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Early View

Review

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

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

Monique Mendelson*, Mathieu Marillier*, Sébastien Bailly, Patrice Flore, Jean-Christian Borel, Isabelle Vivodtzev, Stéphane Doutreleau, Renaud Tamisier, Jean-Louis Pépin[#], Samuel Verges[#]

Affiliations

1. HP2 laboratory, University Grenoble Alps, Grenoble, France
2. Inserm U1042, Grenoble, France
3. Grenoble Alps University Hospital, Grenoble, France

* Both authors have contributed equally and share the first authorship

[#] Both last authors share senior authorship

Corresponding author:

Monique Mendelson, Laboratoire HP2, UM Sports Pathologies, Hôpital Sud, avenue Kimberley, 38434 Echirolles, France.

Email : mmendelson@chu-grenoble.fr; Tel : +(33)476767226

Conflicts of interest

The authors have no conflicts of interest to declare related to this review.

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Take home message

Maximal exercise capacity as a reflection of total body health is reduced in patients with obstructive sleep apnoea

ABSTRACT

Maximal aerobic capacity is a strong health predictor and peak oxygen consumption (VO_{2peak}) is considered a reflection of total body health. No systematic reviews or meta-analysis' to date have synthesized the existing data regarding VO_{2peak} in patients with obstructive sleep apnoea (OSA).

A systematic review of English and French articles using Pubmed/Medline and Embase included studies assessing VO_{2peak} of OSA patients 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 VO_{2peak} expressed in $mL \cdot kg^{-1} \cdot min^{-1}$ was significantly lower in patients with OSA when compared with controls (mean difference = -2.7 $mL \cdot kg^{-1} \cdot min^{-1}$; $p<0.001$; n=850). This reduction in VO_{2peak} was found to be larger in non-obese patients ($BMI<30kg/m^2$). Mean VO_{2peak} in % predicted was 90.7 ± 21.0% - in OSA patients (n=643).

OSA patients present 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.

Registration # CRD42017057319

Keywords: obstructive sleep apnoea, exercise tolerance, peak oxygen consumption, systematic review, meta-analysis

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], responsible for cardio metabolic morbidity [3] and mortality.

Maximal exercise capacity testing, using an incremental whole-body (i.e. 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/surrogate marker of risk of these tests is peak oxygen uptake (VO_{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 has been 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; a multiple of the resting metabolic rate approximating 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$). Taken together, these studies have shown that each 1-MET higher maximal exercise capacity was associated with considerable (10-25%) improvement in survival [9].

The evaluation of maximal exercise capacity in OSA patients can be relevant to assess 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 to

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 generalization 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 summarize 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 statement and recommendations were followed for this meta-analysis (http://www.prisma-statement.org) [17] (see electronical online supplement Table S1 for PRISMA checklist) 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 (see supplemental file for sample search strategy). For the condition, search terms included: "sleep apnea syndromes"[MeSH] OR "sleep apnea, 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) include patients diagnosed with OSA of at

least mild severity (apnea hypopnea index [AHI] ≥ 5 events/h) based on polysomnography or polygraphy; 5) untreated OSA patients; 6) assess aerobic capacity (maximal oxygen consumption, VO_{2max} or VO_{2peak}) by means of a graded exercise test to volitional exhaustion; 7) studies had to report measures as VO_{2peak} in % predicted value OR studies presenting results in $mL.Kg^{-1}.min^{-1}$ had to compare patients with OSA and controls; 8) published in a peer-review 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]. Articles in English and French only were retained.

Data items

Reviewing procedure and data extraction

Database searches were first conducted in February 2017. All obtained references were reviewed, and if retained, data extraction was conducted. The first level of review was title and abstract screening. Irrelevant references were removed. Potentially relevant studies were further assessed by obtaining and reading the full text and checking again the pre-specified eligibility criteria.

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two review authors (MM and MM) to identify studies that potentially met the inclusion criteria outlined above. The full text of these potentially eligible studies were 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).

For each reference, the following variables were systematically extracted and entered into a summary table: 1) author, year; 2) participants; 3) AHI cutoff; 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 Figures 1 (for VO_{2peak} compared with controls in $mL \cdot kg^{-1} \cdot min^{-1}$) and 2 (for VO_{2peak} in % predicted in OSA patients only).

Methodological quality assessment

The quality of the studies was peer-reviewed by MM and MM using a modified version of the Newcastle-Ottawa Scale (NOS) for observational studies (see supplemental file for NOS) [19]. Disagreements were resolved by consensus. For the NOS, a system of points (stars) was given to the eligible categories: sample selection criteria, comparability on the basis of the design or analysis, and evaluation of outcome. The scale 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 VO_{2peak}. If VO_{2peak} was expressed as $mL \cdot kg^{-1} \cdot min^{-1}$, the mean difference was used to compare maximal exercise capacity between OSA patients and controls. For VO_{2peak} in % predicted, we reported the mean value in OSA patients. A DerSimonian and Laird random effects meta-analysis model was used for VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$ 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 the heterogeneity rather than chance. A I^2 index higher than 60% reflects increasing heterogeneity [22]. To investigate the heterogeneity, sensitivity analyses were performed using sub-groups: BMI, AHI and age. Finally, the robustness of the results was assessed using sensitivity analysis by leaving out one study at a time, and the

absence of selection bias was assessed using funnel plot. 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 by 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 1. The search of Medline and Embase databases provided a total of 1,159 citations. After adjusting for duplicates 1,026 remained. Of these, 936 studies were discarded because after reviewing the abstracts it appeared that these papers clearly did not meet the criteria. The full-texts of the remaining 90 citations were examined in more detail. Sixty one studies did not meet the inclusion criteria. Of the twenty-nine studies that met the inclusion criteria, 19 studies reported VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$ in OSA patients compared with controls and 18 reported VO_{2peak} in % predicted values in OSA patients only.

Main findings

VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$ in patients with OSA compared to controls

Mean VO_{2peak} expressed in $mL \cdot kg^{-1} \cdot min^{-1}$ was significantly lower in patients with OSA when compared with controls (mean difference = -2.7 $mL \cdot kg^{-1} \cdot min^{-1}$; 95% CI: -4.0 to -1.4; $p<0.001$; Figure 2, Table 1, Table S1).

VO_{2peak} in % predicted in patients with OSA

Mean VO_{2peak} in OSA patients expressed as % predicted was 90.7 ± 21.0% (Figure 3, Table 2, Table S2).

Subgroup analyses

OSA severity

In patients with severe OSA (AHI > 30 events/h), mean difference in VO_{2peak} was -2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: -3.6 to -1.3; $p<0.001$) when compared with controls (supplemental data file, Figure S1). In patients with mild-moderate OSA (AHI < 30 events/h), mean difference in

VO_{2peak} was -1.9 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: -3.9 to 0.09; p=0.06) when compared with controls. The difference in VO_{2peak} compared to controls did not differ significantly between patients with severe and mild-moderate OSA (p=0.15).

Age

In younger OSA patients (age < 50 years), mean difference in VO_{2peak} was -2.9 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI -4.5 to -1.2; p<0.001) when compared with controls (Figure S2). In older OSA patients (age > 50 years), mean difference in VO_{2peak} was -2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI -3.7 to -1.2; p<0.001) when compared with controls. The difference in VO_{2peak} compared to 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 VO_{2peak} was -4.1 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: -5.4 to -2.2; p<0.001) when compared with controls (Figure S3). In obese OSA patients, the mean difference in VO_{2peak} was -1.2 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: -2.3 to -0.2; p=0.02) when compared with obese controls without OSA. The difference in VO_{2peak} compared to 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 (mean difference: -7.7 $beat \cdot min^{-1}$; 95% CI: -11.1 to -4.2; p=0.02) when compared with controls (Figure S4). Peak diastolic blood pressure tended to be greater in patients with OSA (mean difference: 4.5 mmHg; 95% CI: -0.1 to 9.2; p=0.07; Figure S5). Peak minute ventilation, peak O_2 pulse and peak systolic blood pressure did not differ between OSA patients when compared with controls (Figures S6, S7, S8).

Quality assessment

Studies reporting VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$

The selection of patients with OSA was conducted consecutively in eight studies [24-30] out of 19. Controls were selected from the community in five studies [11, 24, 25, 28, 30] out of 19 and the absence of OSA in controls was confirmed via polysomnography or polygraphy in all but 3 studies [16, 31, 32]. Only two studies out of 19 did not control for co-morbidities, age and BMI [24, 33]. In 4 studies, authors reported at least 2 criteria to define the exercise test as maximal [16, 26, 27, 31]. In all the included studies, OSA patients and controls did the same maximal exercise protocol for the measurement of VO_{2peak}.

In studies of higher quality (i.e. 6 or 7 stars on the modified NOS scale), the mean difference in VO_{2peak} was -3.6 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: -5.7 to -1.5; p<0.001) while as in lower quality studies (i.e. 4 or 5 stars), the mean difference in VO_{2peak} was -2.1 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: -3.7 to -0.5; p=0.01) between OSA patients and controls (Figure S9).

Sensitivity analysis

We observed high heterogeneity (I^2= 85.7%) across all studies reporting VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$ (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, BMI >30 and more than 80% of men in the study. The results showed that the following criteria significantly contributed to the heterogeneity: AHI >30 (est: -1.23 SD: 0.48 – p=0.001) and BMI>30 (est: 2.84 SD:1.32 – p=0.03). The selective reporting bias was not significant (p=0.19). Residuals are 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 VO_{2peak} (expressed in $mL \cdot kg^{-1} \cdot min^{-1}$) of patients with OSA was significantly lower when compared with 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 summarizing all the available literature (19 studies for VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$ and 18 studies for VO_{2peak} in % predicted values), the present meta-analysis confirms the significant impact of OSA on VO_{2peak}. Patients with OSA present VO_{2peak} values that are 2.7 $mL \cdot kg^{-1} \cdot min^{-1}$ lower than controls. In a subgroup analysis, non-obese patients ($BMI<30\ kg.m^{-2}$) versus obese patients presented VO_{2peak} values that were -4.1 and -1.2 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively, lower than controls. Hence, the reduction in maximal exercise capacity associated with OSA, especially leaner patients, can be considered as clinically significant since it has been shown that increasing VO_{2peak} by 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 VO_{2peak} is more pronounced in patients who do not present other mechanisms that are known to decrease VO_{2peak} (i.e. obesity). Furthermore, the reduced VO_{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 when compared with controls, suggesting chronotropic incompetence. For example, Kaleth et al. [34] reported that OSA patients exhibited mean peak exercise heart rate that was 86.5% of 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 [27, 29, 34-36] and it has been hypothesized that the impairment may be due to downregulated beta-adrenergic receptors consequent to sympathetic hyperactivity [37].

We did not find any differences in peak minute ventilation, peak O_2 pulse and 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 [38, 39]. Previous results showed that normotensive OSA patients develop DBP elevation at an earlier stage during exercise compared to controls [32]. This finding is important as it has been shown that diastolic hypertension during exercise is a risk factor for the subsequent development of hypertension [40] and may also constitute a limiting factor for maximal exercise capacity [41].

Other potential mechanisms that we were unable to meta-analyze due to limited data include for example decreased maximal lactate concentration and delayed lactate elimination. This has been observed in OSA patients during exercise 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 fiber in OSA patients [42].

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 [43, 44]. A recent study from our group in healthy men showed for instance that sleep deprivation reduced exercise time to task failure and increased the rating of perceived exertion during exercise testing [45]. Therefore, it is possible that excessive daytime sleepiness contributed to reduced maximal exercise capacity in OSA patients.

Another potential mechanism that may contribute to 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 [46-48]. Only a small number of studies [10, 11, 28, 32] 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 VO_{2peak} [49].

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 the studies, we found that the mean BMI of OSA patients was slightly but significantly greater than control patients (+1.02 kg/m² 95% CI: 0.49-1.54, supplemental 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 BP) and ultimately, VO_{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 VO_{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 (Supplemental 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 [50-53], other studies did not report enhanced VO_{2peak} after 1 to 3 months of CPAP treatment [54-56]. 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 VO_{2peak} after CPAP [50, 52]. Recently, 2 months of CPAP has been shown to increase maximal exercise capacity and this was associated with a decrease 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 and lifestyle during the duration of the study (i.e. physical activity levels assessed via questionnaire) [52]. There is evidence that excessive sympathetic activation, as observed in chronic heart failure at baseline and during exercise, may contribute to limit maximal exercise capacity through muscle energy metabolism and perfusion [57].

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 VO_{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 VO_{2peak} can be a source of variability between studies [58]. Our methodological quality assessment scale did take into account specific elements regarding the maximal exercise testing. However, there was no significant difference between studies of higher or lower quality.

The differences in VO_{2peak} % predicted values can be partly attributed to the different prediction equations used to calculate maximal aerobic capacity. Predicted VO_{2peak} equations allow a normalized evaluation of maximal exercise capacity depending on age, height and gender but some variability has been reported depending on the equation used [59]. In the present meta-analysis, the equation used varied across studies, with 4 studies reporting Wasserman's equation [60], 8 studies citing the ATS guidelines [61], 1 study citing Jones [62] and 5 did not provide information. Data in obese and non-obese adults has shown that the quantification of maximal exercise capacity in % predicted values varies depending on the equation used [61]. Hence, care has to be taken to select the most appropriate equation especially in obese individuals in order to evaluate maximal aerobic capacity in OSA patients as some prediction equations can over- or under-estimate maximal exercise capacity.

The studies included in our meta-analysis did not allow us to conclude as to the effect of sex on maximal exercise capacity in OSA patients. Most studies evaluated men and women, however four studies did not adequately gender-match OSA and control groups [24, 32, 46, 63] and this may have influenced the difference in VO_{2peak} we observed between groups. We re-analyzed the data by excluding these four studies and the effect of OSA on

VO_{2peak} remained similar, which suggests that differences in sex do not contribute significantly to the results observed in this meta-analysis. Another issue regarding sex differences is whether OSA affects VO_{2peak} differently in men versus women. Since no study to date has evaluated women only, our meta-analysis cannot determine whether sex has an influence on the effect of OSA on VO_{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 is the physical activity level of patients. As mentioned previously, physical activity levels were reported in few studies only 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 VO_{2peak} we observed between groups.

The time delay between OSA diagnosis and exercise test was not available from 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 VO_{2peak}.

Clinical implications

The results from the present meta-analysis showing 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 mild-moderate severity. Furthermore, our results show that non-obese OSA patients are those whose maximal exercise capacity is most impacted. 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 used as an effective tool for the identification of individuals at risk for cardiovascular disease [64]. While the impact of

the CPAP 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 to significantly improve maximal exercise capacity [65]. 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. While this effect was lessened when outliers were removed, there were differences in 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 cardio-metabolic dysfunction and to evaluate the effects of treatment.

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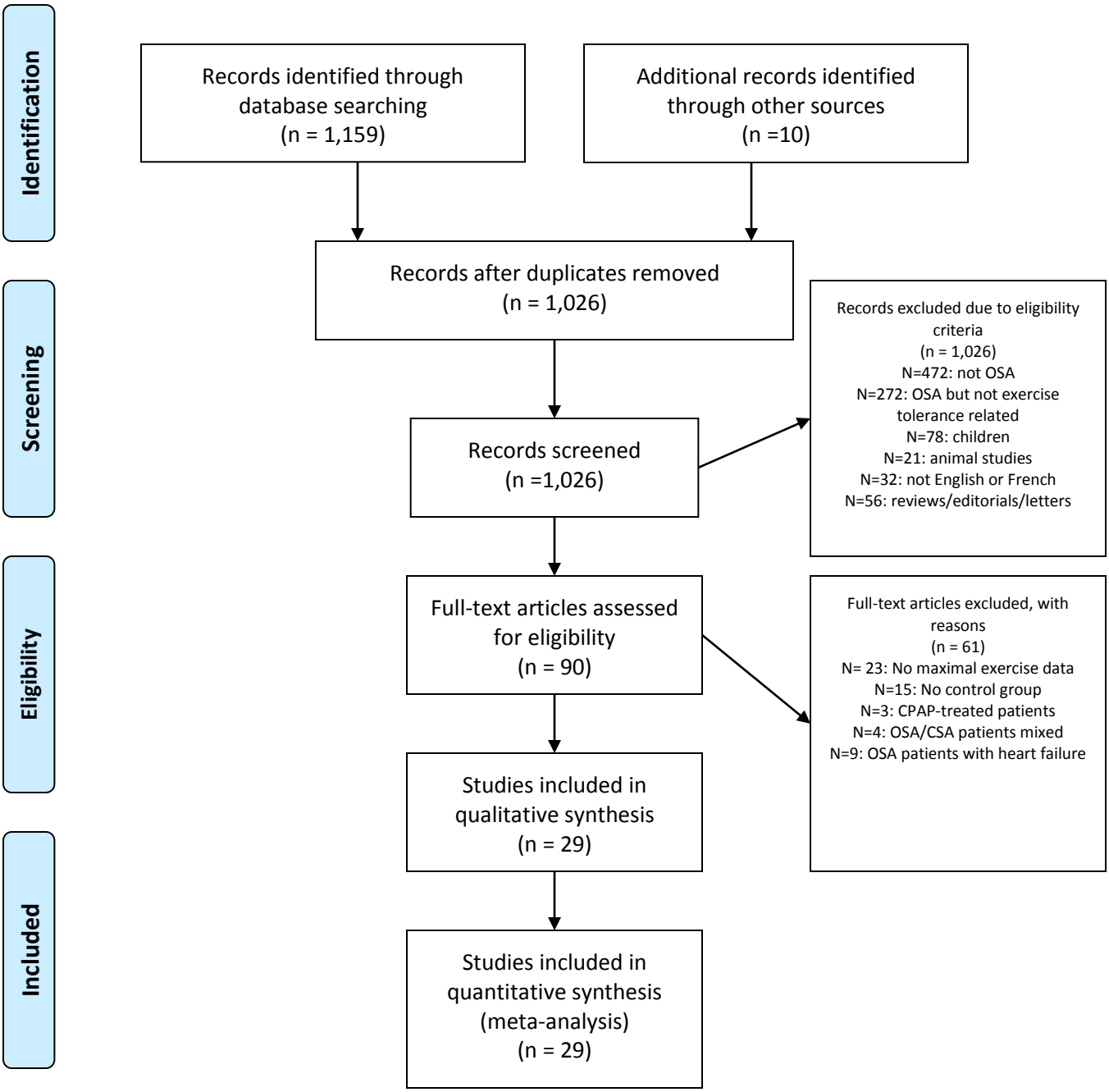
FIGURE LEGENDS

Figure 1. Prisma Flow Chart of articles identified and evaluated during the study selection process.

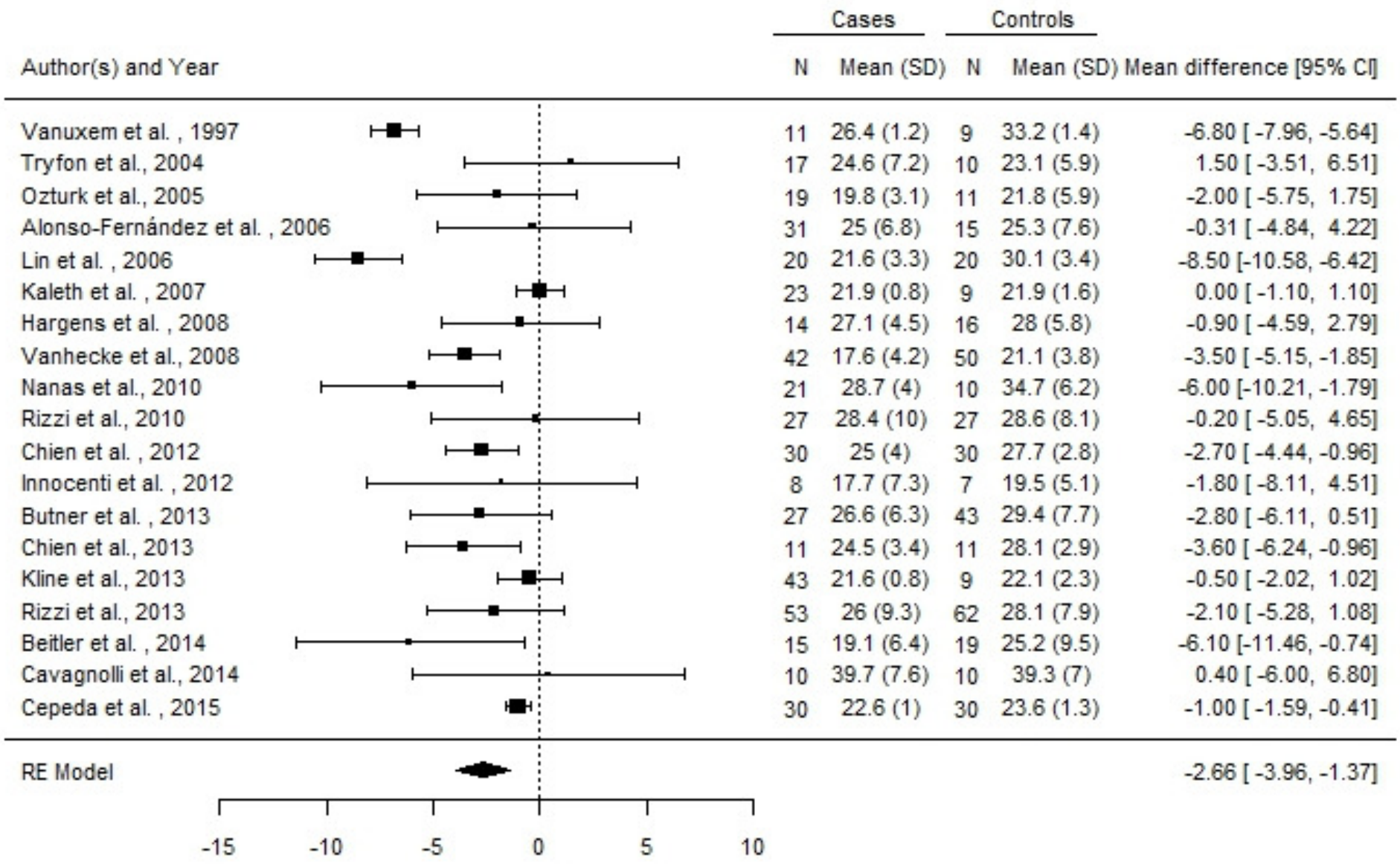
Figure 2. Forest plot for mean difference in VO_{2peak} (in $mL \cdot kg^{-1} \cdot min^{-1}$) between OSA patients and controls. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

Figure 3. Forest plot for mean VO_{2peak} (in % predicted) in OSA patients.

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097


Cases
Controls
Author(s) and Year
N
Mean (SD)
N
Mean (SD)
Mean difference [95% CI]
Vanuxem et al. , 1997 11 26.4 (1.2) 9 33.2 (1.4) -6.80 [-7.96, -5.64]
Tryfon et al., 2004 17 24.6 (7.2) 10 23.1 (5.9) 1.50 [-3.51, 6.51]
Ozturk et al., 2005 19 19.8 (3.1) 11 21.8 (5.9) -2.00 [-5.75, 1.75]
Alonso-Fernández et al. , 2006 31 25 (6.8) 15 25.3 (7.6) -0.31 [-4.84, 4.22]
Lin et al. , 2006 20 21.6 (3.3) 20 30.1 (3.4) -8.50 [-10.58, -6.42]
Kaleth et al. , 2007 23 21.9 (0.8) 9 21.9 (1.6) 0.00 [-1.10, 1.10]
Hargens et al. , 2008 14 27.1 (4.5) 16 28 (5.8) -0.90 [-4.59, 2.79]
Vanhecke et al., 2008 42 17.6 (4.2) 50 21.1 (3.8) -3.50 [-5.15, -1.85]
Nanas et al., 2010 21 28.7 (4) 10 34.7 (6.2) -6.00 [-10.21, -1.79]
Rizzi et al., 2010 27 28.4 (10) 27 28.6 (8.1) -0.20 [-5.05, 4.65]
Chien et al. , 2012 30 25 (4) 30 27.7 (2.8) -2.70 [-4.44, -0.96]
Innocenti et al. , 2012 8 17.7 (7.3) 7 19.5 (5.1) -1.80 [-8.11, 4.51]
Butner et al. , 2013 27 26.6 (6.3) 43 29.4 (7.7) -2.80 [-6.11, 0.51]
Chien et al., 2013 11 24.5 (3.4) 11 28.1 (2.9) -3.60 [-6.24, -0.96]
Kline et al., 2013 43 21.6 (0.8) 9 22.1 (2.3) -0.50 [-2.02, 1.02]
Rizzi et al., 2013 53 26 (9.3) 62 28.1 (7.9) -2.10 [-5.28, 1.08]
Beitler et al. , 2014 15 19.1 (6.4) 19 25.2 (9.5) -6.10 [-11.46, -0.74]
Cavagnolli et al., 2014 10 39.7 (7.6) 10 39.3 (7) 0.40 [-6.00, 6.80]
Cepeda et al. , 2015 30 22.6 (1) 30 23.6 (1.3) -1.00 [-1.59, -0.41]
RE Model -2.66 [-3.96, -1.37]
-15
-10
-5
0
5
10

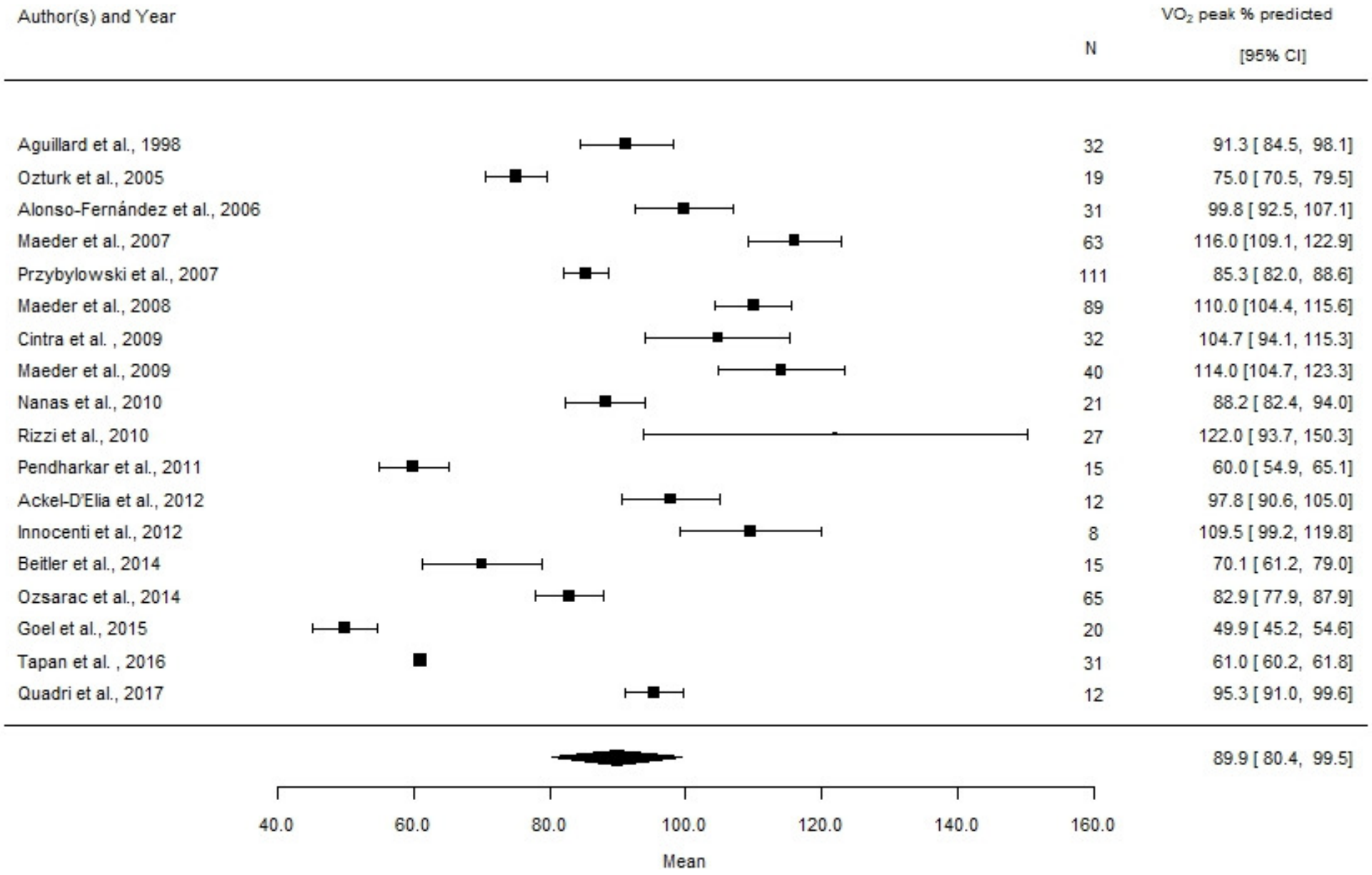

Author(s) and Year
N
VO2 peak % predicted
[95% CI]
Aguillard et al., 1998
32
91.3 [84.5, 98.1]
Ozturk et al., 2005
19
75.0 [70.5, 79.5]
Alonso-Fernández et al., 2006
31
99.8 [92.5, 107.1]
Maeder et al., 2007
63
116.0 [109.1, 122.9]
Przybylowski et al., 2007
111
85.3 [82.0, 88.6]
Maeder et al., 2008
89
110.0 [104.4, 115.6]
Cintra et al. , 2009
32
104.7 [94.1, 115.3]
Maeder et al., 2009
40
114.0 [104.7, 123.3]
Nanas et al., 2010
21
88.2 [82.4, 94.0]
Rizzi et al., 2010
27
122.0 [93.7, 150.3]
Pendharkar et al., 2011
15
60.0 [54.9, 65.1]
Ackel-D'Elia et al., 2012
12
97.8 [90.6, 105.0]
Innocenti et al., 2012
8
109.5 [99.2, 119.8]
Beitler et al., 2014
15
70.1 [61.2, 79.0]
Ozsarac et al., 2014
65
82.9 [77.9, 87.9]
Goel et al., 2015
20
49.9 [45.2, 54.6]
Tapan et al. , 2016
31
61.0 [60.2, 61.8]
Quadri et al., 2017
12
95.3 [91.0, 99.6]
89.9 [80.4, 99.5]
40.0
60.0
80.0
100.0
120.0
140.0
160.0
Mean

Table 1. Summary of findings regarding exercise tolerance ($mL \cdot kg^{-1} \cdot min^{-1}$)

First author, [ref]	Year	Participants	AHI cutoff, events·h^{-1}	Sample size, *n*	Mean AHI, events·h^{-1}	Age, years	BMI, kg·m^{-2}	Design	Sex (M/F)	VO_{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 [66]	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 [33]	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 [67]	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 [68]	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 [69]	2013	OSA	> 30	11	46.2 ± 22.6	50.3 ± 5.1	26.6 ± 3.6	Btw-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	Btw-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 [70]	2012	Morbid Obese + OSA	> 5	8	51.1 ± 24.1	44 ± 10.5	44.9 ± 7.5	Cross sectional	4/4	17.7 ± 7.3
		Morbid 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	Btw-group comparison	15/8	21.9 ± 0.8
		Control-no OSA	< 5	9	2.5 ± 1.6	40.2 ± 8.1	29.5 ± 5.5		2/7	21.9 ± 1.6

Kline [71]	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	Btw-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 [72]	2010	OSA	≥ 25	21	55 ± 13	48 ± 11	29.3 ± 2.2	Btw-group comparison	21/0	28.7 ± 4.0
		Control		10		46 ± 11	28.1 ± 1.4		10/0	34.7 ± 6.2
Ozturk [31]	2005	OSA	> 5	19	46 ± 19	46.9 ± 8.6	30.7 ± 4.6	Btw-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 [30]	2010	Lean, sedentary OSA patients	≥ 5	27	15.4 ± 9.2	52.9 ± 7.9	23.1 ± 1.6	Btw-group comparison	10/17	28.4 ± 10.0
		Controls	< 5	27	3.1 ± 1.1	52.8 ± 8.1	22.7 ± 1.7		10/17	28.6 ± 8.1
Rizzi [63]	2013	Lean OSA	AHI ≥ 5	22	22.4 ± 11.2	53.7 ± 8.1	22.1 ± 1.6	Btw-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 [32]	2004	OSA	> 5	17	33.3 (22.4)	35 (22-45) [$]	34.7 ± 7.6	Btw-group comparison	17/0	24.6 ± 7.2
		Control	< 5	10	*N/A*	35(28-54) [$]	32.5 ± 4.3		6/4	23.1 ± 5.9
Vanhecke [36]	2008	Morbid-obese OSA	AHI > 15 or AHI> 5 with ESS>10	42	32.5 ± 26.6	46.2 ± 11.0	50.5 ± 9.4	Btw-group comparison	13/29	17.6 ±4.2
		Morbid obese w/out OSA		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	Btw-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: VO_{2peak}: peak oxygen consumption; MetS: metabolic syndrome

[$] median-interquartile range, # RDI, N/A: data not available

Table 2. Summary of findings regarding exercise tolerance (% predicted)

First author, [ref]	Year	AHI cutoff	Sample size	AHI, events.hr^{-1}	Age, years	BMI, kg.m^{-2}	Design	Sex (M/F)	Equation for % predicted	VO_{2peak} (%predicted)
Ackel-D'Elia [73]	2012	> 15	12	40.5 ± 22.9	48.4 ± 9.2	28.0 ± 3.1	Baseline data of prospective study	13/0	No info	97.8 ± 12.7
Aguillard [74]	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 [66]	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 [75]	2009	> 5	32	32.5 ± 23.6	57.2 ± 10.9	27.8 ± 4.2	Btw-group comparison (men vs women)	32/0	No info	116.6 ± 27.7
			30	33.9 ± 27.6	60.5 ± 7.4	28.4 ± 6.3		0/30		91.3 ± 28.7
Goel [76]	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 [70]	2012	> 5	8	51.1 ± 24.1	44 ± 10.5	44.9 ± 7.5	Cross-sectional	4/4	Jones	109.5 ± 14.9
Maeder [51]	2009	> 5	40	37 (20-65)*	50 ± 9	30.3 ± 4.5	Cross-sectional	35/5	ATS	114 ± 30
Maeder [77]	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 [78]	2008	> 5	89	34 (17-53)*	49.5 ± 9.7	30.2 ± 4.6	Retrospective analysis	78/11	ATS	110 ± 27
Nanas [72]	2010	≥ 25	21	55 ± 13	48 ± 11	29.3 ± 2.2	Btw-group comparison	21/0	No info	88.2 ± 13.6
Ozturk [31]	2005	> 5	19	46 ± 19	46.9 ± 8.6	30.7 ± 4.6	Btw-group comparison	16/3	No info	75 ± 10

Ozsarac [56]	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 [55]	2011	≥ 15	15	48.1 ± 33.1	49 ± 6	42.6 ± 8.8	Baseline data of prospective study	6/9	ATS	60 #
Przybylowski [79]	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 et al. [52]	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 [30]	2010	≥ 5	27	15.4 ± 9.2	52.9 ± 7.9	23.1 ± 1.6	Btw-group comparison	10/17	No info	122 ± 75
Tapan [80]	2016	> 30	31	54.2 ±3.7	53.4 ± 1.5	N/A	Baseline data of prospective study	27/4	No info	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: VO_{2peak}: peak oxygen consumption
*Median interquartile range, # no SD, N/A: data not available

SUPPLEMENTAL DATA FILES

FIGURES

Figure S1. Forest plot for subgroup analysis of VO_{2peak} (in $mL \cdot kg^{-1} \cdot min^{-1}$) based on AHI. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

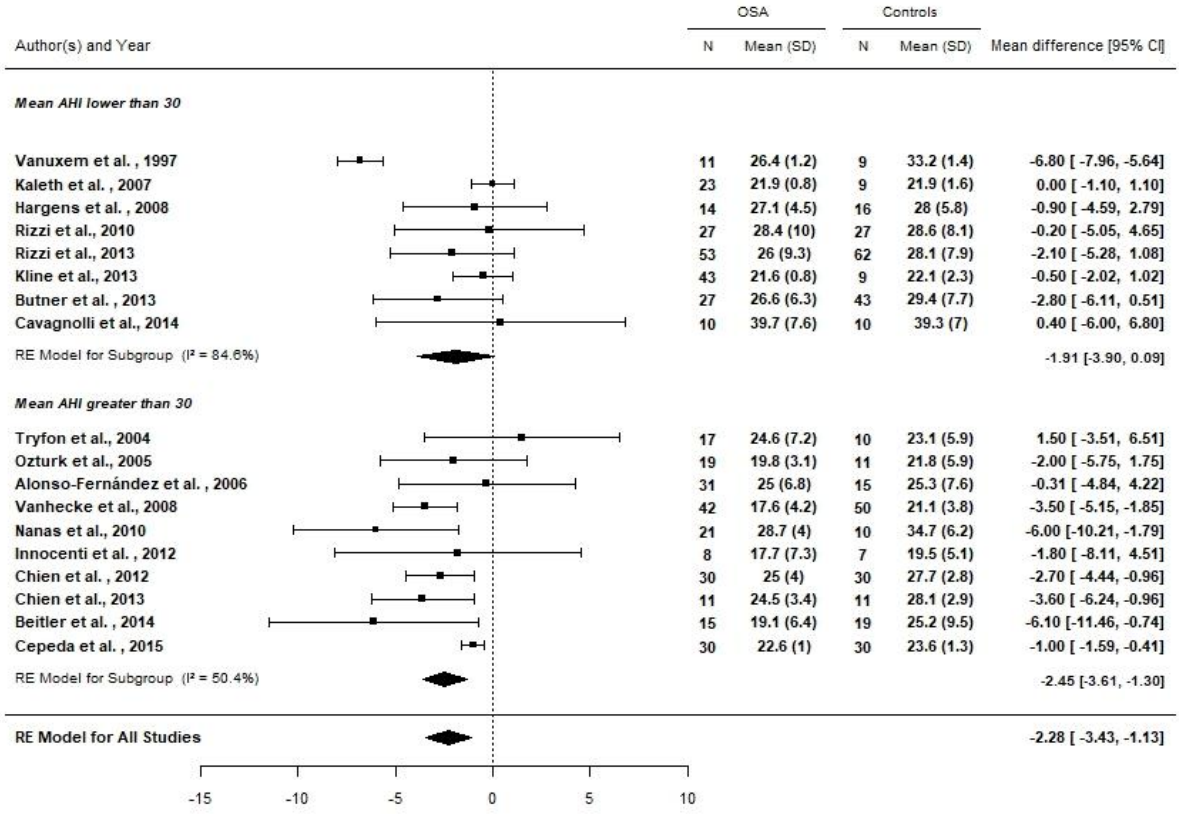


Figure S2. Forest plot for subgroup analysis of VO_{2peak} (in $mL \cdot kg^{-1} \cdot min^{-1}$) based on age. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

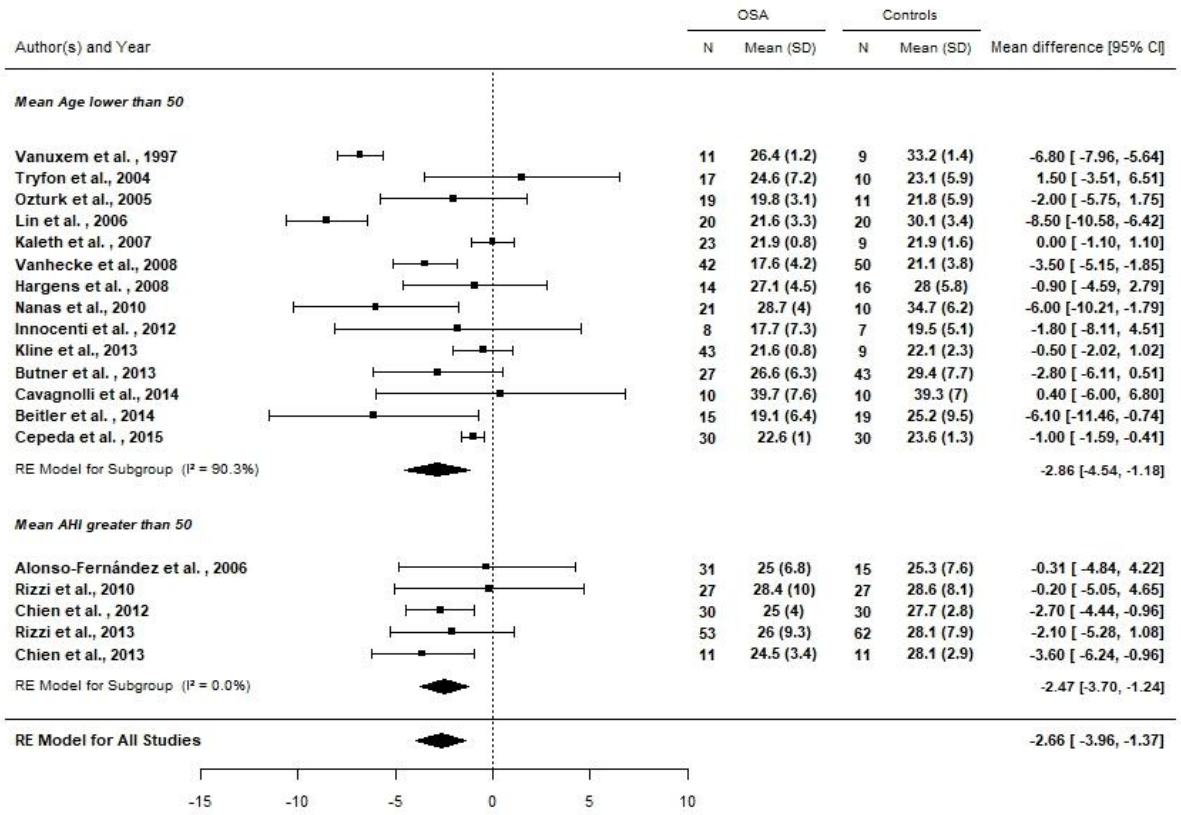


Figure S3. Forest plot for subgroup analysis of VO_{2peak} (in $mL \cdot kg^{-1} \cdot min^{-1}$) based on BMI.

The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

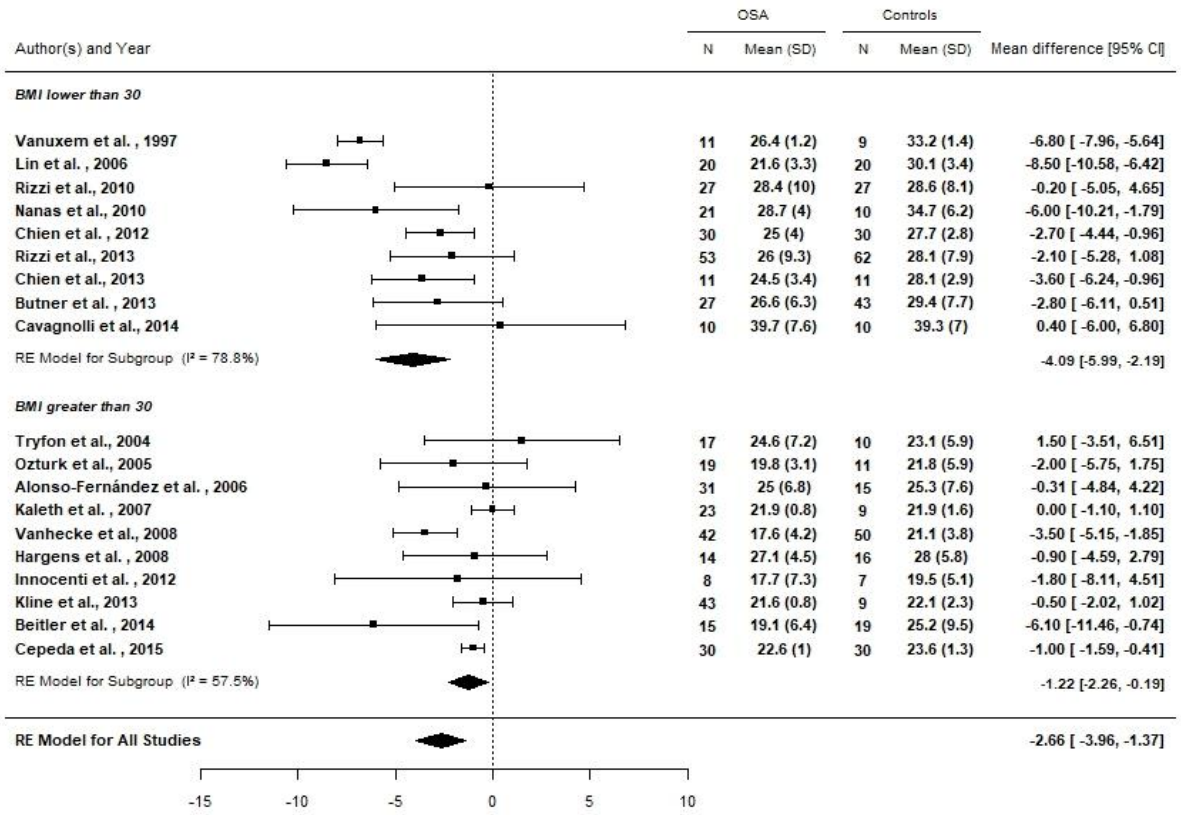


Figure S4. Forest plot for mean difference in peak heart rate (beat·min^{-1}) between OSA patients and controls. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

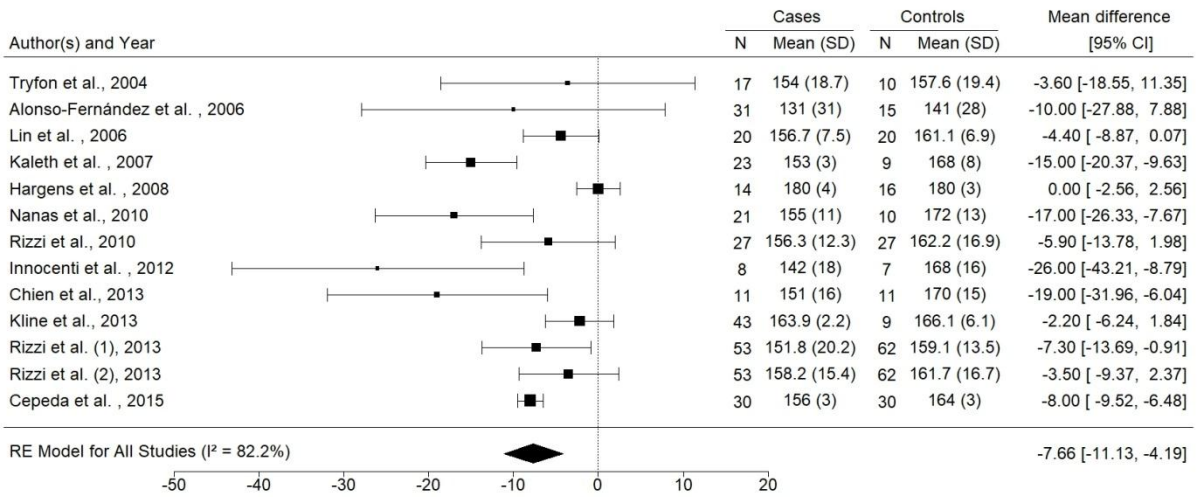


Figure S5. Forest plot for mean difference in peak diastolic blood pressure (mmHg) between OSA patients and controls. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

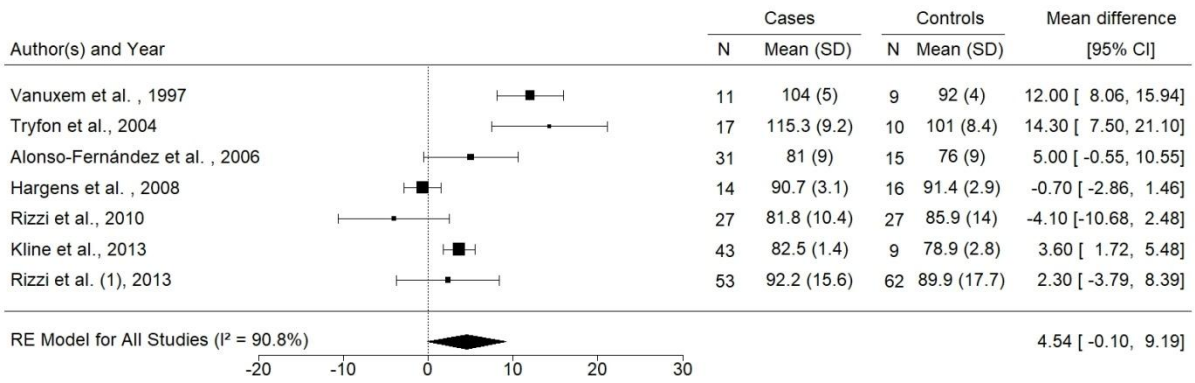


Figure S6. Forest plot for mean difference in peak ventilation ($L \cdot min^{-1}$) between OSA patients and controls. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

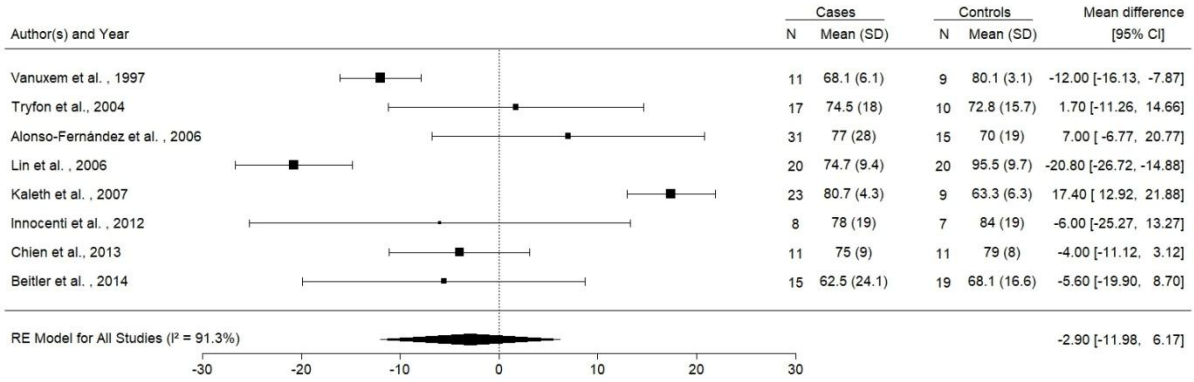


Figure S7. Forest plot for mean difference in peak oxygen pulse (beat $O_2 \cdot min^{-1}$) between OSA patients and controls. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

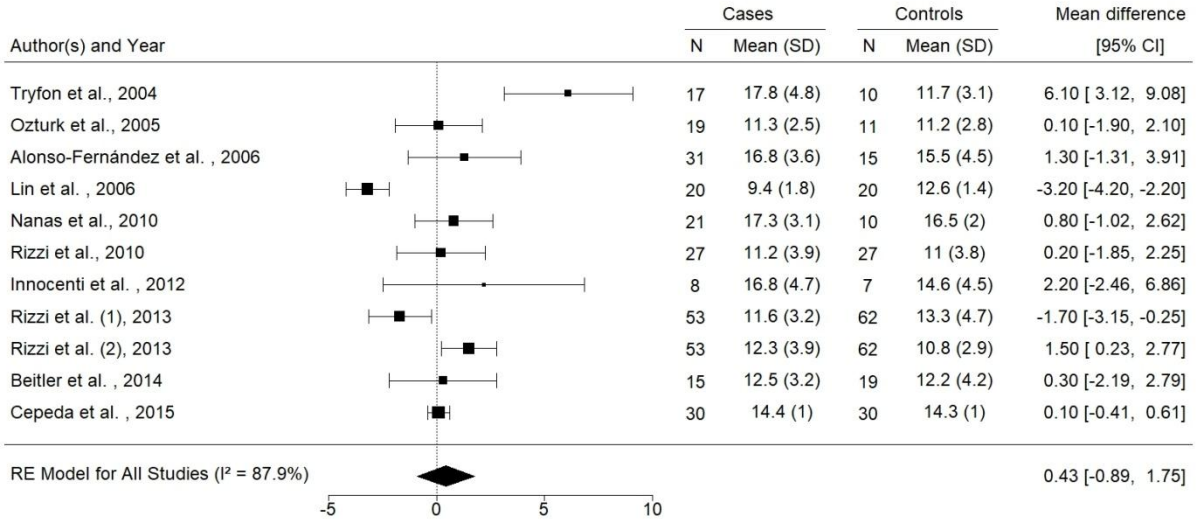


Figure S8. Forest plot for mean difference in peak systolic blood pressure (mmHg) between OSA patients and controls. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

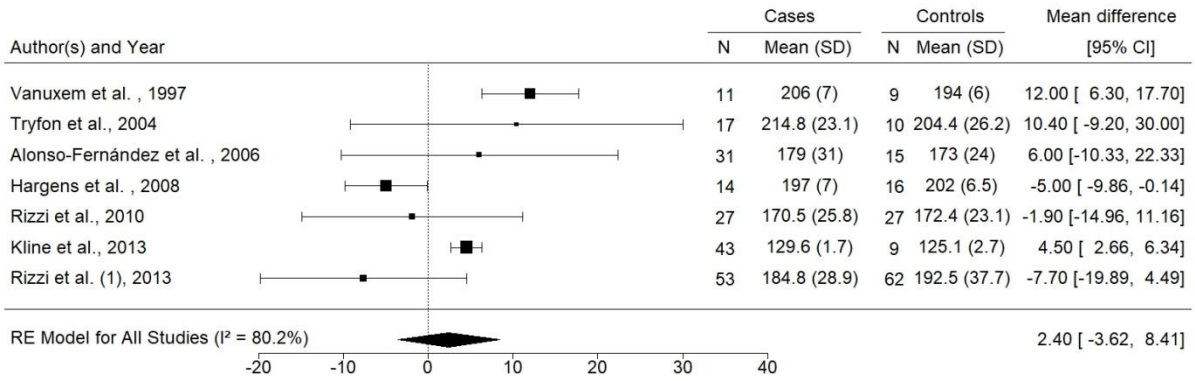


Figure S9. Quality assessment analysis for VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$

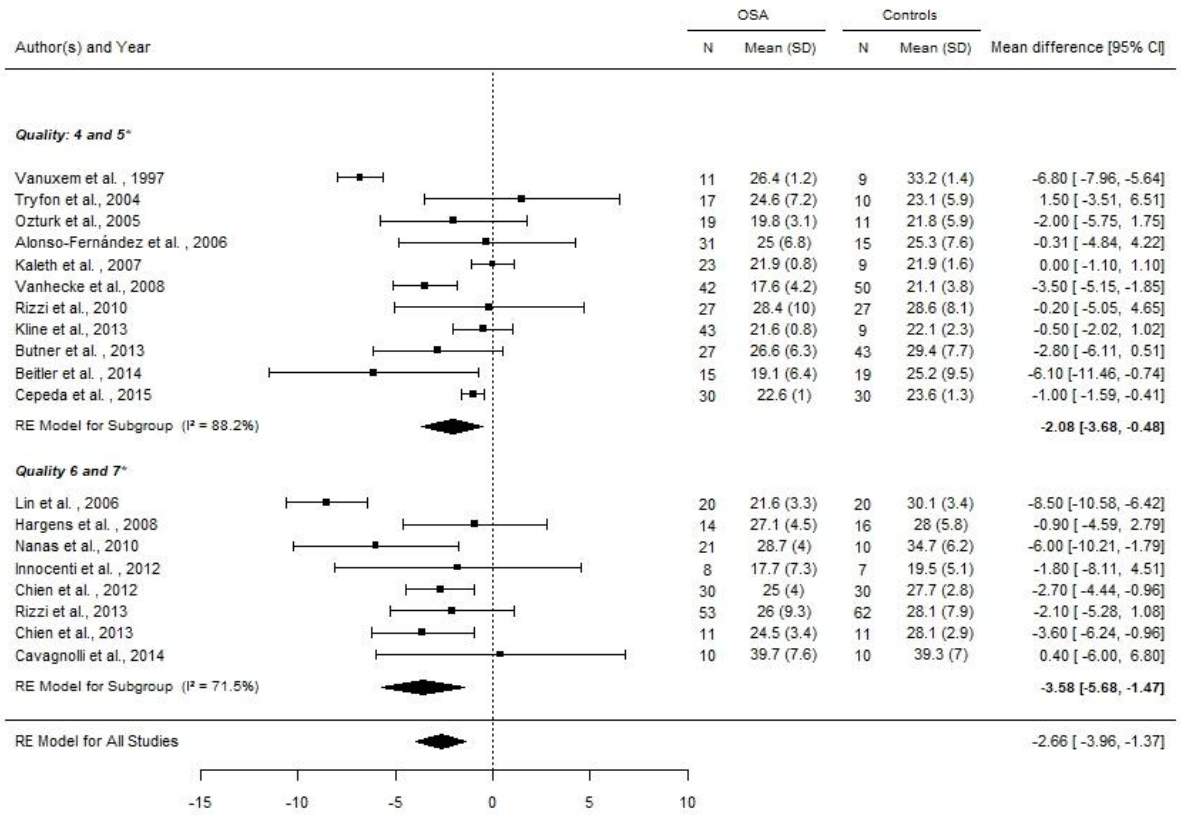


Figure S10. Funnel plot for VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$

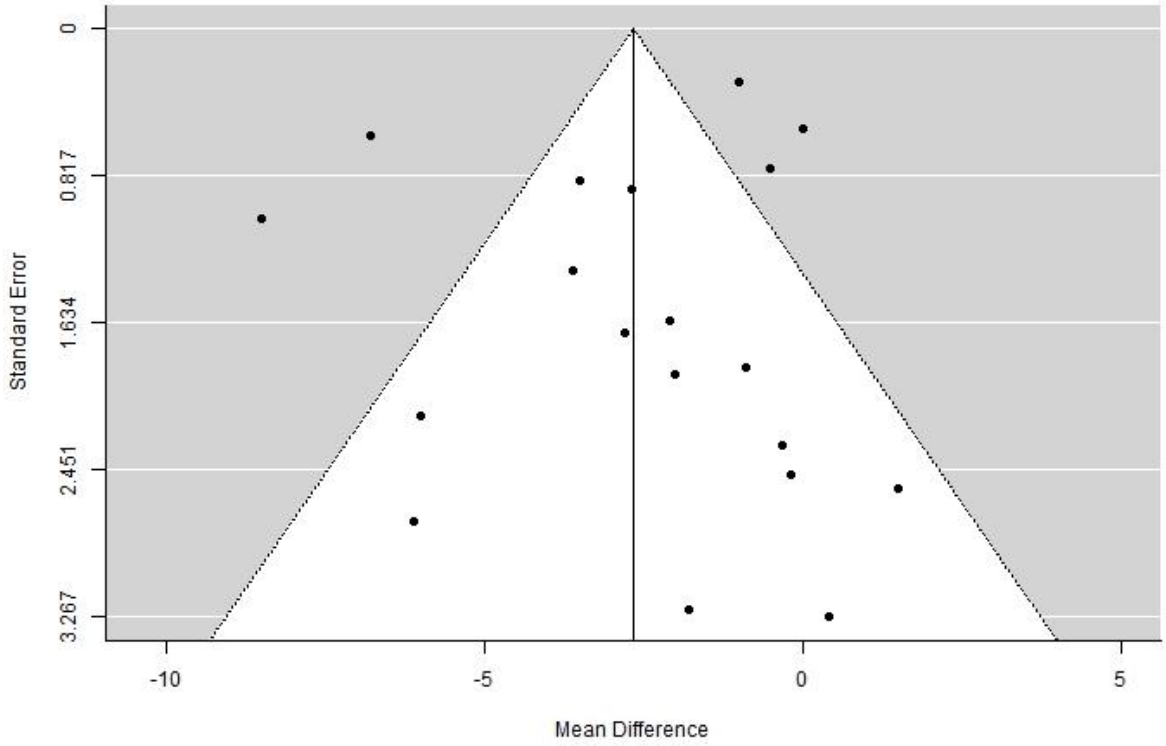


Figure S11. Forest plot for mean difference in BMI (kg/m_2) between OSA patients and controls. The diamond reflects the 95% confidence interval of the pooled estimate of mean difference.

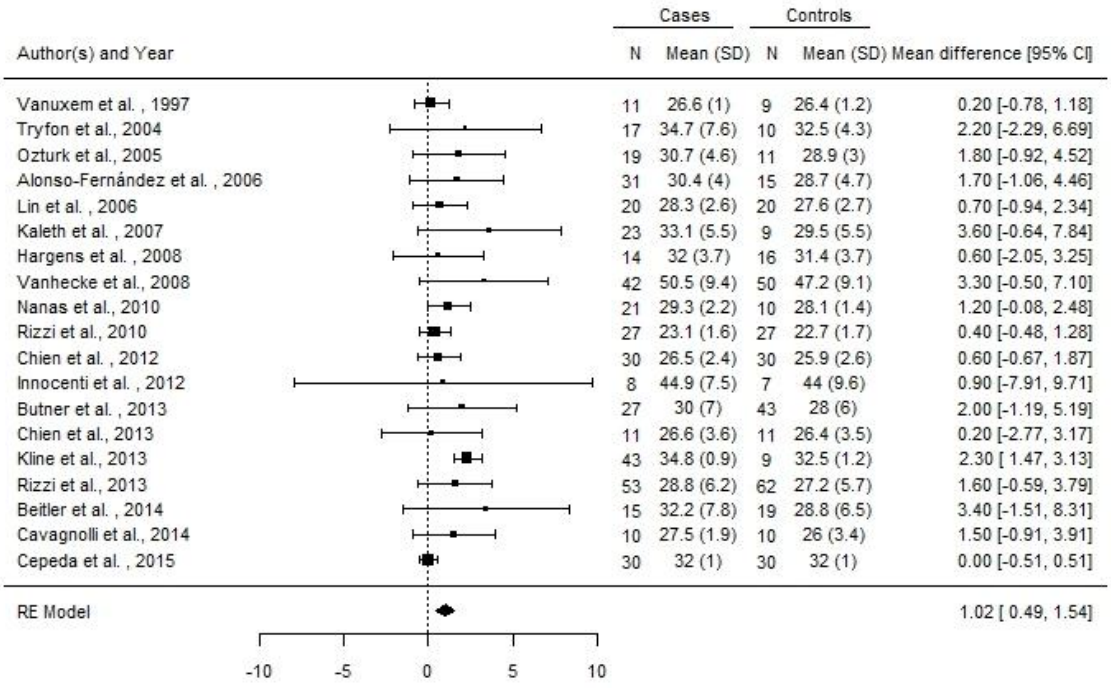


Table S1. PRISMA Checklist

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
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			
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

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.
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.

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**

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