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

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ABSTRACT Maximal aerobic capacity is a strong health predictor and peak oxygen consumption (V'_{O_2peak}) is considered a reflection of total body health. No systematic reviews or meta-analyses to date have synthesised the existing data regarding V'_{O_2peak} in patients with obstructive sleep apnoea (OSA).

A systematic review of English and French articles using PubMed/MEDLINE and Embase included studies assessing V'_{O_2peak} in OSA patients either in $mL \cdot kg^{-1} \cdot min^{-1}$ compared with controls or in % predicted. Two independent reviewers analysed the studies, extracted the data and assessed the quality of evidence.

Mean V'_{O_2peak} expressed in $mL \cdot kg^{-1} \cdot min^{-1}$ was significantly lower in patients with OSA than in controls (mean difference −2.7 $mL \cdot kg^{-1} \cdot min^{-1}$; p<0.001; n=850). This reduction in V'_{O_2peak} was found to be larger in non-obese patients (body mass index <30 $kg \cdot m^{-2}$). Mean V'_{O_2peak} % pred was 89.9% in OSA patients (n=643).

OSA patients have reduced maximal aerobic capacity, which can be associated with increased cardiovascular risks and reduced survival in certain patient subgroups. Maximal exercise testing can be useful to characterise functional limitation and to evaluate health status in OSA patients.

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This study was registered on the Prospero registry (CRD42017057319).

Introduction

Obstructive sleep apnoea (OSA) is a common clinical condition characterised by repeated episodes of apnoea and hypopnoea during sleep. Sleep fragmentation and chronic intermittent hypoxia induce intermediate mechanisms, such as activation of the sympathetic nervous system [1], oxidative stress and systemic inflammation [2], which are responsible for cardiometabolic morbidity [3] and mortality.

Maximal exercise capacity testing using an incremental whole-body (*e.g.* cycling) protocol with complementary respiratory gas-exchange measurements is considered the gold standard when assessing aerobic capacity [4]. Maximal exercise capacity is directly related to the integrated function of numerous systems and is therefore considered a reflection of total body health. The main measurement or surrogate marker of risk of these tests is peak oxygen uptake ($V'O_2peak$). In addition, maximal cardiorespiratory responses at peak exercise can provide useful information in interpreting exercise limitations.

In a growing number of studies, reduced maximal exercise capacity is associated with an increased risk of cardiovascular disease and all-cause mortality. This observation has been made in healthy men and women; those with suspected or known cardiovascular disease; and those with comorbid conditions including obesity, hypertension and lipid abnormalities [5–8]. Furthermore, recent studies have expressed maximal exercise capacity in the context of survival benefit per metabolic equivalence (MET), which is a multiple of the resting metabolic rate approximating 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$. These studies have shown that each 1-MET higher maximal exercise capacity is associated with considerable (10–25%) improvement in survival [9].

The evaluation of maximal exercise capacity in OSA patients can be relevant when assessing functional limitations due to the disease as well as the associated systemic consequences (*e.g.* cardiovascular and metabolic alterations). Furthermore, this type of evaluation can be used as an objective outcome to assess treatment efficiency and for patient follow-up. Nevertheless, the impact of OSA on maximal exercise capacity is still debated. Previous studies have yielded conflicting results, with some studies showing no impairment in maximal exercise capacity in OSA patients [10–12] and others showing reduced maximal exercise capacity [13–16] compared to control subjects. These studies have several methodological limitations that make generalisation of findings difficult owing to the presence of co-morbidities, varying levels of OSA severity and low sample sizes.

To date, no meta-analysis has been conducted to summarise findings regarding the maximal exercise capacity of OSA patients compared with controls. Therefore, the main objective of this systematic review and meta-analysis was to determine if maximal aerobic capacity is reduced in OSA patients. A secondary aim was to investigate maximal exercise capacity as a function of OSA severity and age and to explore the cardiorespiratory responses to maximal exercise in patients with OSA.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and recommendations were followed for this meta-analysis (www.prisma-statement.org) (the PRISMA checklist can be found in supplementary table S1) [17] and the trial was registered on the Prospero registry (CRD42017057319).

Search strategy and data sources

A systematic literature review was conducted to identify manuscripts which investigated maximal exercise capacity in OSA patients. The web-based literature search included PubMed/MEDLINE and Embase databases. Search terms were selected to reflect the condition and outcome parameters. Search terms included a combination of text word terms and medical subject headings (MeSH) or Emtree terms (the sample search strategy is outlined in the supplementary material). For the condition, search terms included "sleep apnoea syndromes" [MeSH] OR "sleep apnoea, obstructive" [MeSH] OR "sleep disordered breathing", "exercise tolerance" [MeSH] OR "exercise test" [MeSH] OR "cardiorespiratory fitness" [MeSH] OR "oxygen consumption" [MeSH] OR physical fitness OR aerobic capacity. Terms were searched in all possible combinations using Boolean logical operators (AND, OR, NOT). Additionally, a manual search of bibliographies of included articles was conducted to identify relevant references which may not have been found by the automated search. Obtained references were indexed and managed using EndNote X7 (Thomson Reuters, New York, NY, USA).

Eligibility criteria

The following criteria were required for selection: 1) original research investigations; 2) conducted in humans; 3) conducted in adults; 4) including patients diagnosed with OSA of at least mild severity (apnoea-hypopnoea index (AHI) $\geqslant$5 events·h^{-1}) based on polysomnography or polygraphy; 5) including untreated OSA patients; 6) assessing aerobic capacity (maximal oxygen consumption ($V'O_2max$) or $V'O_2peak$) by means of a graded exercise test to volitional exhaustion; 7) reporting measures as $V'O_2peak$ in

% predicted or presenting results in mL·kg^{-1}·min^{-1} when comparing patients with OSA and controls; and 8) published in a peer-reviewed journal up to February 2017. We excluded studies that included patients with heart failure because of the known effect of heart failure on maximal exercise capacity [18]. Only articles in English and French were retained.

Data items

Reviewing procedure and data extraction

Database searches were first conducted in February 2017. Titles and/or abstracts of studies retrieved using the search strategy and from additional sources were screened independently by two review authors (MMe and MMa) to identify studies that potentially met the inclusion criteria outlined above. Irrelevant references were removed. Potentially relevant studies were further assessed by obtaining and reading the full text and re-checking the pre-specified eligibility criteria. The full text of these potentially eligible studies was retrieved independently and assessed for eligibility by two review team members. Any disagreements over the eligibility of particular studies were resolved through discussion with a third reviewer (SV). Data extraction was then performed for retained studies.

For each reference, the following variables were systematically extracted and entered into a summary table: 1) author, year; 2) participants; 3) AHI cut-off; 4) sample size; 5) age; 6) body mass index (BMI); 7) study design; 8) outcomes; and 9) main findings. A summary of the studies screened, assessed for eligibility and included is presented in figure 1 (for V'_{O_2}peak compared with controls in mL·kg^{-1}·min^{-1}) and figure 2 (for V'_{O_2}peak % pred in OSA patients only).

Methodological quality assessment

The quality of the studies was peer-reviewed by MMe and MMa using a modified version of the Newcastle-Ottawa Scale (NOS) for observational studies (supplementary material) [19]. Disagreements were resolved by consensus. For the NOS, a system of points (stars) was given to the eligible categories of sample selection criteria, comparability on the basis of the design or analysis, and evaluation of outcome. The scores varied depending on the study design and ranged from 0 to 8. Studies with scores above the median were classified as high-quality studies [20].

Statistical analysis

All included studies in the primary selection were included in the meta-analysis. For the main objective, two approaches were considered according to the units of V'_{O_2}peak. If V'_{O_2}peak was expressed as

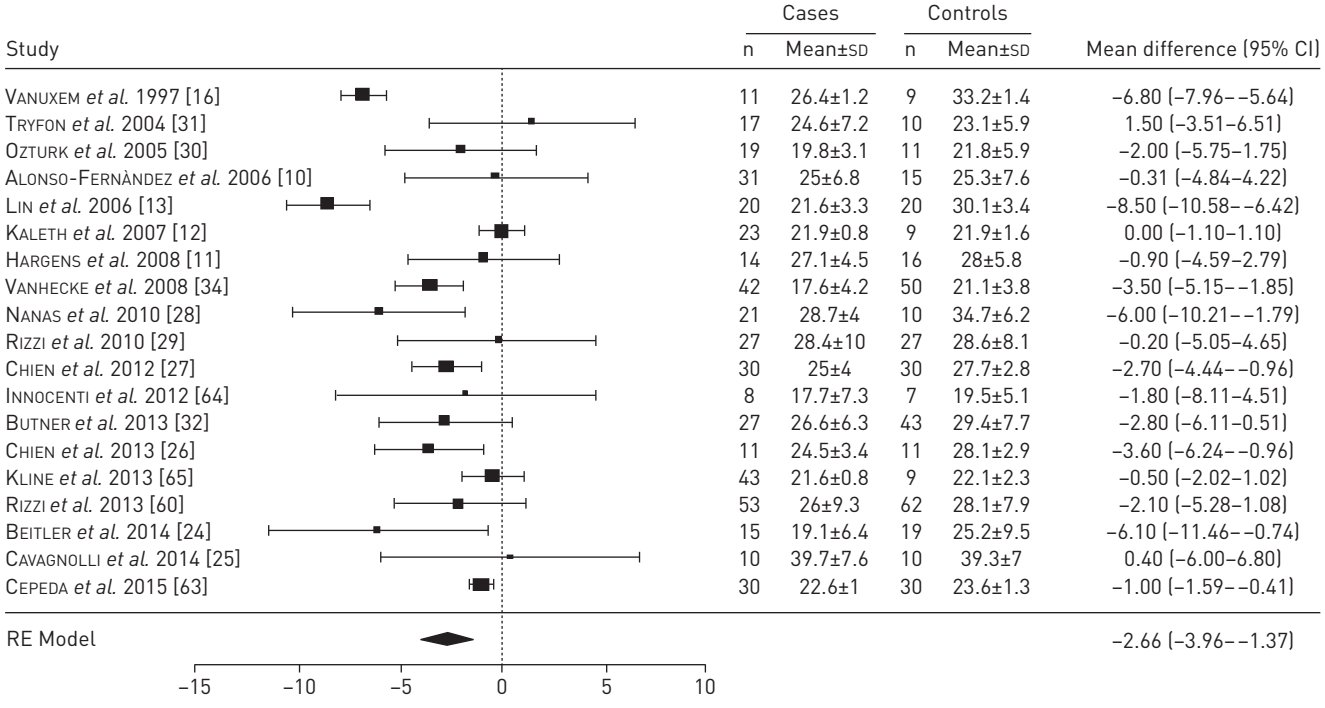

FIGURE 1 Forest plot for mean difference in peak oxygen consumption (V'_{O_2}peak) in mL·kg^{-1}·min^{-1} between patients with obstructive sleep apnoea and controls. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference. RE: random effects.

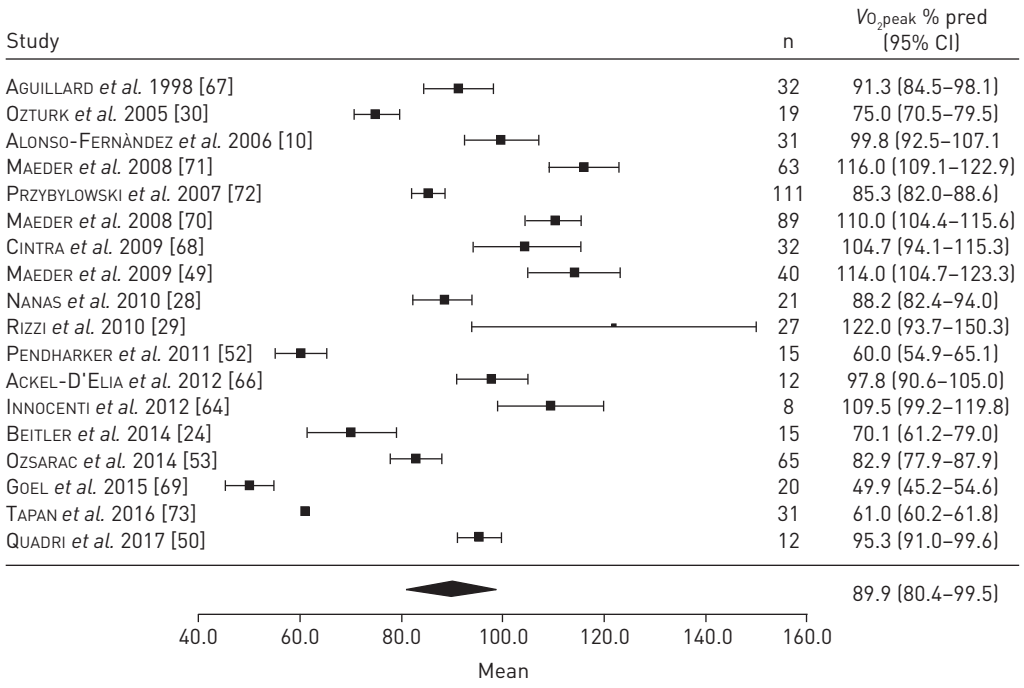

FIGURE 2 Forest plot for mean peak oxygen consumption ($V'O_2$peak) in % predicted in patients with obstructive sleep apnoea.

mL·kg^{-1}·min^{-1}, the mean difference was used to compare maximal exercise capacity between OSA patients and controls. For $V'O_2$peak in % pred, we reported the mean value in OSA patients. A DerSimonian and Laird random effects meta-analysis model was used for $V'O_2$peak in mL·kg^{-1}·min^{-1} to combine weighted mean differences [21]. The heterogeneity between studies was measured using the I^2 inconsistency index, which provides an estimation of the variability due to heterogeneity rather than chance. An I^2 index >60% reflects increasing heterogeneity [22]. To investigate the heterogeneity, sensitivity analyses were performed using subgroups classified according to BMI, AHI and age. Finally, the robustness of the results was assessed using sensitivity analyses by leaving out one study at a time, and the absence of selection bias was assessed using funnel plots. The presence or the absence of asymmetry in the funnel plot was assessed using the Egger test. There was no exclusion of studies based on methodological quality assessment results. Meta-analyses were carried out using the R package metafor in the RStudio software (RStudio v 1.0.136) [23]. A p-value threshold of 0.05 was considered for statistical significance.

Results

The study selection process is presented in figure 3. The search of MEDLINE and Embase databases provided 1159 citations. After adjusting for duplicates, 1026 remained. Of these, 936 studies were discarded because a review of the abstracts indicated that these papers clearly did not meet the criteria. The full texts of the remaining 90 citations were examined in more detail and 61 did not meet the inclusion criteria. Of the 29 studies that met the inclusion criteria, 19 studies reported $V'O_2$peak in mL·kg^{-1}·min^{-1} in OSA patients compared with controls and 18 reported $V'O_2$peak in % pred values in OSA patients only.

Main findings

$V'O_2$peak in mL·kg^{-1}·min^{-1} in patients with OSA compared with controls

Mean $V'O_2$peak expressed in mL·kg^{-1}·min^{-1} was significantly lower in patients with OSA than in controls (mean difference −2.7 mL·kg^{-1}·min^{-1}, 95% CI −4.0– −1.4, p<0.001; figure 1, table 1, supplementary table S2).

$V'O_2$peak in % pred in patients with OSA

Mean $V'O_2$peak in OSA patients expressed as % pred was 89.9 (95% CI 80.4–99.5) (figure 2, table 2).

Subgroup analyses

OSA severity

In patients with severe OSA (AHI>30 events·h^{-1}), mean difference in $V'O_2$peak compared with controls was −2.5 mL·kg^{-1}·min^{-1} (95% CI −3.6– −1.3, p<0.001; supplementary material, supplementary figure S1). In

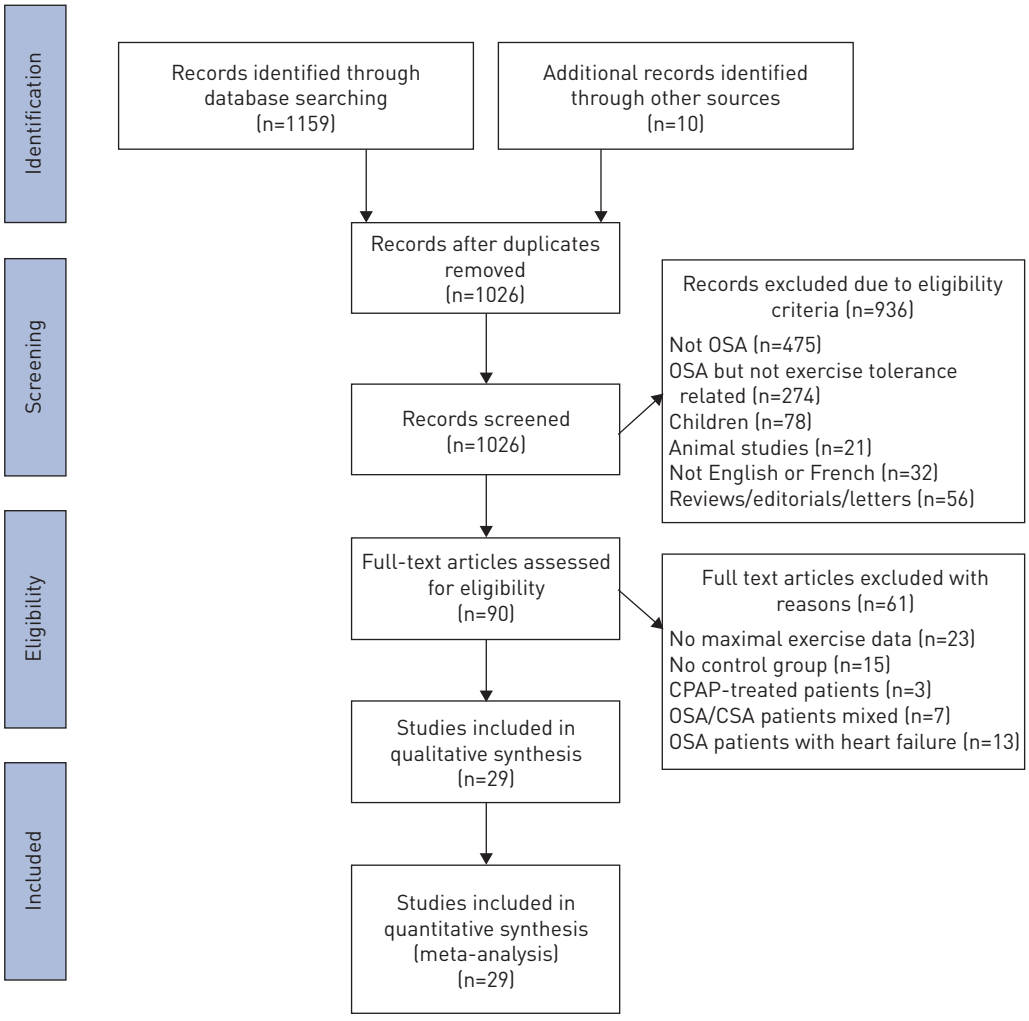

FIGURE 3 PRISMA flow chart of articles identified and evaluated during the study selection process. OSA: obstructive sleep apnoea; CPAP: continuous positive airway pressure; CSA: central sleep apnoea.

patients with mild-moderate OSA (AHI <30 events·h^{-1}), mean difference in V'_{O_2peak} compared with controls was −1.9 mL·kg^{-1}·min^{-1} (95% CI −3.9–0.09, p=0.06). The difference in V'_{O_2peak} compared with controls did not differ significantly between patients with severe and with mild-moderate OSA (p=0.15).

Age

In younger OSA patients (age <50 years), mean difference in V'_{O_2peak} compared with controls was −2.9 mL·kg^{-1}·min^{-1} (95% CI −4.5– −1.2, p<0.001; supplementary figure S2). In older OSA patients (age >50 years), the mean difference in V'_{O_2peak} compared with controls was −2.5 mL·kg^{-1}·min^{-1} (95% CI −3.7– −1.2, p<0.001). The difference in V'_{O_2peak} compared with controls did not differ significantly between older and younger patients (p=0.29).

BMI

In OSA patients who were non-obese (BMI <30 kg·m^{-2}), the mean difference in V'_{O_2peak} compared with controls was −4.1 mL·kg^{-1}·min^{-1} (95% CI −5.4– −2.2, p<0.001; supplementary figure S3). In obese OSA patients, the mean difference in V'_{O_2peak} compared with obese controls without OSA was −1.2 mL·kg^{-1}·min^{-1} (95% CI −2.3– −0.2, p=0.02). The difference in V'_{O_2peak} compared with controls was significantly greater in patients who were non-obese (p<0.001).

Analysis of peak exercise variables

Peak heart rate was significantly lower in patients with OSA than in controls (mean difference −7.7 beat·min^{-1}, 95% CI −11.1– −4.2, p=0.02; supplementary figure S4). Peak diastolic blood pressure

TABLE 1 Summary of findings regarding exercise tolerance for studies reporting results in mL·kg^{-1}·min^{-1}

First author	Year	Participants	AHI cut-off events·h^{-1}	Sample size n	AHI events·h^{-1}	Age years	BMI kg·m^{-2}	Design	Sex M/F	V'_{O_2peak} mL·kg^{-1}·min^{-1}
Alonso-Fernández [10]	2006	OSA	>10	31	43.6±23.6	53±13	30.4±4	Baseline data of prospective study	30/1	25.0±6.8
		Control	<5	15	4±3.3	48±10	28.7±4.7		15/0	25.3±7.6
Beitler [24]	2014	OSA	>15	15	37.6 (26.8–55.3)#	47.9±11.5	32.2±7.8	Cross-sectional	12/3	19.1±6.4
		Control	<15	19	1.5 (0.7–5.4)#	34.3±12.0	28.8±6.5		10/9	25.2±9.5
Butner [32]	2013	Control	<5	43	2.8±1.6	26±9	28±6	Cross-sectional	37/6	29.4±7.7
		Moderate OSA	5–14.9	27	8.7±2.7	30±13	30±7		23/4	26.6±6.3
Cavagnolli [25]	2014	OSA	>5	10	25.7±5.4	32.2±10.2	27.5±1.9	Baseline data of prospective study	10/0	39.7±7.6
		Control	<5	10	3.5±0.5	40.5±10.4	26.0±3.4		10/0	39.3±7.0
Cepeda [63]	2015	MetS + OSA	⩾15	30	42±4	49±1.7	32±1	Cross-sectional	18/12	22.6±1.0
		MetS – OSA	<15	30	7±1	46±1.4	32±1		14/16	23.6±1.3
Chien [27]	2012	Severe OSA	>30	30	48.4±17.3	50.5±5.7	26.5±2.4	Baseline data of prospective study	30/0	25.0±3.97
		Control		30	2.7±1.3	49.9±6.8	25.9±2.6		30/0	27.7±2.8
Chien [26]	2013	OSA	>30	11	46.2±22.6	50.3±5.1	26.6±3.6	Between-group comparison	11/0	24.5±3.4
		Control	<5	11	2.7±1.1	50.6±5.7	26.4±3.5		11/0	28.1±2.9
Hargens [11]	2008	OSA	>5	14	22.7±18.5	22.4±2.8	32.0±3.7	Between-group comparison	14/0	27.1±4.5
		Control	<5	16	2.5±1.3	21.4±2.6	31.4±3.7		16/0	28.0±5.8
Innocenti [64]	2012	Morbidly obese + OSA	>5	8	51.1±24.1	44±10.5	44.9±7.5	Cross-sectional	4/4	17.7±7.3
		Morbidly obese control	<5	7	3.2±1.1	34.8 ±10.6	44.0±9.6		4/3	19.5±5.1
Kaleth [12]	2007	OSA	⩾5	23	24.7±13.5	45.6±10.7	33.1±5.5	Between-group comparison	15/8	21.9±0.8
		Control – OSA	<5	9	2.5±1.6	40.2±8.1	29.5±5.5		2/7	21.9±1.6
Kline [65]	2013	OSA	⩾15	43	29.3±4.1	46.9±1.2	34.8±0.9	Ancillary study to RCT	24/19	21.6±0.8
		Control	<5	9	4.7±0.9	46.5±2.9	32.5±1.2		5/4	22.1±2.3
Lin [13]	2006	OSA	RDI >30	20	44.0±8.2¶	47±7	28.3±2.6	Between-group comparison	18/2	21.6±3.3
		Control	RDI <10	20	5.1±1.6¶	44±7	27.6±2.7		18/2	30.1±3.4
Nanas [28]	2010	OSA	⩾25	21	55±13	48±11	29.3±2.2	Between-group comparison	21/0	28.7±4.0
		Control		10		46±11	28.1±1.4		10/0	34.7±6.2
Ozturk [30]	2005	OSA	>5	19	46±19	46.9±8.6	30.7±4.6	Between-group comparison	16/3	19.8±3.1
		Control		11		40.6±8.4	28.9±3.0		7/4	21.8±5.9
Rizzi [29]	2010	Lean, sedentary OSA	⩾5	27	15.4±9.2	52.9±7.9	23.1±1.6	Between-group comparison	10/17	28.4±10.0
		patients	<5	27	3.1±1.1	52.8±8.1	22.7±1.7		10/17	28.6±8.1
		Controls								
Rizzi [60]	2013	Lean OSA	AHI⩾5	22	22.4±11.2	53.7±8.1	22.1±1.6	Between-group comparison	10/12	32.1±9.5
		Lean control	AHI<5	36	2.8±1.3	50.8±6.4	22.8±1.6		9/27	30.5±7.4
		Obese OSA	AHI⩾5	31	33.3±22.9	50.7±6.4	33.6±2.9		7/24	21.7±6.3
		Obese control	AHI<5	26	2.9±1.5	49.1±7.6	33.4±2.6		5/21	24.7±7.5
Tryfon [31]	2004	OSA	>5	17	33.3±22.4	35 (22–45)#	34.7±7.6	Between-group comparison	17/0	24.6±7.2
		Control	<5	10	N/A	35 (28–54)#	32.5±4.3		6/4	23.1±5.9
Vanhecke [34]	2008	Morbidly obese + OSA	AHI>15 or	42	32.5±26.6	46.2±11.0	50.5±9.4	Between-group comparison	13/29	17.6 ±4.2
		Morbidly obese – OSA	AHI>5 with ESS>10	50	2.5±2.3	45.0±8.7	47.2±9.1		15/35	21.1±3.8
Vanuxem [16]	1997	OSA	>10	11	25.6±1.2	47.8±4.1	26.6±1.0	Between-group comparison	N/A	26.4±1.2
		Control		9		41.9±3.1	26.4±1.2			33.2±1.4

Data are presented as n or mean±SD, unless otherwise stated. AHI: apnoea-hypopnea index; BMI: body mass index; M: male; F: female; V'_{O_2peak}: peak oxygen consumption; OSA: obstructive sleep apnoea; MetS: metabolic syndrome; RDI: respiratory disturbance index; ESS: Epworth Sleepiness Scale; RCT: randomised controlled trial; N/A: data not available. #: median (interquartile range); ¶: RDI provided by the investigators instead of AHI.

TABLE 2 Summary of findings regarding exercise tolerance for studies reporting results in % pred

First author	Year	AHI cut-off events·h^{-1}	Sample size n	AHI events·h^{-1}	Age years	BMI kg·m^{-2}	Design	Sex M/F	Equation for % pred	V'_{O_2peak} % pred
Ackel-D'Elia [66]	2012	>15	12	40.5±22.9	48.4±9.2	28.0±3.1	Baseline data of prospective study	13/0	N/A	97.8±12.7
Aguillard [67]	1998	>5	32	53.1±34.2	47.1±10.1	35.2±7.2	Cross-sectional	27/5	Wasserman	91.3±19.7
Alonso-Fernández [10]	2006	>10	31	43.6±23.6	53±13	30.4±4	Baseline data of prospective study	30/1	ATS	99.8±20.6
Beitler [24]	2014	>15	15	37.6 (26.8–55.3)[#]	47.9±11.5	32.2±7.8	Cross-sectional	12/3	Wasserman	70.1±17.5
Cintra [68]	2009	>5	32	32.5±23.6	57.2±10.9	27.8±4.2	Between-group comparison	32/0	N/A	116.6±27.7
			30	33.9±27.6	60.5±7.4	28.4±6.3	(men *versus* women)	0/30		91.3±28.7
Goel [69]	2015	>20	15	35.3±17	56.5±9.1	30.7±5.2	Baseline data of prospective study	11/4	ATS	51.0±9.2
		>20	5	36.7±23.9	57.8±9.7	32.7± 7.4		5/0		46.6±15.1
Innocenti [64]	2012	>5	8	51.1±24.1	44±10.5	44.9±7.5	Cross-sectional	4/4	Jones	109.5±14.9
Maeder [49]	2009	>5	40	37 (20–65)[#]	50±9	30.3±4.5	Cross-sectional	35/5	ATS	114±30
Maeder [70]	2007	>5	63	30.3 (13.0–51.7)[#]	49.2±9.8	30.1±4.8	Retrospective analysis	54/9	ATS	116±28
Maeder [71]	2008	>5	89	34 (17–53)[#]	49.5±9.7	30.2±4.6	Retrospective analysis	78/11	ATS	110±27
Nanas [28]	2010	⩾25	21	55±13	48±11	29.3±2.2	Between-group comparison	21/0	N/A	88.2±13.6
Ozturk [30]	2005	>5	19	46±19	46.9±8.6	30.7±4.6	Between-group comparison	16/3	N/A	75±10
Ozsarac [53]	2014	>5	33	40.7±19.6	48.8±9.2	31.3±3.8	Baseline data of prospective study	28/5	ATS	87.4±21.8
		>5	32	35.2±26.4	41.7±10.9	32.2±5.8		29/3		78.3±18.3
Pendharkar [52]	2011	⩾15	15	48.1±33.1	49±6	42.6±8.8	Baseline data of prospective study	6/9	ATS	60[¶]
Przybylowski [72]	2007	>30	111	47.2±23.1	50.2±10.0	31.0±4.6	Cross-sectional	109/2	Wasserman	85.3±17.8
Quadri [50]	2017	>30	12	45.4±14.9	58.0±9.7	33.3±5.2	Baseline data of intervention	8/4	Wasserman	95.3±7.6
Rizzi [29]	2010	⩾5	27	15.4±9.2	52.9±7.9	23.1±1.6	Between-group comparison	10/17	N/A	122±75
Tapan [73]	2016	>30	31	54.2±3.7	53.4±1.5	N/A	Baseline data of prospective study	27/4	N/A	61.0±2.2

Data are presented as n or mean±SD, unless otherwise stated. AHI: apnoea-hypopnea index; BMI: body mass index: M: male; F: female; % pred: percentage predicted; V'_{O_2peak}: peak oxygen consumption; N/A: data not available; ATS: American Thoracic Society. [#]: median (interquartile range); [¶]: no standard deviation available.

tended to be greater in patients with OSA (mean difference 4.5 mmHg, 95% CI −0.1–9.2, p=0.07; supplementary figure S5). Peak minute ventilation, peak O_2 pulse and peak systolic blood pressure did not differ between OSA patients and controls (supplementary figures S6, S7, S8).

Quality assessment

Studies reporting V'_{O_2peak} in mL·kg^{-1}·min^{-1}

The selection of patients with OSA was conducted consecutively in eight of the 19 studies [24–29]. Controls were selected from the community in five of the 19 studies [11, 13, 24, 25, 29] and the absence of OSA in controls was confirmed *via* polysomnography or polygraphy in all but three studies [16, 30, 31]. Only two studies out of 19 did not control for co-morbidities, age and BMI [24, 32]. In four studies, authors reported at least two criteria to define the exercise test as maximal [16, 26, 27, 30]. In all the included studies, OSA patients and controls did the same maximal exercise protocol for the measurement of V'_{O_2peak}.

In studies of higher quality (*i.e.* 6 or 7 stars on the modified NOS scale), the mean difference in V'_{O_2peak} was −3.6 mL·kg^{-1}·min^{-1} (95% CI −5.7– −1.5, p<0.001) while in lower quality studies (*i.e.* 4 or 5 stars), the mean difference in V'_{O_2peak} was −2.1 mL·kg^{-1}·min^{-1} (95% CI −3.7– −0.5, p=0.01) between OSA patients and controls (supplementary figure S9).

Sensitivity analysis

We observed high heterogeneity (I^2=85.7%) across all studies reporting V'_{O_2peak} in mL·kg^{-1}·min^{-1} (supplementary figure S10). Using the leave-one-out method, there was no difference in the final estimation of the mean difference. To explain this heterogeneity, a meta-regression was performed using the following moderators as binary variables in the model: AHI >30, age >50 years, BMI >30 kg·m^{-2} and >80% men in the study. The results showed that the following criteria significantly contributed to the heterogeneity (estimate±SD): AHI >30 (−1.23±0.48, p=0.001) and BMI >30 (2.84±1.32, p=0.03). The selective reporting bias was not significant (p=0.19). Residuals were normally distributed and the final random effects meta-analysis can be considered acceptable. The Egger test showed no selective reporting bias (p=0.50).

Discussion

Main results

This is the first meta-analysis to provide a comprehensive overview of the maximal exercise capacity of patients with OSA. In summary, we showed that the V'_{O_2peak} (expressed in mL·kg^{-1}·min^{-1}) of patients with OSA was significantly lower than that of matched controls without OSA. Prior studies over the past 20 years have provided conflicting results regarding the effect of OSA on maximal exercise capacity. The limited data have been derived from small studies which were not adequately designed to discern the effects of the severity of OSA, BMI and age on maximal exercise capacity. By summarising all the available literature (19 studies for V'_{O_2peak} in mL·kg^{-1}·min^{-1} and 18 studies for V'_{O_2peak} in % pred), the present meta-analysis confirms the significant impact of OSA on V'_{O_2peak}. Patients with OSA presented with V'_{O_2peak} values that were 2.7 mL·kg^{-1}·min^{-1} lower than those of controls. In a subgroup analysis, non-obese patients (BMI <30 kg·m^{-2}) *versus* obese patients presented V'_{O_2peak} values that were −4.1 and −1.2 mL·kg^{-1}·min^{-1}, respectively, lower than controls. The reduction in maximal exercise capacity associated with OSA, especially in leaner patients, can be considered clinically significant because it has been shown that an increase in V'_{O_2peak} of 3.5 mL·kg^{-1}·min^{-1} is associated with considerable improvements in survival (10–25%) [9]. This result suggests that the effect of OSA on V'_{O_2peak} is more pronounced in patients who do not present with other mechanisms that are known to decrease V'_{O_2peak} (*i.e.* obesity). Furthermore, the reduced V'_{O_2peak} in OSA patients was associated with lower maximal heart rate and slightly higher peak diastolic blood pressure but similar maximal minute ventilation compared to controls, suggesting some potential altered cardiovascular responses to exercise.

Potential physiological mechanisms

Several potential physiological mechanisms have been suggested to explain impaired maximal exercise capacity in OSA patients. In the present meta-analysis, heart rate at peak exercise was significantly lower in OSA patients than in controls, suggesting chronotropic incompetence. For example, Kaleth *et al.* [12] reported that OSA patients exhibited a mean peak exercise heart rate that was 86.5% of the age-adjusted predicted maximal heart rate compared to 93.5% for controls. A number of other studies have reported this chronotropic impairment during exercise in OSA patients [12, 27, 28, 33, 34] and it has been hypothesised that the impairment may be due to downregulated beta-adrenergic receptors consequent to sympathetic hyperactivity [35].

We did not find any differences in peak minute ventilation, peak O_2 pulse or peak systolic blood pressure between OSA patients and controls. However, peak diastolic blood pressure tended to be greater in patients with OSA (p=0.07), which may suggest impaired peripheral vasodilation [36, 37]. Previous results showed that normotensive OSA patients develop elevated diastolic blood pressure at an earlier stage during exercise compared to controls [31]. This finding is important because it has been shown that diastolic hypertension during exercise is a risk factor for the subsequent development of hypertension [38] and may also constitute a limiting factor for maximal exercise capacity [39].

Other potential mechanisms that we were unable to meta-analyse owing to limited data include decreased maximal lactate concentration and delayed lactate elimination. This has been observed in OSA patients during exercise when compared to age- and BMI-matched controls and may suggest impaired glycolytic and oxidative metabolism, respectively [16]. The reduction in maximal exercise capacity in OSA patients has also been potentially attributed to abnormalities of the skeletal muscles. For example, muscle biopsy studies have demonstrated structural and bioenergetics changes in skeletal muscle fibre in OSA patients [40].

OSA patients may exhibit excessive daytime somnolence, which can affect the ability to achieve a maximal exercise workload. Several studies have indeed demonstrated reduced exercise performance under conditions of sleep deprivation [41, 42]. A recent study from our group in healthy men showed that sleep deprivation reduced exercise time to task failure and increased the rating of perceived exertion during exercise testing [43]. Therefore, it is possible that excessive daytime sleepiness contributes to a reduced maximal exercise capacity in OSA patients.

Another potential mechanism that may contribute to the differences observed between OSA patients and controls is habitual physical activity levels. It is well known that habitual physical activity levels influence maximal exercise capacity [6]. Furthermore, a number of observational studies have reported low levels of objectively measured physical activity in OSA patients [44–46]. Only a small number of studies [10, 11, 13, 31] included in the present meta-analysis reported physical activity levels in OSA and controls. Therefore, we cannot exclude the possibility that patients with OSA had lower levels of physical activity than controls and that this contributed to their lower $V'O_2peak$ [47].

Controlling for BMI is imperative in studies assessing maximal aerobic capacity. All the studies included in the meta-analysis except one matched OSA patients with controls with respect to weight or BMI. However, when we compiled the BMI data across all studies, we found that the mean BMI of OSA patients was slightly but significantly greater than that of control patients (+1.02 $kg{\cdot}m^{-2}$, 95% CI 0.49–1.54, p=0.0002; supplementary figure S11). Therefore, we cannot exclude the possibility that differences in BMI between studies may have contributed, at least in part, to the difference in maximal aerobic capacity we observed.

Differences in co-morbidities and medication intake between OSA patients and controls can also contribute to differences in exercise responses (*e.g.* heart rate, systolic and diastolic blood pressure) and, ultimately, $V'O_2peak$. However, because the majority of studies included in the present meta-analysis had the same inclusion/exclusion criteria with respect to co-morbidities for OSA patients and controls, we do not think that co-morbidities contributed to the differences observed in $V'O_2peak$ between OSA patients and controls. Regarding medication, this was more scarcely reported but because co-morbidities were matched, one can expect few differences in medication intake (supplementary table S2).

Evaluating the effect of treatment of OSA on exercise responses can provide useful information concerning the effects of OSA on maximal exercise capacity. Several studies have examined this question but provide conflicting results. Although an improvement in maximal exercise performance has been observed after varying treatment durations from 1 week to 8 months [48–51], other studies have not reported enhanced $V'O_2peak$ after 1–3 months of continuous positive airway pressure (CPAP) treatment [10, 52, 53]. These inconsistencies may be due to differences in treatment adherence, disease severity or physical activity levels. In two of the aforementioned studies, a significant correlation was found between AHI reduction and increase in $V'O_2peak$ after CPAP [48, 50]. Recently, 2 months of CPAP was shown to increase maximal exercise capacity and this was associated with decreased sympathetic hyperactivity assessed by heart rate variability. In this study, the authors ensured that the patients enrolled in the study did not change their BMI or lifestyle during the study (*i.e.* physical activity levels assessed *via* questionnaire) [50]. There is evidence that excessive sympathetic activation, as observed in chronic heart failure at baseline and during exercise, may contribute to limiting maximal exercise capacity through muscle energy metabolism and perfusion [54].

Sources of heterogeneity between studies

The high level of heterogeneity observed in the present meta-analysis can be explained by several factors including the variability of $V'O_2peak$ measurements, the type of study (*i.e.* prospective, cross-sectional, between-group comparisons) and other factors such as patient characteristics.

Differences in protocols and criteria used to determine $V'O_{2peak}$ can be a source of variability between studies [55]. However, our methodological quality assessment scale did take into account specific elements regarding the maximal exercise testing.

The differences in $V'O_{2peak}$ % pred values can be partly attributed to the different prediction equations used to calculate maximal aerobic capacity. Predicted $V'O_{2peak}$ equations allow a normalised evaluation of maximal exercise capacity depending on age, height and sex but some variability has been reported depending on the equation used [56]. In the present meta-analysis, the equation used varied across studies, with four studies reporting Wasserman's equation [57], eight studies citing the American Thoracic Society (ATS) guidelines [58] and one study citing Jones [59]; five did not provide information. Data in obese and non-obese adults have shown that the quantification of maximal exercise capacity in % pred values varies depending on the equation used [58]. Hence, care has to be taken to select the most appropriate equation, especially in obese individuals, to evaluate maximal aerobic capacity in OSA patients because some prediction equations can over- or underestimate maximal exercise capacity.

The studies included in our meta-analysis did not allow us to draw conclusions regarding the effect of sex on maximal exercise capacity in OSA patients. Most studies evaluated men and women; however, four studies did not adequately sex-match OSA and control groups [24, 31, 44, 60] and this may have influenced the difference in $V'O_{2peak}$ we observed between groups. To examine this, we re-analysed the data by excluding these four studies. The effect of OSA on $V'O_{2peak}$ remained similar, which suggests that differences in sex did not contribute significantly to the results observed in this meta-analysis. Another issue regarding sex differences is whether OSA affects $V'O_{2peak}$ differently in men *versus* women. Because no study to date has evaluated women only, our meta-analysis cannot determine whether sex has an influence on the effect of OSA on $V'O_{2peak}$. A meta-analysis on individual data would allow a clearer picture on the effects of sex on maximal exercise capacity in OSA patients.

Another potential source of heterogeneity across studies was the physical activity level of patients. As mentioned previously, physical activity levels were only reported in a few studies and one cannot exclude the possibility that differences in physical activity levels between OSA patients and controls may explain, at least in part, the differences in $V'O_{2peak}$ we observed between groups.

The time delay between OSA diagnosis and exercise test was not available for the included studies. Moreover, the duration of exposure to OSA prior to diagnosis was unknown and is difficult to determine, although it may influence the amplitude of the effect of OSA on $V'O_{2peak}$.

Clinical implications

The results from the present meta-analysis showing a reduction in maximal exercise capacity in OSA patients have important clinical implications. Our results shed light on the debilitating consequences of OSA on maximal exercise capacity, even in patients with OSA of mild-moderate severity. Furthermore, our results show that maximal exercise capacity is most affected in non-obese OSA patients. This highlights the importance of adapted treatment for these patients and also suggests that maximal exercise testing could be used in routine evaluation. Maximal exercise capacity testing has long been considered an effective tool to identify individuals at risk for cardiovascular disease [61]. While the impact of CPAP therapy on maximal exercise capacity remains to be elucidated with future well-designed studies, other interventions, which have been shown to improve maximal exercise capacity, should be promoted in patients with OSA. For example, exercise-based rehabilitation has been shown to not only reduce the severity of OSA and improve daytime symptoms of sleepiness, but also significantly improve maximal exercise capacity [62]. In order to limit cardiovascular and metabolic morbidity in OSA patients, this type of therapy should be encouraged.

Limitations

There are several limitations to this study. While this was the first meta-analytic study to report maximal exercise capacity in OSA patients, we did observe moderate-high heterogeneity in the included studies. Although this effect was lessened when outliers were removed, there were differences between studies of different quality (low *versus* moderate-high). Additional high-quality controlled studies are needed to evaluate the effect of OSA on maximal exercise capacity, with a particular focus on under-represented populations such as women.

Conclusion

Maximal exercise capacity is impaired in patients with OSA when compared with controls and when expressed relative to predictive values. Maximal exercise testing may be used to help characterise the nature of cardiopulmonary stress attendant to OSA, as well as the associated cardiometabolic dysfunction, and to evaluate the effects of treatment.

Conflict of interest: J-C. Borel has received fees for lectures, congress invitations and a grant for a study from Philips, salaries from AGIR à dom (home care provider), fees for lectures and congress invitations from Resmed, and a patent from Nomics, outside the submitted work. J-L. Pépin reports grants from Resmed, during the conduct of the study; and grants and personal fees from Resmed, Philips, Sefam, AGIR à dom and Vitalaire; grants from Fisher and Paykel, and AstraZeneca; and personal fees from Elevie and Boehringer, outside the submitted work.

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