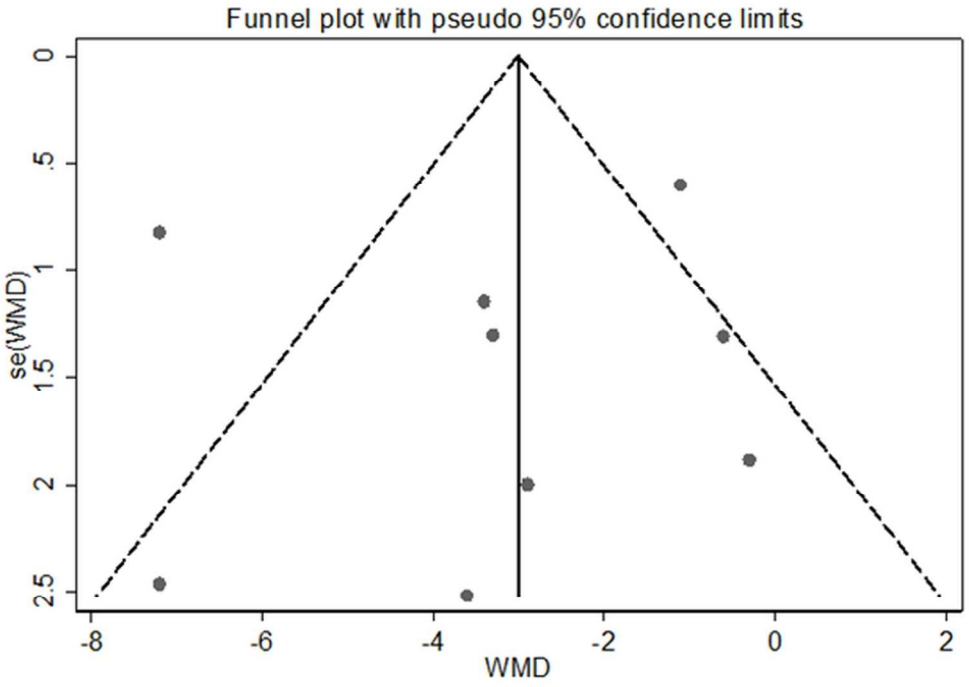

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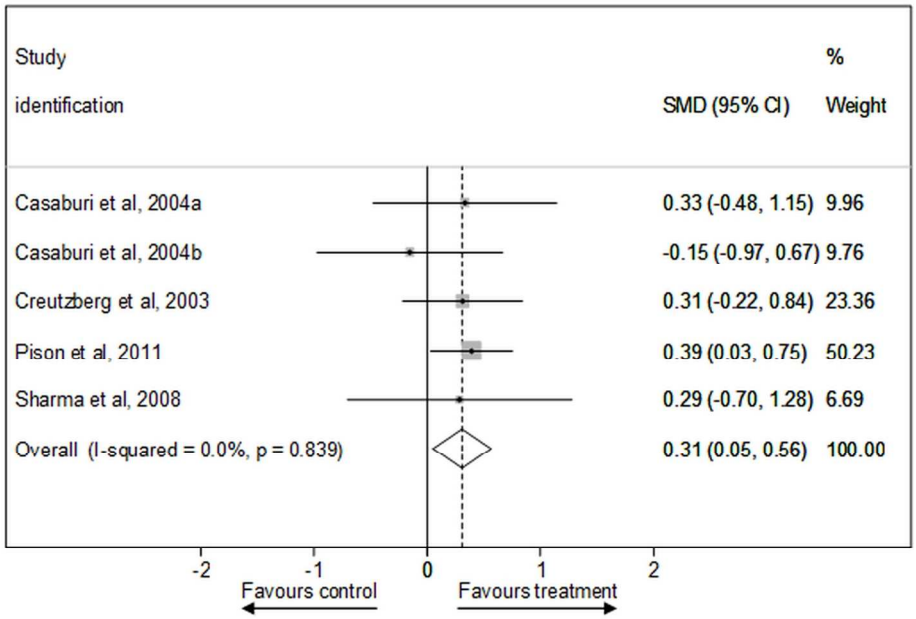

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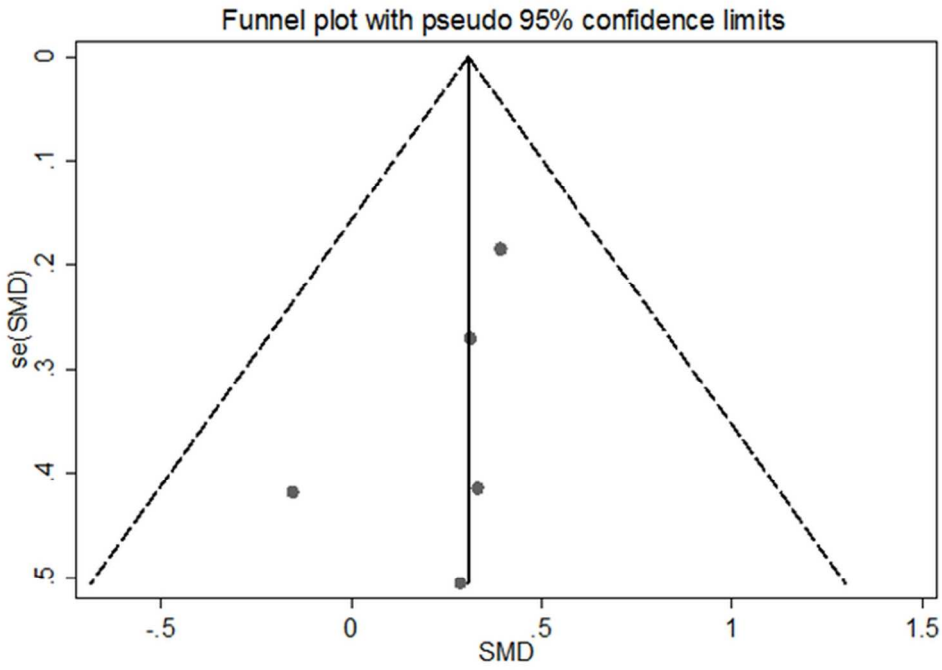

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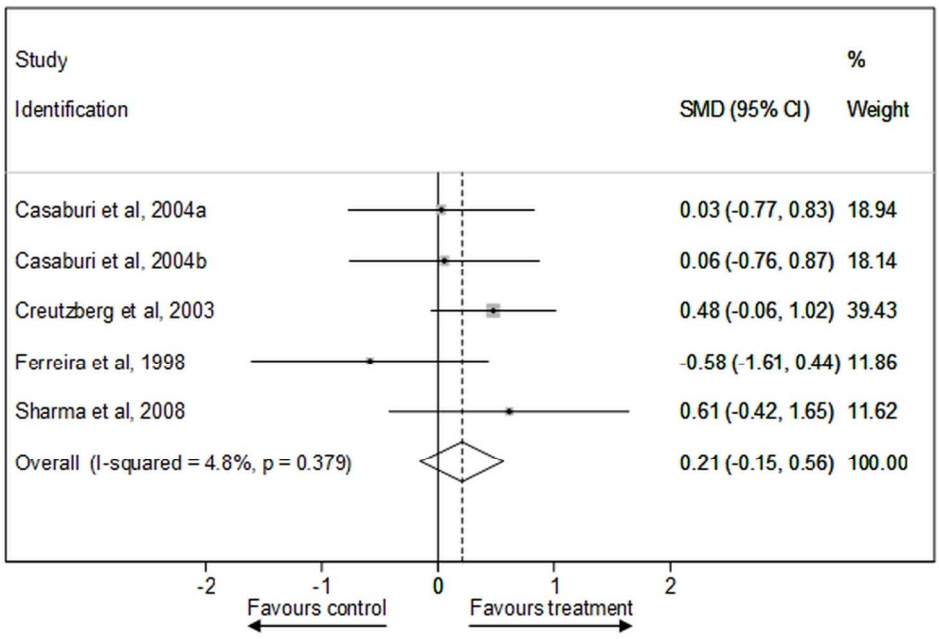

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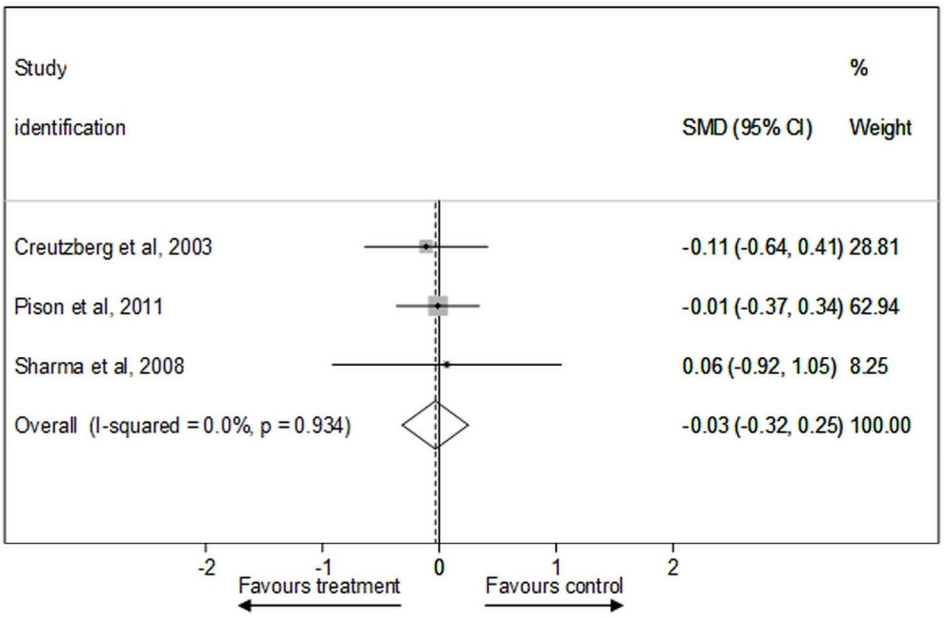

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