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Physical activity for lower urinary tract symptoms secondary to benign prostatic obstruction (Protocol)

Silva V, Grande AJ, Stanton KR, Peccin MS

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[Intervention Protocol]

Physical activity for lower urinary tract symptoms secondary to benign prostatic obstruction

Valter Silva[1], Antonio Jose Grande[2], Kenneth R Stanton[3], Maria S Peccin[1]

[1]Department of Human Movement Sciences, Universidade Federal de São Paulo, Santos, Brazil. [2]Laboratory of Evidence-Based Practice, Universidade do Extremo Sul Catarinense, Criciuma, Brazil. [3]Coppin State University, Baltimore, Maryland, USA

Contact address: Valter Silva, Department of Human Movement Sciences, Universidade Federal de São Paulo, Santos, Brazil. v.silva@ymail.com.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of physical activity for lower urinary tract symptoms due to benign prostatic obstruction.

BACKGROUND

Description of the condition

Lower urinary tract symptoms (LUTS) presumably due to benign prostatic obstruction (BPO) (LUTS/BPO) represent one of the most common clinical complaints in men (Gratzke 2015; McVary 2011). LUTS comprise storage, voiding, and post-micturition symptoms (Abrams 2003; Gratzke 2015; McVary 2011). Storage symptoms include urinary frequency, nocturia, urgency, incontinence, and bladder pain or dysuria. Voiding symptoms include urinary hesitancy, delay in initiating micturition, intermittency, involuntary interruption of voiding, weak urinary stream, straining to void, a sensation of incomplete emptying, and terminal dribbling. Post-micturition symptoms include sensation of incomplete emptying and post-micturition dribble. Symptom scores (e.g. International Prostate Symptom Score (IPSS), Danish Prostate Symptom Score (DAN-PSS)) have become a standard tool for assessing and monitoring male LUTS and identifying which type of symptoms are predominant (Gratzke 2015).

Although male LUTS have multifactorial etiology, BPO is recognized as a major cause and probably is the condition that most clinicians want to treat. A physiologic increase in the number of cells in the prostate, reduced rate of cell death, or both, can cause a hyperplastic epithelial and stromal growth that coalesces into microscopic and macroscopic nodules in the prostate gland and defines a non-neoplastic histologic pattern called benign prostatic hyperplasia (BPH); BPH can result in benign prostatic enlargement (BPE) and, together with the increased prostatic smooth muscle tone, will compress the urethra, leading to bladder outlet obstruction (BOO) and resulting in LUTS due to BPO (Abrams 2003; Gratzke 2015; McVary 2011; Nicholson 2011; Roehrborn 2008; Tang 2009).

The prevalence of BPH by histologic approach can reach around 10% in men aged 30 to 39 years, 40% in men aged 40 to 59 years, 60% in men aged 60 to 69 years, 80% in men aged 70 to 79 years, and 90% in men aged 80 to 89 years old (Roehrborn

2008). Among men aged 40 years or older (age-dependent), approximately 50% of all men who have a histologic diagnosis of BPH have moderate to severe LUTS (Roehrborn 2008). BOO occurs in 64% of men with LUTS (D'Silva 2014). As the worldwide population grows old (men aged 60 years or over represented 7% of the global population in 1950, 11% in 2015 and could rise to 27% in 2100) (United Nations 2015), the probability of new cases of LUTS/BPO will increase. Among the 10 most prevalent diseases in men aged 50 years or older, LUTS/BPO is positioned at seventh place in the most frequently diagnosed and most costly diseases, and is the second most likely disease to have a significant clinical event (acute urinary retention or surgeries occurring in around 20% of men with LUTS/BPO) within one year of initiating treatment (Fenter 2006). The direct cost of LUTS/BPO treatment in 2007 was estimated to be USD 1.41 billion, with inpatient, hospital outpatient, ambulatory surgery, physician office, and emergency room visits (UDA 2012). Although LUTS/BPO is not often a life-threatening condition, it is associated with significant bother, as well as high personal and societal costs (direct and indirect), impacting negatively on quality of life of men and their partners and should not be underestimated (McVary 2011; Speakman 2015).

Description of the intervention

The treatment alternatives for men with LUTS/BPO include (McVary 2011): watchful waiting based on monitoring of symptoms combined with changes in lifestyle factors (e.g. physical activity, diet); medical therapies by single drugs or combinations (e.g. alpha blockers and 5-alpha reductase inhibitors (5-ARIs)); complementary and alternative medicines (e.g. *Serenoa repens*, *Pygeum africanum*, and also physical activity); minimally invasive therapies; and surgical therapies. Drug treatments have shown adverse effects such as dizziness, asthenia, and headaches; the invasive intervention includes the risk of causing impotence. Physical activity appears to be a potential intervention to prevent and treat several health issues (Gillespie 2012; Howe 2011; Mishra 2012). In the case of LUTS/BPO, physical activity could be an attractive first-line and complementary option since studies do not suggest adverse effects (Barkin 2011; De Nunzio 2011; Donnell 2011; Dumoulin 2015; Russo 2015).

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, including occupational activities, daily activities, exercise, and sports (Caspersen 1985). Intensity, frequency, and volume are important characteristics in interventions of physical activities (Ainsworth 2011; Ainsworth 2012), mainly when a comorbidity is present such as LUTS/BPO (Parsons 2008; Sea 2009). Physical activity can be classified by metabolic equivalent of task (MET) as: light intensity (1.6 to 2.9 METs), moderate intensity (3 to 5.9 METs) and vigorous intensity (6 METs or greater). MET expresses the energy cost of physical activities, set by convention to 3.5 mL O_2/kg per minute, equivalently 1 kcal/kg per hour or 4.184 kJ/kg per hour (Ainsworth 2011; Ainsworth 2012).

How the intervention might work

It is well known that physical activity brings general benefits in health (Warburton 2006), and physical activity might be a first-line and complementary intervention for treating LUTS/BPO (Parsons 2008; Russo 2015; Sea 2009). Physical activity interventions for LUTS/BPO might work by multiple pathways in different physiologic dimensions (Barkin 2011; Barnard 2008; Chang 2008; De Nunzio 2011; Donnell 2011; Dumoulin 2015; Jung 2012; Parsons 2008; Sea 2009; Silva 2015): strengthening the pelvic floor muscle; promoting the activity of the parasympathetic nervous system and reducing the excitement of the sympathetic nervous system (this last effect is similar to alpha-blocker drugs); decreasing resting sympathetic tone in the prostate; improving hormonal milieu through modulating insulin and testosterone; reducing prostate inflammation through decreased oxidative damage; reducing the contractile response of smooth muscle; and reducing growth of prostate primary epithelial cells. In addition, immunologic function and antioxidant defense show improvement with exercise, further protecting against comorbidities (Warburton 2006).

Physical activity might also have a clinically important placebo effect. Based on a network meta-analysis of monodrug therapy for LUTS/BPO (Yuan 2015), the placebo effect on the IPSS was around 20%: mean changes from baseline (17.85) of -3.39 (95% credible interval -6.68 to -0.10; 89 trials, 48,854 men).

Why it is important to do this review

Due to the prevalence of LUTS/BPO increasing with age, the burden and number of men complaining of LUTS will rise as life expectancy and the elderly population grow. Therefore, we will have an increased demand for treatment services, and will need to incorporate evidence-based medicine in treatments. There are several Cochrane intervention reviews for LUTS/BPO published in the Cochrane Library focusing on drug and supplements, health technology assessment, and surgery (Garimella 2009; Hoffman 2000; Hoffman 2012; Tacklind 2010; Tacklind 2012; Wilt 1998; Wilt 1999). Physical activity might be a first-line and complementary intervention for treating LUTS/BPO (Parsons 2008; Russo 2015; Sea 2009). The American Urological Association (AUA) considers lifestyle interventions, including physical activity, as a high priority area for future research of LUTS/BPO (McVary 2011). Evidence at different levels, including clinical trials (e.g. Jung 2012), and non-Cochrane systematic reviews of non-randomized trials, has shown that physical activity may improve LUTS/BPO (Parsons 2008; Sea 2009). However, no Cochrane review to date has as-

sessed the evidence of physical activity as a potential intervention for LUTS/BPO.

OBJECTIVES

To assess the effects of physical activity for lower urinary tract symptoms due to benign prostatic obstruction.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials (RCTs) published and unpublished, without restriction of language, date, or publication status.

Types of participants

Men diagnosed with LUTS by symptom scores (e.g. IPSS, DAN-PSS) presumably due to BPO. We will exclude studies that include men with a history suggesting non-BPO causes of LUTS (see D'Silva 2014; Gratzke 2015). We will use the study description regarding medical, neurologic, and urologic history to understand the causes of LUTS other than BPO; when necessary, we will contact study authors to ask for additional details.

We will exclude studies that include men who have previously received invasive therapies for LUTS/BPO, since the subsequent cause of LUTS can be other than BPO.

If we find studies involving a subset of relevant participants, we will contact the study authors requesting individual data. If the study authors do not provide the data, we will exclude the study with reasons.

Types of interventions

Experimental interventions

- Any type of physical activity with or without concomitant interventions. Concomitant interventions will have to be the same in the intervention and comparator groups to establish fair comparisons.

We will exclude studies that used electrical stimulation, since this type of intervention does not fulfil the conceptual definition of physical activity. We will exclude studies in which physical activity is applied after invasive therapies for LUTS/BPO, since the subsequent cause of LUTS can be other than BPO.

Comparator interventions

- Usual care (e.g. alpha-blockers, 5-ARIs, combination alpha-blocker and 5-ARI therapy, invasive therapies);
- Watchful waiting list (e.g. drinking fewer liquids before bedtime, drinking less caffeine and alcohol, avoiding non-prescription cold and sinus medicines with decongestants);
- Complementary and alternative medicines (e.g. *Serenoa repens*, *Pygeum africanum*);
- Sham physical activity, that is, where the probability of treatment effect may be attributed to a placebo effect (e.g. stretching, respiratory exercise).

Types of outcome measures

The outcomes listed will not be used as criteria for including studies.

Primary outcomes

- Change in symptom score for LUTS using a validated instrument (e.g. IPSS, BPO Impact Index (BII)).
- Number of men reporting a 20% improvement in symptom score for LUTS from baseline.
- Number of men withdrawing due to adverse events.

Secondary outcomes

- Number of men with a reduction of medication use.
- Number of men with a need for an invasive procedure (e.g. open prostatectomy, laser therapies, transurethral needle ablation, transurethral resection of the prostate, transurethral microwave therapy).
- Post-void residual urine (PVR), measured by bladder scanner, transabdominal ultrasonography, or catheterization.

Timing of outcome measurement

We will include outcomes that are measured for as long as follow-up was done at any given time point. We will classify the outcome measurement as short, medium, and long term, that is, we will define short term as measurement taken within three months or less; medium term as more than three months to less than 12 months; and long term as 12 months or more. We will use the data at the longest follow-up available as reported in the individual studies for the meta-analyses.

Main outcomes for 'Summary of findings' tables

We will present a 'Summary of findings' table reporting the following outcomes listed according to priority:

- Change in symptom score for LUTS.
- Number of men reporting a 20% improvement in symptom score for LUTS from baseline.
- Number of men withdrawing due to adverse events.

Search methods for identification of studies

Electronic searches

We will make an electronic search strategy from inception to the date of search, and identify all potential studies from:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library);
- MEDLINE (via PubMed);
- EMBASE (via Elsevier);
- Web of Science (via ISI Web of Knowledge);
- LILACS (Latin American and Caribbean Health Sciences) (via BIREME).

We will use the sensitivity-maximizing version of the Cochrane Highly Sensitive Search Strategy to identify randomized trials in MEDLINE (Lefebvre 2011). We will adapt the complete search strategy for MEDLINE provided in Appendix 1 for all databases under consideration.

We will search independently the following trials registers:

- ClinicalTrials.gov (U.S. National Institutes of Health; clinicaltrials.gov/);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (www.who.int/trialsearch).

Searching other resources

We will check the reference lists of all included RCTs and review articles for additional references.

We will contact authors of included RCTs and ask them about other published and unpublished RCTs.

We will handsearch potential RCTs published as abstracts in the following conference proceedings (conference proceedings will be considered from the last three years):

- AUA Annual Meeting;
- Annual European Association of Urology (EAU) Congress;
- Annual Meeting of the American College of Sports Medicine (ACSM).

Data collection and analysis

We will perform data collection and analysis as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Selection of studies

Two review authors (VS, AJG) will independently decide whether identified studies meet inclusion criteria. We will resolve disagreements by discussion. If necessary, a third review author (MSP) will settle the differences.

Data extraction and management

Two review authors (VS, AJG) will extract the data independently using a standard extraction form, which we will pilot-test ahead of time. We will translate studies reported in non-English language journals before assessment. The data extraction form will include PICO characteristics (participants, intervention, control, and outcome) and results from all selected studies. When necessary, we will write to study authors for further information. We will adapt the Cochrane Data Extraction and Assessment Form template to meet MECIR standards and the needs of this systematic review. This form will contain the information about characteristics of included studies such as: study design, dates when the study was conducted, sample size for each included study and intervention/control groups, information about the study population (baseline demographics, e.g. age) and study inclusion and exclusion criteria, outcomes measured that are relevant to this review, how outcomes were measured and the times at which they were measured, funding source for each study, and the declarations of interest.

We will extract outcomes data relevant to this Cochrane review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we will attempt to obtain numbers of events and totals for population of a 2 x 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we will attempt to obtain means and standard deviations or data necessary to calculate this information. One review author (VS) will enter all data into Review Manager 5 (RevMan 2014) and a second review author (AJG) will double check entries. We will resolve disagreement with discussion; however, without a consensus, a third review author (MSP) will make the judgment.

We will provide information, including trial identifier, about potentially relevant ongoing studies in the 'Characteristics of ongoing studies' table.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we will maximize yield of information by mapping all publications to unique studies and

collating all available data. We will use the most complete dataset aggregated across all known publications. In case of doubt, we will give priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (VS and AJG) will independently use the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess risk of bias for all included studies (Higgins 2011b). A third review author (MSP) will resolve any disagreements. We will assess risk of bias according to the following domains.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias (other sources of bias related to a particular trial design, e.g. cross-over or cluster-randomized, or specific circumstances, e.g. interventions mixed).

We will classify risk of bias as low risk of bias, high risk of bias, or unclear risk of bias in accordance with the Cochrane tool for assessment of risk of bias (Higgins 2011b).
For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we will evaluate the risk of bias separately for each outcome, and we will group outcomes according to whether measured subjectively or objectively when reporting our findings in the 'Risk of bias' tables.
We will also assess attrition bias (incomplete outcome data) on an outcome-specific basis, and will group outcomes with like judgments when reporting our findings in the 'Risk of bias' tables.
We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.
We will define the following endpoints as subjective outcomes:

- change in symptom score for LUTS;
- number of men reporting a 20% improvement in symptom score for LUTS from baseline.

We define the following endpoints as objective outcomes:

- number of men withdrawing due to adverse events;
- number of men with a reduction of medication use;
- number of men with a need for an invasive procedure;
- PVR.

Measures of treatment effect

For dichotomous data, we will summarize results as risk ratios (RRs). In addition, we will convert a statistical parameter for effect size to the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH). For continuous outcomes, we will use the mean difference (MD) for measures in the same unit or the standardized mean difference (SMD) for different scales used to evaluate the same outcome. All statistical parameters will use 95% confidence intervals (CIs).

Unit of analysis issues

We will consider the individual participant as the unit of analysis. In cross-over RCTs, we will use only the first period before the treatments are crossed over. Should we identify trials with more than two intervention groups for inclusion in the review, we will handle these in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Dealing with missing data

If the included studies have missing data, we will employ strategies for dealing with missing data in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

- At first, we will try to contact the study authors by sending at least two emails to request additional information (e.g. incomplete reporting, lack of intention-to-treat analysis, summary data missing for an outcome, randomization process not described, or any other necessary data). If we receive no answer, we will report and discuss this in the text.
- We will describe any methods used to cope with missing data.
- We will perform sensitivity analyses to test the robustness of these assumptions.
- We will discuss the impact of missing data on the results of the review.

We will perform intention-to-treat analyses, if data are available; otherwise, we will perform available-case analyses. We will not impute missing data.

Assessment of heterogeneity

We will assess heterogeneity by visual inspection of the forest plot, considering the Chi^2 test (with a significance level of P value < 0.10). Together, we will use the I^2 statistic when we perform a fixed-effect meta-analysis, with heterogeneity considered substantial if I^2 is greater than 50%, and Tau^2 when we perform a random-effects meta-analysis, with heterogeneity considered substantial if Tau^2 is greater than 1.

Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting.

If at least 10 trials are included in a given analysis, we will assess the likelihood of publication bias using funnel plots.

Data synthesis

Unless there is good evidence for homogeneous effects across studies, we will summarize data using a random-effects model. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will perform meta-analysis using preferably an inverse-variance method for dichotomous and continuous outcomes. When data are sparse for dichotomous outcomes (e.g. event rates being low or study size being small), we will use the Mantel-Haenszel method. We will use Review Manager 5 software to perform analyses (RevMan 2014). If meta-analysis is not possible, we will provide a narrative synthesis of the available evidence.

'Summary of findings' table

We will present the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (VS, AJG) will independently rate the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT. We will resolve any discrepancies by consensus, or, if needed, by arbitration by a third review author. For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2011). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

If possible, we plan to investigate heterogeneity by performing subgroup analyses according to:

- Intensity of physical activity (e.g. light intensity (1.6 to 2.9 METs), moderate intensity (3 to 5.9 METs), and vigorous intensity (6 METs or greater)).
- Timing of outcome measurement (i.e. short term (within three months or less), medium term (more than three months to less than 12 months), and long term (12 months or more)).
- Severity of LUTS (e.g. mild, moderate, and severe).

We will assess statistical differences in subgroup analyses by CI overlap and by performing the test for subgroup differences available in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We plan to perform sensitivity analyses in order to explore the influence of the following factors (when applicable) on effect sizes:

- restricting the analysis by taking into account risk of bias, by excluding studies at 'high risk' and 'unclear risk';
- using the alternative model (fixed-effect or random-effects) for analysis, to check the robustness of results.

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REFERENCES

Additional references

Abrams 2003
Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 2003;**61**(1):37–49. [DOI: 10.1016/S0090-4295(02)02243-4]

Ainsworth 2011
Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, et al. 2011 Compendium of physical activities: a second update of codes and MET values. *Medicine and Science in Sports and Exercise* 2011;**43**(8):1575–81. [DOI: 10.1249/MSS.0b013e31821ece12]

Ainsworth 2012
Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, et al. The compendium of physical activities tracking guide. Healthy Lifestyles Research Center, College of Nursing & Health Innovation, Arizona State University. sites.google.com/site/compendiumofphysicalactivities/home (accessed 7 May 2012).

Barkin 2011
Barkin J. Benign prostatic hyperplasia and lower urinary tract symptoms: evidence and approaches for best case

management. *Canadian Journal of Urology* 2011;**18**(1): 14–9. [PUBMED: 21501546]

Barnard 2008
Barnard RJ, Kobayashi N, Aronson WJ. Effect of diet and exercise intervention on the growth of prostate epithelial cells. *Prostate Cancer and Prostatic Diseases* 2008;**11**(4): 362–6. [DOI: 10.1038/pcan.2008.6]

Caspersen 1985
Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports (Washington, DC: 1974)* 1985;**100**(2):126–31. [PUBMED: 3920711]

Chang 2008
Chang RY, Koo M, Yu ZR, Kan CB, Chu IT, Hsu CT, et al. The effect of tai chi exercise on autonomic nervous function of patients with coronary artery disease. *Journal of Alternative and Complementary Medicine* 2008;**14**(9): 1107–13. [DOI: 10.1089/acm.2008.0166]

D'Silva 2014
D'Silva KA, Dahm P, Wong CL. Does this man with lower urinary tract symptoms have bladder outlet obstruction? The Rational Clinical Examination: a systematic review. *JAMA* 2014;**312**(5):535–42. [DOI: 10.1001/jama.2014.5555]

De Nunzio 2011
De Nunzio C, Ahyai S, Autorino R, Bachmann A, Bialek W, Briganti A, et al. Benign prostatic hyperplasia and lower urinary tract symptoms: research priorities. *European Urology* 2011;**60**(6):1205–6. [DOI: 10.1016/j.eururo.2011.08.055]

Donnell 2011
Donnell RF. Benign prostate hyperplasia: a review of the year's progress from bench to clinic. *Current Opinion in Urology* 2011;**21**(1):22–6. [DOI: 10.1097/MOU.0b013e32834100dd]

Dumoulin 2015
Dumoulin C, Hay-Smith J, Frawley H, McClurg D, Alewijnse D, Bo K, et al. 2014 consensus statement on improving pelvic floor muscle training adherence: International Continence Society 2011 State-of-the-Science Seminar. *Neurourology and Urodynamics* 2015;**34**(7):600–5. [DOI: 10.1002/nau.22796]

Fenter 2006
Fenter TC, Naslund MJ, Shah MB, Eaddy MT, Black L. The cost of treating the 10 most prevalent diseases in men 50 years of age or older. *American Journal of Managed Care* 2006;**12**(4 Suppl):S90–8. [PUBMED: 16551207]

Garimella 2009
Garimella PS, Fink HA, MacDonald R, Wilt TJ. Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007360.pub2]

Gillespie 2012
Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD007146.pub3]

GRADEpro GDT
GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from www.gradepro.org.

Gratzke 2015
Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, et al. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *European Urology* 2015;**67**(6):1099–109. [DOI: 10.1016/j.eururo.2014.12.038]

Guyatt 2008
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Schünemann HJ, et al. GRADE: what is "quality of evidence" and why is it important to clinicians?. *BMJ (Clinical Research Ed.)* 2008;**336**(7651):995–8. [DOI: 10.1136/bmj.39490.551019.BE]

Guyatt 2011
Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383–94. [DOI: 10.1016/j.jclinepi.2010.04.026]

Higgins 2011a
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011c
Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoffman 2000
Hoffman RM, MacDonald R, Wilt T. Laser prostatectomy for benign prostatic obstruction. *Cochrane Database of Systematic Reviews* 2000, Issue 1. [DOI: 10.1002/14651858.CD001987.pub2]

Hoffman 2012
Hoffman RM, Monga M, Elliott SP, MacDonald R, Langsjoen J, Tacklind J, et al. Microwave thermotherapy for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD004135.pub3]

Howe 2011
Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858.CD000333.pub2]

Jung 2012
Jung S, Lee E-N, Lee S-R, Kim M-S, Lee MS. Tai chi for lower urinary tract symptoms and quality of life in elderly patients with benign prostate hypertrophy: a randomised controlled trial. *Evidence-based Complementary and Alternative Medicine* 2012;**2012**:624692. [DOI: 10.1155/2012/624692]

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

McVary 2011
McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *Journal of Urology* 2011;**185**(5):1793–803. [DOI: 10.1016/j.juro.2011.01.074]

Mishra 2012
Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database of Systematic Reviews* 2012, Issue 8. [DOI: 10.1002/14651858.CD008465.pub2]

Nicholson 2011
Nicholson TM, Ricke WA. Androgens and estrogens in benign prostatic hyperplasia: past, present and future. *Differentiation; Research in Biological Diversity* 2011;**82**(4-5):184–99. [DOI: 10.1016/j.diff.2011.04.006]

Parsons 2008
Parsons JK, Kashefi C. Physical activity, benign prostatic hyperplasia, and lower urinary tract symptoms. *European Urology* 2008;**53**(6):1228–35. [DOI: 10.1016/j.eururo.2008.02.019]

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roehrborn 2008
Roehrborn CG. Pathology of benign prostatic hyperplasia. *International Journal of Impotence Research* 2008;**20**(3):S11–8. [DOI: 10.1038/ijir.2008.55]

Russo 2015
Russo GI, Castelli T, Urzì D, Privitera S, La Vignera S, Condorelli RA, et al. Emerging links between non-neurogenic lower urinary tract symptoms secondary to benign prostatic obstruction, metabolic syndrome and its components: a systematic review. *International Journal of Urology* 2015;**22**(11):982–90. [DOI: 10.1111/iju.12877]

Schünemann 2011
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 11: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Sea 2009
Sea J, Poon KS, McVary KT. Review of exercise and the risk of benign prostatic hyperplasia. *Physician and Sports Medicine* 2009;**37**(4):75–83. [DOI: 10.3810/psm.2009.12.1745]

Silva 2015
Silva TL, Mota MM, Fontes MT, Araújo JE, Carvalho VO, Bonjardim LR, et al. Effects of one resistance exercise session on vascular smooth muscle of hypertensive rats. *Arquivos Brasileiros de Cardiologia* 2015;**105**(2):160–7. [DOI: 10.5935/abc.20150070]

Speakman 2015
Speakman M, Kirby R, Doyle S, Ioannou C. Burden of male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) - focus on the UK. *BJU International* 2015;**115**(4):508–19. [DOI: 10.1111/bju.12745]

Tacklind 2010
Tacklind J, Fink HA, MacDonald R, Rutks I, Wilt TJ. Finasteride for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews* 2010, Issue 10. [DOI: 10.1002/14651858.CD006015.pub3]

Tacklind 2012
Tacklind J, MacDonald R, Rutks I, Stanke JU, Wilt TJ. *Serenoa repens* for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD001423.pub3]

Tang 2009
Tang J, Yang J. Etiopathogenesis of benign prostatic hyperplasia. *Indian Journal of Urology* 2009;**25**(3):312–7. [DOI: 10.4103/0970-1591.56179]

UDA 2012
Urologic Diseases in America. Table 14-10. Economic impact of urologic disease. In: Litwin MS, Saigal CS (editors). Urologic Diseases in America. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office, 2012; NIH Publication No.

12-7865, pp. 463-496. Available from urology.ucla.edu/workfiles/Research/UDA_2012_Compendium.pdf (accessed 7 January 2015).

United Nations 2015
United Nations, Department of Economic and Social Affairs, Population Division. World population prospects: the 2015 revision, key findings and advance tables. 2015. Working Paper No. ESA/P/WP.241. Available from esa.un.org/unpd/wpp/ (accessed 18 August 2015).

Warburton 2006
Warburton DER, Nicol CR, Bredin SSD. Health benefits of physical activity: the evidence. *Canadian Medical Association Journal* 2006;**174**(6):801–9. [DOI: 10.1503/cmaj.051351]

Wilt 1998
Wilt TJ, Ishani A. Pygeum africanum for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews* 1998, Issue 1. [DOI: 10.1002/14651858.CD001044]

Wilt 1999
Wilt TJ, Ishani A, MacDonald R, Stark G, Mulrow CD, Lau J. Beta-sitosterols for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews* 1999, Issue 3. [DOI: 10.1002/14651858.CD001043]

Yuan 2015
Yuan JQ, Mao C, Wong SY, Yang ZY, Fu XH, Dai XY, et al. Comparative effectiveness and safety of monodrug therapies for lower urinary tract symptoms associated with benign prostatic hyperplasia: a network meta-analysis. *Medicine* 2015;**94**(27):e974. [DOI: 10.1097/MD.0000000000000974]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (via PubMed) search strategy

#1	"Motor Activity"[MeSH] OR "Motor Activity"[All Fields] OR "Motor Activities"[All Fields] OR "Physical Activity" [All Fields] OR "Physical Activities" [All Fields] OR "Locomotor Activity" [All Fields] OR "Locomotor Activities"[All Fields]
#2	"Exercise"[MeSH] OR "Exercise"[All Fields] OR "Exercises"[All Fields]
#3	"Resistance Training"[MeSH] OR "Resistance Training"[All Fields] OR "Strength Training"[All Fields] OR "Weight Lifting"[All Fields] OR "Weight Bearing"[All Fields]
#4	"Physical Fitness"[MeSH] OR "Physical Fitness"[All Fields] OR "Physical Conditioning"[All Fields] OR "Physical Conditionings"[All Fields]
#5	"Sports"[MeSH] OR "Sports"[All Fields] OR "Sport"[All Fields] OR "Athletics"[All Fields] OR "Athletic"[All Fields]
#6	"Tai Ji"[MeSH] OR "Tai Ji"[All Fields] OR "Tai Chi"[All Fields] OR "Tai Ji Quan"[All Fields] OR "Taiji"[All Fields] OR "Taijiquan"[All Fields] OR "T'ai Chi"[All Fields] OR "Tai Chi Chuan"[All Fields]
#7	"Physical Therapy Modalities"[MeSH] OR "Physical Therapy Modality"[All Fields] OR "Physical Therapy Modalities"[All Fields] OR "Physiotherapy"[All Fields] OR "Physiotherapies"[All Fields]
#8	"Physical Therapy Specialty"[MeSH] OR "Physical Therapy"[All Fields] OR "Physical Therapies"[All Fields] OR "Rehabilitation"[MeSH] OR "Rehabilitation"[All Fields] OR "Rehab"[All Fields]

(*Continued*)

#9	"Physical Therapy Department, Hospital"[MeSH] OR "Physical Therapy Department"[All Fields] OR "Physical Therapy Departments"[All Fields]
#10	"Sedentary Lifestyle"[MeSH] OR "Sedentary Lifestyle"[All Fields] OR "Sedentary Lifestyles"[All Fields] OR "Sedentary Life Style"[All Fields] OR "Sedentary Life Styles"[All Fields]
#11	"Kegel exercise"[All Fields] OR "Kegel exercises"[All Fields] OR "Pelvic floor exercise"[All Fields] OR "Pelvic floor exercises"[All Fields] OR "Pelvic floor muscle training"[All Fields] OR "Pelvic floor muscle exercise"[All Fields] OR "Pelvic floor muscle exercises"[All Fields]
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13	"Prostatic Hyperplasia"[MeSH] OR "Adenofibromyomatosis"[All Fields] OR "BPH"[All Fields] OR "Prostate Benign Hyperplasia"[All Fields] OR "Prostate Benign Hyperplasias"[All Fields] OR "Prostate Benign Hypertrophies"[All Fields] OR "Prostate Benign Hypertrophy"[All Fields] OR "Prostate Enlargement"[All Fields] OR "Prostate Enlargements"[All Fields] OR "Prostate Gland Hypertrophies"[All Fields] OR "Prostate Gland Hypertrophy"[All Fields] OR "Prostate Hyperplasia"[All Fields] OR "Prostate Hyperplasias"[All Fields] OR "Prostate Hyperthrophies"[All Fields] OR "Prostate Hyperthrophy"[All Fields] OR "Prostate Hypertrophy"[All Fields] OR "Prostate Hypertrophies"[All Fields] OR "Prostate Hypertrophia"[All Fields] OR "Prostate Hypertrophias"[All Fields] OR "Prostatic Adenoma"[All Fields] OR "Prostate Adenomas"[All Fields] OR "Prostatic Benign Hyperplasia"[All Fields] OR "Prostatic Benign Hyperplasias"[All Fields] OR "Prostatic Benign Hypertrophies"[All Fields] OR "Prostatic Benign Hypertrophy"[All Fields] OR "Prostatic Hyperplasia"[All Fields] OR "Prostatic Hyperplasias"[All Fields] OR "Prostatic Hypertrophies"[All Fields] OR "Prostatic Hypertrophy"[All Fields] OR "Prostatic Hypertrophia"[All Fields] OR "Prostatic Hypertrophias"[All Fields] OR "Enlarged prostate"[All Fields] OR "Enlarged prostates"[All Fields]
#14	"Urinary Bladder Neck Obstruction"[MeSH] OR "Bladder Neck Obstruction"[All Fields] OR "Bladder outlet obstruction"[All Fields] OR "BOO"[All Fields] OR "Bladder neck strangulation"[All Fields] OR "Bladder stenosis"[All Fields] OR "Vesicourethral fistula"[All Fields] OR "Obstructio vesicae urinariae"[All Fields] OR "Urinary bladder neck obstruction"[All Fields] OR "Urinary bladder neck stenosis"[All Fields] OR "Urinary bladder obstruction"[All Fields] OR "Bladder neck strangulations"[All Fields] OR "Bladder stenoses"[All Fields] OR "Vesicourethral fistulas"[All Fields] OR "Bladder obstruction"[All Fields] OR "Bladder obstructions"[All Fields]
#15	"Benign prostatic obstruction"[All Fields] OR "Benign prostatic obstructions"[All Fields] OR "BPO"[All Fields] OR "Benign prostatic enlargement"[All Fields] OR "Benign prostatic enlargements"[All Fields] OR "BPE"[All Fields]
#16	#13 OR #14 OR #15
#17	"Lower Urinary Tract Symptoms"[MeSH] OR "LUTS"[All Fields] OR "Lower Urinary Tract Symptoms"[All Fields] OR "Lower Urinary Tract Symptom"[All Fields] OR "lower urinary tract disease"[all fields] OR "lower urinary tract diseases"[all fields] OR "lower urinary tract disorder"[all fields] OR "lower urinary tract disorders"[all fields] OR "lower urinary tract dysfunction"[all fields] OR "lower urinary tract dysfunctions"[all fields] OR "LUTD"[all fields] OR "dysuria"[all fields] OR "nocturia"[all fields] OR "prostatism"[all fields] OR "overactive urinary bladder"[all fields] OR "urinary incontinence"[all fields]
#18	#12 AND #16 AND #17
#19	randomized controlled trial [pt]
#20	controlled clinical trial [pt]

(*Continued*)

#21	randomized [tiab]
#22	placebo [tiab]
#23	drug therapy [sh]
#24	randomly [tiab]
#25	trial [tiab]
#26	groups [tiab]
#27	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28	animals [mh] NOT humans [mh]
#29	#18 AND #27
#30	#29 NOT #28

CONTRIBUTIONS OF AUTHORS

Co-ordination of the protocol: VS.

Searching studies to contextualize background: VS, AJG.

Planning the methods section, drafting the protocol, and approving the final version of the protocol: VS, AJG, KRS, MSP.

Valter Silva is the guarantor of the protocol.

DECLARATIONS OF INTEREST

VS: none known.

AJG: none known.

KRS: none known.

MSP: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

We received no sources of support.

External sources

- None, Other.

We received no sources of support.

NOTES

We have based parts of the Methods section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by the Cochrane Urology Group.