Maximal exercise capacity in patients with obstructive sleep apnoea syndrome: A systematic review and meta-analysis

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Table S1. PRISMA 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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	5
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.	5-6
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.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	EOS
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).	6-7
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.	6-7

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Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
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
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
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.	7-8

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.	7-8
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.	9
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.	9
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).	12
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.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			

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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).	13
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).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	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.	1

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Table S2. Information regarding medication, co-morbidities in studies reporting VO_{2peak} in $mL.min^{-1}.kg^{-1}$

Author, year	Information regarding medication, co-morbidities, exclusion criteria
Alonso-Fernández et al. 2006 *ERJ [1]*	Exclusion criteria for both OSA and controls: comorbid disorders or situations that could affect cardiac response to exercise. No information about medication.
Beitler et al. 2014 *J Clin Sleep Med [2]*	Exclusion criteria for both OSA and controls: known heart disease, HF, COPD. **Co-morbidities:** Hypertension: 3/15 OSA versus 4/19 CTRL Diabetes: 2/15 OSA versus 0/19 CTRL *Two OSA patients on atenolol (beta blocker).
Butner et al. 2013 North Am J Med Sci [4]	Exclusion criteria for both OSA and controls: a history of cardiovascular or pulmonary disease, current smoker, currently taking any prescriptive or over the counter medications known to affect cardiovascular or metabolic functions (e.g., anti-hypertensives, hypnotics, sedatives, analgesics, psychotropics, steroids or sympathomimetics), diabetes, musculoskeletal disorders
Cavagnolli et al. 2014 *Eur J Sport Sci [5]*	Exclusion criteria for both OSA and controls: BMI > 30, cardiovascular pathologies or other diseases (pre-existing or diagnosed during the clinical evaluation) that would interfere with the response to exercise
Cepeda et al. *Sleep* 2015 [6] * Mean ± SE	OSA and controls had the metabolic syndrome. Exclusion criteria for both OSA and controls: pulmonary or cardiovascular disease, musculoskeletal disease.
Chien et al. *Sleep Breath* 2012 [7]	Exclusion criteria for both OSA and controls: subjects treated with negative chronotropic drugs (i.e., β- blockers, amiodarone, verapamil, or diltiazem), glucose lowering drugs (i.e., metformin), lipid-lowering drugs (i.e. statin), and those with a history of coronary artery disease or other manifestations of atherosclerosis, heart failure, renal failure, diabetes mellitus, or any conditions that may limit exercise capacity (e.g., osteoarthritis)
Chien et al. Muscle Nerve 2013 [8]	Exclusion criteria for both OSA and controls: coronary heart disease, nervous system disease, abnormal pulmonary function, morbid obesity, diabetes under oral hypoglycemic agent management, alcoholism (>50 g/day), and recent infection.
Hargens et al. 2008 *Sleep [10]*	Exclusion criteria for both OSA and controls: cardiovascular, pulmonary, metabolic, musculoskeletal disease. Subjects were not taking any prescribed vasoactive medications, hypnotics, sedatives, analgesics, psychotropics, steroids, or sympathomimetics.
Innocenti et al. Resp Physiol Neurobiol 2012 [12]	Exclusion criteria for both OSA and controls: cardiorespiratory, neuromuscular or musculoskeletal disease
Kaleth et al. *Sleep Med* 2007 [13]	Exclusion criteria for both OSA and controls: a history of cardiovascular or pulmonary disease, metabolic or endocrine disorders, receiving anti-hypertensive medications, diagnosed hypertension, current smokers, sedatives or muscle relaxers, orthopedic or musculoskeletal limitations that precluded vigorous exercise, or recent history of regular participation in moderately vigorous physical activity.

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Kline et al. *Intl J Cardiol* 2013 [14]	Exclusion criteria for both OSA and controls: known or suspected significant cardiovascular, pulmonary or metabolic disease, uncontrolled hypertension (> 159/99 mmHg), use of beta-blocker medication, pregnancy, or health problems that contraindicated exercise. Due to the high prevalence of hypertension in this population, use of antihypertensive medication was not a reason for exclusion provided that the dose remained stable during the study and the medication was not known to alter the chronotropic response to exercise.
Lin et al. 2006 *Resp Physiol Neurobiol [15]*	Exclusion criteria for both OSA and controls: no evidence of cardiopulmonary failure, diabetes mellitus, primary central nervous system, systemic or neuromuscular diseases,
Nanas et al. 2010 *Clin Cardiol [16]*	Exclusion criteria for both OSA and controls: obstructive or restrictive lung disease documented by pulmonary function testing; known valvular heart disease; diabetes mellitus or a fasting blood glucose >110 mg/dL; known neuromuscular disease that could limit their exercise capacity; known hypertension; or abnormal thyroid function.
Ozturk et al. 2005 *Tuberk Toraks[18]*	Exclusion criteria for both OSA and controls: cardiovascular disease, no beta-blockages or other drug treatment.
Rizzi et al. 2010 *Chest [19]*	Exclusion criteria for both OSA and controls: BMI >25 kg/m^2 , pulmonary disease, or New York Heart Association class III or IV heart failure, unstable angina, valvular heart disease, life-threatening arrhythmia, atrial fibrillation, left bundle branch block, uncontrolled hypertension, renal disease, neuromuscular conditions, pregnancy Medication: 2 patients on beta-blocker, atenolol (1 OSA and 1 Control). The medication was gradually changed to enalapril 20 to 40 mg/d 3 days before the test. The b -blocker was reintroduced after test completion.
Rizzi et al. 2013 *Sleep [20]*	Exclusion criteria for both OSA and controls: pulmonary disease forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio less than 70% of predicted or New York Heart Association class III or IV heart failure, unstable angina, valvular heart disease, life-threatening arrhythmia, atrial fibrillation, left bundle branch block, uncon trolled hypertension, renal disease, neuromuscular conditions, pregnancy. Medication: Nine subjects were using β-blockers (one lean patient with OSA, one lean control, four obese patients with OSA, and three obese control subjects). The β-blockers were gradually replaced by 20 to 40 mg/day of enalapril the wk before the test. The patients remained on enalapril for another wk after which the test was performed. β-blockers were reintroduced after test completion.
Tryfon et al. *Respiration* 2004 [21]	Exclusion criteria for both OSA and controls: known cardiovascular disease.
Vanhecke et al. 2008 *Chest [23]*	Exclusion criteria for both OSA and controls: left ventricular ejection fraction (LVEF) < 45%. Patients on beta-blockers told not to take medication night before.
Vanuxem et al. 1997 *Respir Med [24]*	Exclusion criteria for both OSA and controls: congestive heart failure, cardiorespiratory disease.

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Sample search strategy in Pubmed/Medline

Date: 23/02/2017	
"Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea Syndromes"	28546
Sleep Apnea, Obstructive[Mesh] OR "Sleep Apnea, Obstructive"	14319
Sleep disordered breathing	30180
# 1 OR 2 OR 3	30195
Exercise Tolerance[Mesh] OR "Exercise Tolerance"	15843
Exercise Test [Mesh] OR "Exercise Test"	62424
Cardiorespiratory fitness [Mesh] OR " Cardiorespiratory fitness "	3578
Oxygen Consumption [Mesh] and "Oxygen Consumption"	98728
Physical Fitness	37687
Aerobic Capacity	9280
#5 OR 6 OR 7 OR 8 OR 9 OR 10	191328
Combined Search #4 AND #12	**442**

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Modified version of the Newcastle - Ottawa Quality Assessment Scale for case control studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection (max 4 *)

1) Diagnosis of obstructive sleep apnoea

   a) Clinical polysomnography or polygraphy ✵

   b) yes, eg record linkage or based on self reports

   c) no description

2) Representativeness and selection of patients with OSA

   a) consecutive or obviously representative series of cases ✵

   b) potential for selection biases or not stated

3) Selection of Controls

   a) community controls ✵

   b) hospital controls

   c) no description

4) Definition of Controls

   a) no history of disease (confirmed by polysomnography or polygraphy) ✵

   b) no description of source (i.e. no confirmation of absence of OSA, or self-report)

Comparability (max 2 *)

1) Comparability of cases and controls on the basis of the design or analysis

   a) study controls for *co-morbidities* (Select the most important factor.) ✵

   b) study controls for any additional factor (*age or BMI*) ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Evaluation of maximal exercise capacity (max 2 *)

1) Evaluation of maximal exercise capacity

   a) *maximal exercise test* with explicit criteria for maximal exercise testing defined (at least 2) ✵

   b) structured interview where blind to case/control status ✵

   c) interview not blinded to case/control status

   d) written self report or medical record only

   e) no description

2) Same method of ascertainment for cases and controls (*both groups did maximal exercise test*)

   a) yes ✵

   b) no