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Quality of life of obstructive sleep apnoea patients receiving continuous positive airway pressure treatment: A systematic review and meta-analysis

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ABSTRACT

Background: Previous studies have shown conflicting results on the effect of continuous positive airway pressure (CPAP) on quality of life (QoL) in obstructive sleep apnoea (OSA) patients.
Objectives: To evaluate the effect of CPAP on QoL in OSA patients compared to sham CPAP, placebo pills, and conservative treatment.
Methods: Studies were identified via Web of Knowledge, PubMed, PsychInfo, CINAHL, EMBASE, OpenGrey, and the Cochrane Library. Subgroup analyses and sensitivity analyses were conducted to assess the robustness of the findings.
Results: Meta-analysis of 13 randomised controlled trials showed no significant differences in overall and psychological QoL comparing values of CPAP treated patients with controls; however, physical QoL improved. CPAP significantly affected the overall QoL in studies with controls receiving sham CPAP, parallel design, low risk of bias, and mild OSA patients.
Conclusion: CPAP treatment may help to improve physical symptoms of OSA, whereas impaired psychological QoL still cannot be alleviated.

Introduction

Obstructive sleep apnoea (OSA) is an incapacitating chronic disease characterized by repetitive sleep-related episodes of complete (apnoea) or partial (hypopnoea) breathing pauses. It is a prevalent disorder associated with a multitude of adverse outcomes.[1] Symptoms of OSA include snoring, sleepiness, and fatigue.[2] Most studies have found that OSA concerns 2–10% of the adult population.[3,4] The prevalence of undiagnosed OSA syndrome in Western countries is up to 5%.[5] The impact of OSA on both morbidity and socioeconomic costs is enormous. Costs concern, in particular, health care expenditures and reduced work capacity and work participation.[3,6] Although the exact costs are difficult to calculate, data from 106 countries showed that increased healthcare spending to treat undiagnosed OSA varies between 1950 and 3899 dollars per patient per year.[7]

OSA is associated with poor quality of life (QoL)[6,8,9] and has been linked to severe public health issues, such as obesity, diabetes, metabolic syndrome, cardio-vascular diseases,[3,10] and neuropsychiatric problems.[10] The occurrence of an impairment in cognitive functioning, reduced vigilance,[11] microsleeps or accidents is typical in people with OSA.[12] Sharafkhaneh et al.[8] showed a significantly higher prevalence of mood disorders, posttraumatic stress disorder, psychosis and dementia among OSA patients. Some studies report an increased prevalence of suicidal ideation in OSA patients when compared to the general population.[13]

In terms of treatment, continuous positive airway pressure (CPAP) is the first treatment of choice in most OSA patients.[14] CPAP has been reported to be effective in reducing OSA symptoms, cardiovascular morbidity and mortality, neurocognitive consequences and sleepiness, and in improving QoL.[15–18] Krahn et al.[19] described a decrease in depression and suicidal ideation in untreated OSA patients immediately after the initiation of CPAP treatment. In recent years, increasing attention has been paid to the effectiveness of CPAP treatment on QoL improvement. The efficiency of OSA treatment has typically been judged based on polysomnography (PSG) outcomes. However,

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patients' reports of improvement were often found to be discordant with PSG results. Thus, other clinically important outcomes, including QoL and functional status, have been recommended as complementary outcomes in the evaluation of treatment response.[20]

Previous meta-analyses[18,21,22] and systematic reviews[15,23] and have shown conflicting results on the effect of CPAP treatment on QoL in OSA patients. The findings vary from improvement of QoL after receiving CPAP treatment[15,23] to improvement in the physical QoL domain only,[21] or overall QoL improvement only when disease specific QoL measures,[22] and also when all prospective studies, i.e. not only randomised controlled trials (RCTs),[18] were included.

Furthermore, earlier meta-analyses of RCTs included only one type of QoL measure[18]; analysed studies focusing exclusively on elderly OSA patients[18,21,23] and included studies where the whole sample of OSA patients suffered from major comorbidities, such as stroke or heart failure,[18,21,22] or studies of a combination of CPAP treatment with conservative treatment.[21,22] We therefore aimed to systematically evaluate the effect of CPAP treatment on QoL in OSA patients compared to sham CPAP, placebo pills, and conservative treatment. Our systematic review and meta-analysis was restricted to RCTs only, with the exclusion of studies having a clear focus on major comorbidities, populations of children or elderly OSA patients, and studies that combined CPAP treatment with conservative treatment.

Methods

A systematic literature review was conducted in accordance with the current guidelines for systematic reviews and meta-analyses.[24] The multidisciplinary systematic review team consisted of six reviewers (VT, IN, SAR, RT, JPvD, and UB). Two authors had expertise in psychology (VT, IN), one in pulmonology, tuberculosis and respiratory diseases (RT), and three authors were trained in epidemiological methods and public health (SAR, JPvD, and UB).

Formulation of the research question

The research question was formulated according to the PICO method,[24] i.e.: 'In obstructive sleep apnoea patients, what is the effect of CPAP treatment on QoL compared to placebo pills, sham CPAP, and conservative treatment?' The anticipated *outcome* was improved overall QoL as well as the improvement in psychological and physical QoL after CPAP treatment.

Search strategy and study identification

Studies were identified via Web of Knowledge, PubMed, PsychInfo, CINAHL, EMBASE, and the Cochrane Library from the inception date of the databases to March 2019. OpenGrey database was searched for any resources that might have been missed. Previous systematic reviews, meta-analyses, and guidelines were sought, and their reference lists were scanned. We did not include dissertations, economical evaluations, technical reports, conference abstracts, case studies, and letters. We did not use any language restrictions. Titles and abstracts were screened to identify potentially relevant studies. If the suitability of an article was uncertain, the full text was reviewed. We used keywords (Table 1) according to the PICO method.[24] The detailed literature search strings for each of the databases can be found in Appendix A. Inclusion criteria were: RCTs examining the effect of CPAP treatment on QoL in OSA patients compared to controls using placebo pills, sham CPAP, or conservative treatment.

Table 1
Description of used keywords according to the PICO method.

P = population/patients/problem	'sleep apnea', 'sleep apnoea', 'OSA'
I = intervention	'continuous positive airway pressure', 'CPAP'
C = comparison/control	'placebo pills', 'sham CPAP', 'conservative treatment'
O = outcome	'quality of life', 'health status', 'self-rated health', 'self-perceived health', 'functional status'

Exclusion criteria

We excluded reviews, meta-analyses, studies focusing only on compliance with CPAP treatment or side effects of CPAP and different healthcare services, studies including only baseline comparison without a control group, and studies focusing on other types of treatment, or a combination of CPAP treatment with conservative treatment, such as lifestyle interventions. Studies including children, adolescents (<18), and elderly OSA patients (≥65 years of age) only were also excluded because of a possible increased vulnerability, functional changes, and a decline in abilities and/or performance related to age. Since major comorbidities may influence QoL, sleep, and affective symptomatology,[25] studies including a primary study sample with an acute or severe comorbid medical illness, such as stroke, neurological disorders, heart failure, myocardial infarction, cognitive decline, or psychiatric diagnoses, were also excluded. The verification of the presence of major comorbidities in the full sample of OSA patients was based on Title, Abstract, and full-text screening.

We developed a form to standardize the first selection of relevant studies, based on the following criteria: 1) the study is an RCT, quantitative, and interventional; 2) the study population consists of adult OSA patients diagnosed by a medical professional; 3) the intervention is CPAP, and a control condition is present; and 4) generic or disease-specific QoL is measured. The title, abstract, and full-text screening were conducted independently by VT and IN. Disagreements were resolved by reaching a consensus of opinion. A third author (UB) was invited if consensus could not be achieved. Full-text screening was conducted by VT.

Types of studies

We included RCTs with parallel[26–32] and crossover design.[33–38]

Type of participants

Included were OSA patients newly diagnosed by a medical professional using nocturnal, laboratory-based PSG or oximetry. The standard criterion of five or more apnoeas/hypopnoeas per hour of sleep was used to diagnose OSA by PSG. OSA patients were diagnosed as mild, moderate and severe, with an AHI greater than 5/h, 15/h, and 30/h, respectively.[39] In oximetry, an apnoea was defined as a minimum of 10 s of airflow cessation, and a hypopnoea was determined by a 30% reduction in airflow preceding a period of normal breathing for a minimum of 10 s and oxyhemoglobin desaturation (decrease in SpO_2 ≥4%).[40] Severity of OSA was measured by the number of falls in arterial oxygen saturation (SaO_2) of more than 4% in each hour of study.[26] All participants were treatment naïve at the start of the research. Controls/comparisons were defined as placebo pills, sham CPAP, and conservative treatment.

The intervention

The intervention was defined as CPAP treatment with a duration of at least two weeks. CPAP devices were titrated to an effective pressure to overcome respiratory disturbances.

Concept of quality of life and health-related quality of life

The World Health Organization Quality of Life (WHOQoL) group defined QoL as 'an individual's perception of their position in life, in the context of the culture and values in which they live and in relation

to their goals, expectations, standards and concerns'.[41] QoL has several domains, such as functional competence, health-related complaints, and psycho-social functioning. Health-related QoL (HRQoL) is understood as an integral QoL domain and is increasingly used as an outcome of treatment effectiveness. In broad terms, HRQoL serves as a restricted QoL definition, as it was designed to exclude external domains, such as housing, financial situation, living conditions or spirituality. HRQoL is associated with an expanded concept of health status, embracing social interaction as well as emotional and psychological well-being.[42] The concepts of QoL and HRQoL are closely tied to each other.[43] When QoL is discussed in relation to health or diseases, it almost always means HRQoL, unless specified otherwise.[43] According to Schipper[44] QoL in clinical medicine represents the functional effect of disease and its consequent treatment upon patient, as perceived by the patient. It is concluded that the concept of HRQoL as used now is confusing as most of the definitions fail to distinguish between HRQoL and health or between HRQoL and QoL.[45,46] Perhaps more reasonable is the variant of the definition, where HRQoL is the aspects of QoL the most significantly affected by ill health. However, in practice, this definition may not eliminate the number of QoL domains much because it is problematic to define 'most'.[46] Furthermore, most of the previous systematic reviews and meta-analyses[15,21,22,47] as well as all RCTs included in our meta-analysis used the term QoL, while one RCT used both terms interchangebly.[29] Thus, we will use in this paper the term QoL, with omission of external domains, such as spirituality or living conditions.

Main comparisons

Based on the type of QoL scales we aimed to conduct the following comparisons: a) the effect of CPAP treatment on overall QoL (using general QoL scales); b) the effect of CPAP treatment on psychological QoL (using psychological QoL subscales); c) the effect of CPAP treatment on physical QoL (using physical QoL subscales).

Sensitivity analyses

We conducted sensitivity analyses to reveal the potential sources of heterogeneity, such as the number of participants in analysed studies, the duration of CPAP treatment, the level of compliance with CPAP treatment, and risk of bias (RoB). We repeated the analyses with restrictions regarding: *a) number of participants* $N > 100$ (the effect of CPAP treatment on overall/psychological/physical QoL in RCTs involving participants of $N > 100$[48,49]; *b) duration of CPAP treatment >6 weeks* (the effect of CPAP treatment on overall/psychological/physical QoL in RCTs with duration of CPAP treatment of more than 6 weeks); *c)* compliance level ≥4 h/night (the effect of CPAP treatment on overall/psychological/physical QoL in RCTs involving participants with CPAP compliance level of ≥4 h/night); and *d) low RoB* (the effect of CPAP treatment on overall/psychological/physical QoL restricted to RCTs with low RoB).

Subgroup analyses

We analysed how the CPAP treatment effect varies across different subgroups of patients or trials. The covariates included type of control group, OSA severity, study design, and type of QoL measures. The following subgroup comparisons were conducted based on: *a) type of control group* (the separate analyses of the effect of CPAP treatment on overall/psychological/physical QoL in RCTs involving controls using placebo pills, sham CPAP, and conservative treatment); *b) OSA severity* (the separate analyses of the effect of CPAP treatment on overall/psychological/physical QoL in RCTs involving patients with mild OSA and moderate to severe OSA); *c) study design* (the separate analyses of the effect of CPAP treatment on overall/psychological/physical QoL in RCTs with a crossover design and parallel design); d) *type of Qol measures* (the separate analyses of the effect of CPAP treatment on overall/psychological/physical QoL in RCTs using generic QoL measures and disease-specific measures).

Data extraction and management

Two authors (VT, IN) extracted the following information from each study: *a) general:* title, country, language of publication, year of publication; *b) methods:* study design, setting, inclusion and exclusion criteria, follow-up, standardized QoL instruments, QoL domains; *c) participants:* OSA diagnosis, adult population (age of the whole group >18 years, ≤65 years), no focus on major comorbidid diseases other than OSA (such as stroke, myocardial infarction, neuropsychiatric disorder), age, sex distribution; *d) intervention per treatment group:* use of CPAP treatment, duration of CPAP treatment; compliance with CPAP treatment; *e) controls/comparisons*: placebo pills, sham CPAP, conservative treatment; *f) outcomes:* QoL improvement, overall QoL scores, and psychological/physical QoL; *g) results:* CPAP treatment effect on QoL improvement in OSA patients. In case of disagreement in data extraction, consensus was achieved by discussion between the two review authors (VT, IN). If needed, a third author (UB) was invited to resolve disputes. Mean differences between the groups for the continuous outcomes, and standard deviations/standard errors of the group differences were extracted for the meta-analysis.

Dealing with missing data

When information for the meta-analysis was missing, we asked the author to provide the information. If the author did not reply, or the information was no longer available, the study was not included in the meta-analysis.

Assessment of risk of bias

The risk of bias (RoB) was assessed by two authors (VT, UB) using the Cochrane Collaboration tool for assessing RoB, as described in the *Cochrane Handbook for the Systematic Review of Interventions*, version 5.1.0.[24] The following nine criteria were assessed: Random sequence generation, Allocation concealment, Blinding of participants, Blinding of personnel, Blinding of outcome assessment, Co-interventions avoided, Treatment fidelity, Incomplete outcome data and Selective outcome reporting. We scored the criteria as 'low RoB, 'high RoB', or 'unclear RoB'.[24] When the two independent authors disagreed about the RoB, they tried to reach a consensus. If consensus could not be achieved, a third author (IN) was invited in. Key domains for summary RoB assessment were identified, such as random sequence generation, allocation concealment, and incomplete outcome data.[50] We judged studies to have a high RoB when one or more key domains were rated as high RoB. We judged studies to have an unclear RoB when one or more key domains were rated as "unclear". We judged studies to have a low RoB when all the key domains were rated as low RoB.[24,50] Subsequently, we calculated the proportion of items that were scored as having low, unclear, or high RoB.

Assessment of heterogeneity

Heterogeneity was investigated using Cochrane's Q statistic and I^2 statistics. Due to differences in sample sizes of the included studies, we used random-effects models, as study weights were defined to be more balanced under the random-effects model than under the fixed-effects model.[51] Furthermore, when studies are gathered from the published literature, the random-effects model is found to be generally a more plausible match.[51] As Cochrane's Q is considered to be vulnerable to small sample sizes, the I^2 provided an estimate of the proportion of real variance caused by extraneous study variables.

I^2 thresholds have been proposed,[52] with 25, 50, and 75% representing low, moderate, and high variance, respectively.

Assessment of reporting biases

Visual inspection with funnel plots and the Egger test[53] were used to evaluate publication bias in the reviewed studies.

Quality of the evidence

We applied GRADE criteria[54] to assess the confidence in the estimated effects within the studies. Two reviewers (VT, IN) worked independently to assess the quality of the evidence and resolve disagreements. At the start of the GRADE assessment we assumed the presence of high quality for all included studies. We downgraded a starting rating of "high quality" evidence by one level (or by two levels for very serious concerns) for RoB, inconsistency, indirectness, imprecision, and publication bias.[54]

We considered random sequence generation, allocation concealment, and incomplete outcome data as prerequisites for high quality (following Nieuwenhuijsen et al.[50]). We only considered studies with low risks on these items to have a low RoB. To assess the RoB for a comparison, we considered the RoB for each study included in that comparison (following Ryan and Hill[54]). For each comparison we downgraded the quality due to the RoB (−1) if most of the outcome information was from studies at low or unclear RoB, as this could seriously alter the results. We applied a −2 downgrade in case of a high RoB for one criterion, or multiple criteria, that were considered as likely to very seriously alter the results. For inconsistency, we considered an I^2 value of 50% to 75% downgrade (−1). Indirectness of the evidence was not an issue in our review, as all comparisons in the included studies directly addressed the comparison. For imprecision of results, we judged serious imprecision leading to downgrading (−1) if a comparison either included less than 400 participants or a wide CI around the effect estimate. For a non-significant effect, we considered a CI to be wide if it included an effect size of both 0 and a moderate effect size (>0.5 or <−0.5). For a significant effect, we considered a CI to be wide if it included both a small and large effect size (small = 0.2 or −0.2; large = 0.8 or −0.8). We applied a −2 downgrade in case of imprecision based on the both assessed points.

In the GRADE system, the quality of evidence for each outcome is scored as high, moderate, low, or very low. In high quality studies, further research is very unlikely to change our confidence in the estimate of effect. In studies with moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality of evidence means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. In studies with very low quality of the evidence any estimate of effect is very uncertain.[54]

Measures of treatment effect and data synthesis

A total of 13 RCTs were included in the MA. The analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS 23) and Microsoft Office Excel, following Neyeloff et al.[55] We used random-effects models by calculating the Cohen's d effect sizes (ES) with their standard errors (SE) as the standardized outcome of the CPAP treatment effect.[56] ES was calculated for each QoL outcome for which a complete assessment was possible. ESs were calculated from means and standard deviations (SD). When the SD was not available it was calculated from the SE of the mean using the following formula: $SD = SE\sqrt{N}$. Cohen's d ES was calculated according to the following formula:

$$ES = \frac{\text{mean controls} - \text{mean CPAP}}{\text{pooled SD}};$$

ES was positive, if the mean difference was in the predicted direction and favoured real CPAP treatment (where 0.20–0.40 means a small ES; 0.50–0.70 a medium ES; and 0.80 or higher a large ES). The comparison of CPAP treatment effect vs. the control group was described as: 'negative direction of ES' for differences favouring the control group; and 'positive direction of ES' for differences favouring the real CPAP treatment group. Finally, the effect summary ($\overline{ES_V}$) was computed using a random effects model by calculating a new weight (w_v) for each QoL outcome adjusted with the constant (v). $\overline{ES_V}$ was calculated using the following formula: $\overline{ES}_V = \frac{\sum(W_V * ES)}{\sum W_V}$. Additionally, the confidence intervals (CIs) for the ES of each study and $\overline{ES_V}$ were computed with the 95% confidence coefficient used as the default, following Hedges and Olkin.[56] CIs were calculated with the formula CI = $ES \pm 1.96.\ SE$. Forest plots were used for graphical representations of the MA.

Results

Results of the search process

After title, abstract, and full-text screening, 13 RCTs describing the effectiveness of CPAP treatment met the inclusion criteria (see flowchart Fig. 1). One of the eligible studies[57] was excluded from our MA, as we did not receive the missing, additional information.

Description of included studies

All studies included in our meta-analysis investigated whether real CPAP treatment affected QoL more significantly compared to the control condition. Seven RCTs had a parallel design and six RCTs had a crossover design. As the study by Montserrat et al.[28] combined a partial crossover and parallel design, we analysed the parallel comparisons only. The duration of CPAP treatment ranged between 3 and 24 weeks. Most of the studies used only one treatment centre, two studies were multi-centre studies.[27,32] Data in all the studies were collected during the patients' clinical visits.

A total of 678 participants formed the control group and 795 participants received real CPAP treatment. The number of participants in the reviewed studies varied between 8[33] and 409.[32] The reported ages of the patients ranged from 25 to 72 years. The number of female patients varied from 0 to 103. Two studies[26,30] included only male OSA patients. In all included RCTs, all subjects underwent a baseline assessment with PSG first and were then randomised to CPAP, treatment with placebo pills, sham CPAP, or conservative treatment (Table 2). Oximetry was used to diagnose OSA in one study.[26] Patients suffered from mild to severe OSA.

Five crossover studies[33–37] compared CPAP treatment with placebo pills. With the permission of local ethic committee, patients were informed that the oral placebo tablet (Glaxo pills, UK) may improve their daytime function in total of three studies.[33–35] In two studies[36,37] no specific information on placebo pills was provided.

Six parallel[26–28,30–32] and one crossover study[38] used a machine set at subtherapeutic pressure, connected to a mask with holes to produce a leak as placebo (sham CPAP). Chakravorty et al.[29] conducted a study with parallel design and used conservative treatment, including weight loss and sleep hygiene, to compare with CPAP treatment.

When a repeated measures design was used,[32] the longer duration of CPAP treatment on QoL was analysed. If possible, we also included groups of participants with a higher compliance level (≥4 h/night)[32,33] and a longer treatment duration[32] in the final meta-analysis. If more than one similar QoL estimator was used,[29,30] we used the estimator that could provide us with the most comprehensive information related to QoL. More detailed information about the study design, number of included participants, disease severity, type of control group, duration of the intervention, and instruments used to

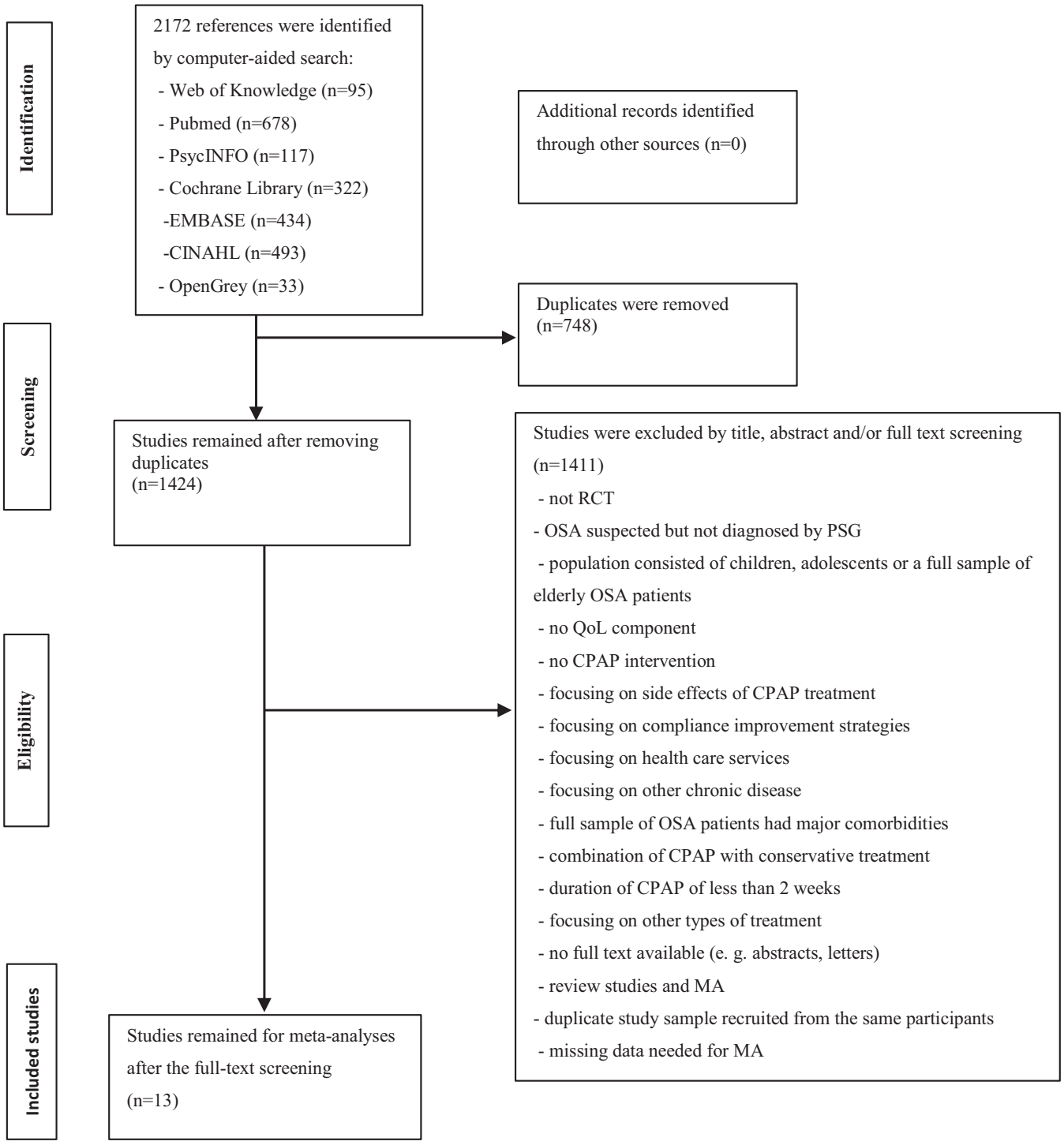

Fig. 1. Flow diagram of study selection process.[58]

measure QoL is provided in Table 2. The criteria for inclusion and exclusion of the participants in the particular study type, sociodemographic data, clinical data, and mean values of CPAP compliance are presented in Table B.1, Appendix B.

Quality of life measures

QoL was measured using generic questionnaires – the Short Form 36 Health Survey – (SF-36), the Nottingham Health Profile (NHP), the European Quality of Life Questionnaire (EuroQoL) and disease specific QoL questionnaires – the Calgary Sleep Apnea Quality of Life Index (SAQLI) and the Functional Outcomes of Sleep Questionnaire (FOSQ). Out of the 13 analysed RCTs, 12 studies measured overall QoL and four studies assessed the level of psychological and physical QoL.

Risk of bias in the included studies

As shown in Table 3, we considered the overall RoB to be high in three studies.[29,30,37] These studies had either unclear[29,37] or inadequate[30] allocation concealment. Two[29,37] of these three studies also

Table 2
Overview of the included studies.

Study	Design	*N*	OSA severity	Intervention, type of control group, treatment duration	d; 95%CI	QoL instruments
Engleman et al.[33 a]	-RCT, Crossover	-8 patients with compliance ≥5	Mild	-CPAP patients/ placebo pills	1.07; 95%CI (−0.72; 2.14)	NHP
Scotland		-8 CPAP 8 controls		-1 month		
Engleman et al.[34 a]	-RCT, crossover	-23 CPAP	moderate to severe	-CPAP patients/ placebo pills	0.09; 95%CI (−0.73; 0.91)	NHP
Scotland	-single blind	-23 controls		-1 month		
Engleman et al.[35 a]	-RCT,	-34 CPAP	mild	-CPAP patients/ placebo pills	0.24; 95%CI (−0.43; 0.92)	NHP
Scotland	-crossover	-34 controls		-1 month		
Jenkinson et al.[26]	-RCT, parallel	-52 CPAP	moderate to severe	-CPAP patients/ sham CPAP	1.00; 95%CI (0.46; 1.25)	SF-36 mental component
UK	-double blind	-49 controls		-1 month	0.38; 95%CI (0.01; 0.76)	SF-36pphysical component
Barbé et al.[27]	-RCT, parallel	-29 CPAP		-CPAP patients/ sham CPAP	−0.10; 95%CI (−0.63; 0.44)	SF-36 mental component
Spain	-double blind	-25 controls	severe	-1.5 month	0.19; 95%CI (−0.34; 0.73)	SF-36 physical component
					−0.27; 95%CI (−0.73; 0.54)	FOSQ
Faccenda et al.[36]	-RCT, Crossover	-68 CPAP	moderate and severe	-CPAP patients/ placebo pills	0.16; 95%CI (−0.30; 0.60)	FOSQ
UK		-68 controls		-1 month		
Montserrat et al.[28]	-RCT parallel, (partial crossover)	-23 CPAP	moderate and severe	-CPAP patients/ sham CPAP	0.52; 95%CI (−0.08; 1.11)	FOSQ
Spain	-double blind	-22 controls		-1.5 month	−0.30; 95%CI (−0.89; 0.29)	SF-36 mental component
					0.21; 95%CI (−0.38; 0.79)	SF-36 physical component
Chakravorty et al.[29]	-RCT, Parallel	-32 CPAP	moderate to severe	-CPAP patients/ CT controls	0.00; 95%CI (−0.07; 0.07)	EuroQoL (Usq)
UK		-21 CT controls		-3 months		
Barnes et al.[37]	-RCT, crossover	-80 CPAP	mild to moderate	-CPAP patients/ placebo pills	0.00; 95%CI (−0.48; 0.48)	FOSQ
Australia		-80 controls		-3 months		
Marshall et al.[38]	-RCT, crossover	-29 CPAP	mild	-CPAP patients/ sham CPAP	0.30; 95%CI (−0.50; 1.10)	FOSQ
New Zealand		-29 controls		-3 weeks		
Siccoli et al.[30]	-RCT, parallel	-50 CPAP	moderate to severe	-CPAP patients/ sham CPAP	0.42; 95%CI (−0.14; 0.97)	SF-36 mental component
UK	-double blind	-49 controls		-1 month	0.04; 95%CI (−0.35; 0.44)	SF-36 physical component
					0.44; 95%CI (−0.12; 0.99)	SAQLI
Weaver et al.[31]	-RCT, parallel	-113 CPAP	mild to moderate	-CPAP patients/sham CPAP/	0.41; 95%CI (0.14; 0.67)	FOSQ
USA	-double blind	-110 controls		-2 months		
Batool-Anwar et al.[32]	-RCT, parallel	-249 CPAP -160 controls CPAP with compliance >4	mild to severe	-CPAP patients/sham CPAP/-6 months	0.14; 95%CI (−0.06; 0.34)	SAQLI
USA	-double blind	*Subgroup analyses* -mild OSA -16 controls -37 patients with compliance >4		-6 months	−0.13; 95%CI (−0.72; 0.46)	
		-moderate to severe OSA -98 controls -146 OSA patients with compliance >4		-6 months	0.27; 95%CI (0.01; 0.53)	

CPAP: continuous positive air pressure; QoL: quality of life; RCT: randomised control trial; d: effect sizes for subscales comparison of CPAP effect vs. control group; (d− a statistically significant difference favouring the control group; d+ a statistically significant difference favouring the treatment group); 0.20–0.40 - small effect size; 0.50–0.70 - medium effect size; 0.80 ≥ large effect size. CI: confidence interval, CT: conservative treatment.

[a] All participants in the studies by Engleman et al.[33–35] were recruited from the new attenders at the sleep clinic.[35]

had incomplete outcome data. We considered seven studies to have an overall unclear RoB.[26–28,31–34] We judged three studies to have low RoB.[35,36,38] Fig. 2 shows the proportion of items that were scored as low, unclear, or high RoB.

Assessment of reporting biases

A total of three estimators favoured the control group, and two estimators showed no difference in CPAP treatment effects when compared to controls (Fig. 3a–c). In general, the funnel plots showed a low possibility of publication bias. The results of the Egger tests for publication bias were not significant for the overall QoL ($p = 0.59$), the psychological QoL domain ($p = 0.44$), and the physical Qol domain ($p = 0.29$).

Meta-analyses

Meta-analyses were conducted with 13 RCTs. ESs were computed for overall QoL and the physical and psychological domains. $\overline{ES_V}$ was

Table 3
Risk of bias assessment.

Study ID	Level of RoB[a]	a	b	c	d	e	f	g	h	i
Engleman et al.[33]	unclear	?	?	–	–	?	+	+	+	+
Engleman et al.[34]	unclear	+	?	+	–	–	+	+	+	+
Engleman et al.[35]	low	+	+	–	–	?	+	+	+	+
Jenkinson et al.[26]	unclear	+	?	+	+	?	+	?	+	+
Barbé et al.[27]	unclear	+	?	+	+	+	+	+	+	+
Faccenda et al.[36]	low	+	+	–	?	+	+	?	+	+
Montserrat et al.[28]	unclear	+	?	+	?	+	–	+	+	+
Chakravorty et al.[29]	high	+	?	–	–	?	+	?	–	+
Barnes et al.[37]	high	+	?	–	–	?	+	+	–	+
Marshall et al.[38]	low	+	+	–	+	?	+	+	+	+
Siccoli et al.[30]	high	+	–	+	+	–	+	+	+	+
Weaver et al.[31]	unclear	?	?	+	+	+	?	+	?	+
Batool-Anwar et al.[32]	unclear	+	?	+	+	?	+	+	+	+

+ Low risk of bias; – High risk of bias; ? Unclear risk of bias; a. Random sequence generation, b. Allocation concealment, c. Blinding of participants; d. Blinding of personnel; e. Blinding of outcome assessment; f. Co-interventions avoided; g. Treatment fidelity; h. Incomplete outcome data; i. Selective outcome reporting.
[a] Level of RoB per study based on a, b, and h.

used as the standardized outcome of the CPAP treatment effect. The forest plots show the ESs with CIs for scales and subscales and the final $\overline{ES_V}$ obtained by using a random effects model.

Overall QoL score

The effect of CPAP treatment compared to placebo pills, sham CPAP treatment, and conservative treatment was examined in 12 RCTs. The meta-analysis demonstrated a negligible improvement in overall QoL score with CPAP treatment (0.18; 95%CI = 0.10, 0.26) in OSA patients compared to controls. A moderate I^2 (68%) was found (Fig. 4a).

Psychological QoL score

CPAP did not show significant superiority to controls in terms of psychological QoL (0.25; 95%CI = −0.23; 0.72). A low I^2 (31%) was found (Fig. 4b).

Physical QoL score

The meta-analysis demonstrated a small, but significant improvement in physical QoL (0.20; 95%CI = 0.04, 0.35) with CPAP treatment in OSA patients compared to controls. A low I^2 (26%) was observed (Fig. 4c).

Sensitivity analyses

We performed sensitivity analyses to assess the effect of CPAP treatment on overall QoL when controlled for the number of included participants, duration of intervention, level of compliance with CPAP treatment, and RoB. As the studies measuring psychological and physical QoL[26–28,30] were homogenous in terms of the number of included participants ($N \leq 100$), duration of intervention (≤6 weeks), compliance level (≥4 h/night), and RoB, not enough data were available to conduct sensitivity analyses for psychological and physical QoL.

The effect of CPAP treatment on overall QoL controlled for number of participants (N > 100)

Sensitivity analysis of four studies,[31,32,36,37] controlled for the number of participants ($N > 100$), showed small, non-significant improvement in overall QoL score with CPAP treatment (0.19; 95%CI = −0.01; 0.38; I^2 = 4%).

The effect of CPAP treatment on overall QoL controlled for duration of CPAP (>6 weeks)

CPAP did not show superiority to controls in terms of effect on overall QoL score (0.13; 95%CI = 0.03; 0.22; I^2 = 31%) in the four studies[29,31,32,37] with a treatment duration of more than 6 weeks.

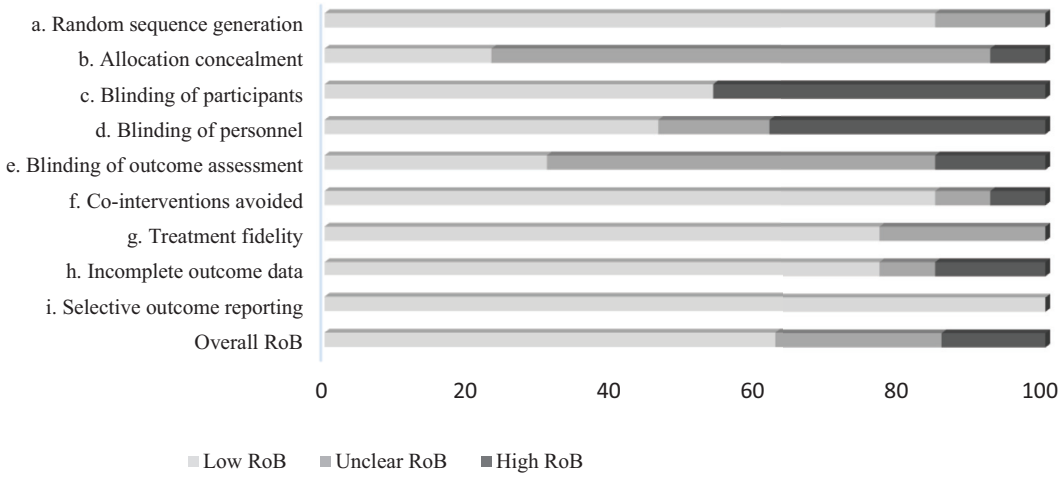

Fig. 2. Flow chart of the risk of bias graph: judgements about each risk of bias item presented as percentages across all the included studies.

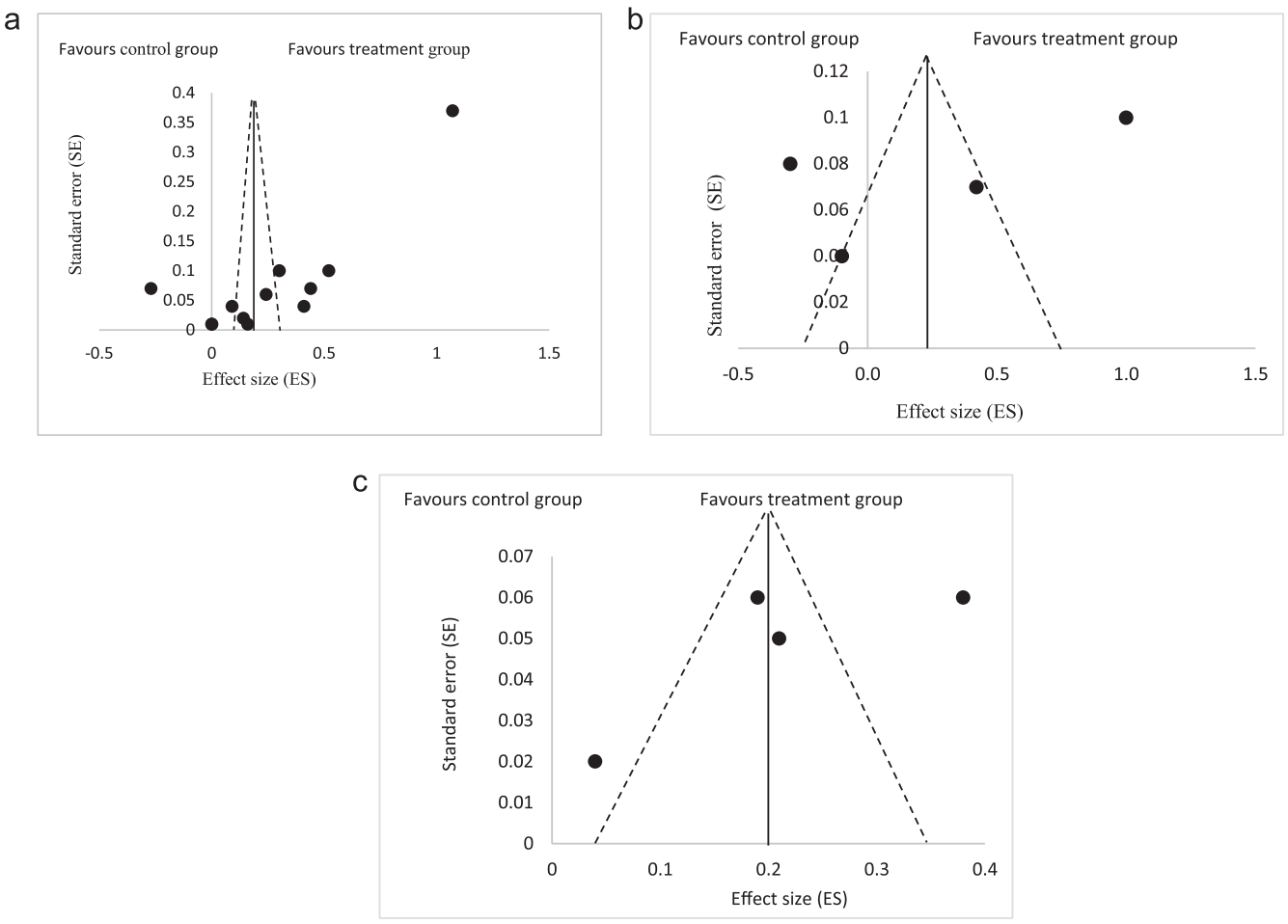

Fig. 3. (a) Funnel plot of publication bias for overall QoL. (b) Funnel plot of publication bias for psychological QoL. (c) Funnel plot of publication bias for physical QoL.

The effect of CPAP treatment on overall QoL controlled for compliance with CPAP treatment (≥4.0 h/night)

We found no significant difference in overall QoL comparing CPAP treated patients with controls (0.32; 95%CI = −0.20; 0.79; I^2 = 10%) in four studies with a CPAP compliance level of at least 4 h per night.[27,30,33,38]

The effect of CPAP treatment on overall QoL controlled for risk of bias

CPAP showed superiority to controls in terms of the effect on overall QoL score (0.20; 95%CI = 0.12; 0.27; I^2 = 13%) in three studies with low RoB.[35,36,38]

Subgroup analyses

We performed subgroup analyses to investigate whether the effect of CPAP treatment on overall QoL varies across different subgroups of patients or trials. We analysed subgroups based on the type of control group, OSA severity, study design, and type of QoL measures. As studies measuring psychological and physical QoL[26–28,30] were homogenous in terms of the type of the control group (sham CPAP), OSA severity (moderate to severe), study design (parallel), and type of QoL measures (generic), not enough data were available for the predefined subgroup comparisons.

The effect of CPAP treatment on overall QoL controlled for type of control group

We found a small but significant improvement in overall QoL in subgroup analyses of six studies[27,28,30–32,38] using sham CPAP as a control condition (0.25; 95%CI = 0.04; 0.46). A value of 32% indicated moderate heterogeneity. CPAP led to negligible improvement in overall QoL in the subgroup analyses of five studies[33–37] using placebo pills (0.14; 95%CI = 0.03; 0.25). A value of 52% indicated moderate heterogeneity. CPAP did not show superiority to controls receiving conservative treatment in terms of effect on overall QoL score (0.00; 95%CI = 0.07; 0.07) in a single study.[29]

The effect of CPAP treatment on overall QoL controlled for OSA severity

Subgroup analyses of mild OSA patients showed small CPAP treatment effect on overall QoL (0.31; 95%CI = 0.13; 0.50; I^2 = 27%) in four studies.[32,33,35,38] A negligible improvement in overall QoL was found in subgroup analyses of six studies[27,28,30,32,34,36] with participants suffering from moderate to severe OSA (0.19; 95%CI = 0.03; 0.34; I^2 = 53%).

The effect of CPAP treatment on overall QoL controlled for study design

CPAP led to a small but significant improvement in overall QoL score (0.22; 95%CI = 0.07, 0.38; I^2 = 70%) in six studies with a parallel

design.[27–32] CPAP did not show superiority to controls in terms of the effect on overall QoL (0.16; 95%CI = 0.10, 0.26; I^2 = 35%) in subgroup analyses of six studies with a crossover design.[33–38]

The effect of CPAP treatment on overall QoL score controlled for the type of QoL measures

A total of four studies[29,33–35] using generic QoL questionnaires showed non-significant improvement in overall QoL with CPAP treatment (0.13; 95%CI = −0.001; 0.28; I^2 = 53%). A negligible improvement in overall QoL score was found in eight studies[27,28,30–32,36–38] using OSA-specific QoL questionnaires (0.14; 95%CI = 0.04, 0.24; I^2 = 64%).

Summary of the quality of the findings

The quality of the evidence within the studies was assessed based on levels of RoB, inconsistency, indirectness, and imprecision.[54] The evidence for improvement in overall QoL was of low quality and was downgraded by one level, as most of the studies had an unclear selection bias. For inconsistency, we considered an I^2 value of 68% to downgrade by one level.

The meta-analysis of psychological QoL provided very low quality of evidence. The evidence for psychological QoL was downgraded by one level due to a small number of included studies, and an unclear allocation concealment in most of the included studies. We also downrated the quality of evidence by two levels for imprecision due to a small sample size (N<400) and a wide CI around effect estimate that included an effect size of 0 and moderate effect size.

The evidence for physical QoL provided low quality of evidence. The evidence for improvement in physical QoL was downgraded by one level due to a small number of included studies and an unclear allocation concealment in most of the included studies. We also downrated the quality of evidence by one level for imprecision due to a small sample size (N<400).

Discussion

The aim of this study was to systematically evaluate the effect of continuous positive airway pressure (CPAP) treatment on quality of life (QoL) in patients with obstructive sleep apnoea (OSA) compared

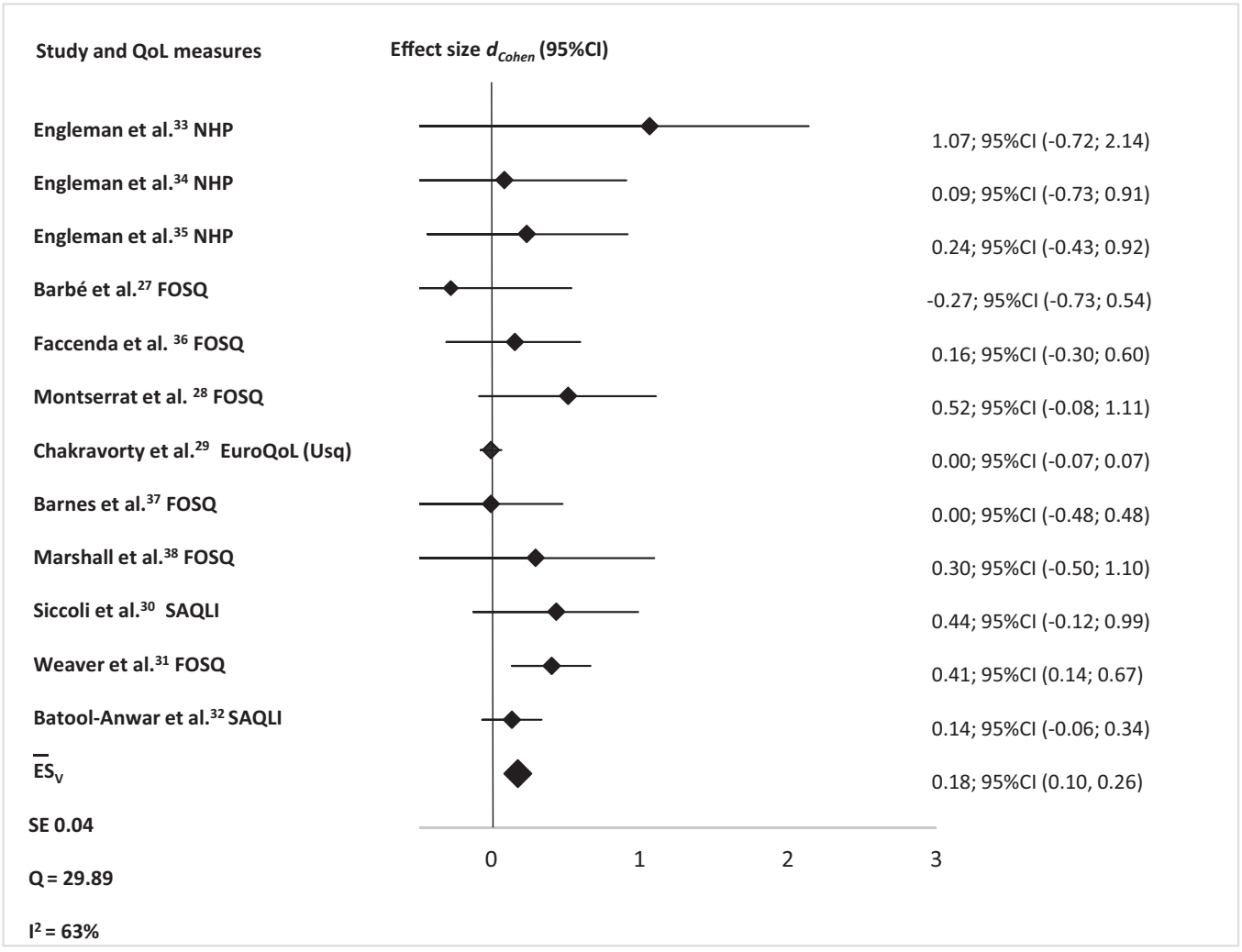

Fig. 4. (a) Meta-analysis of CPAP treatment effect on improvement in overall QoL score; effect sizes and 95% confidence intervals. (b) Meta-analysis of CPAP treatment effect on improvement in psychological QoL score; effect sizes and 95% confidence intervals. (c) Meta-analysis of CPAP treatment effect on improvement in physical QoL score; effect sizes and 95% confidence intervals.

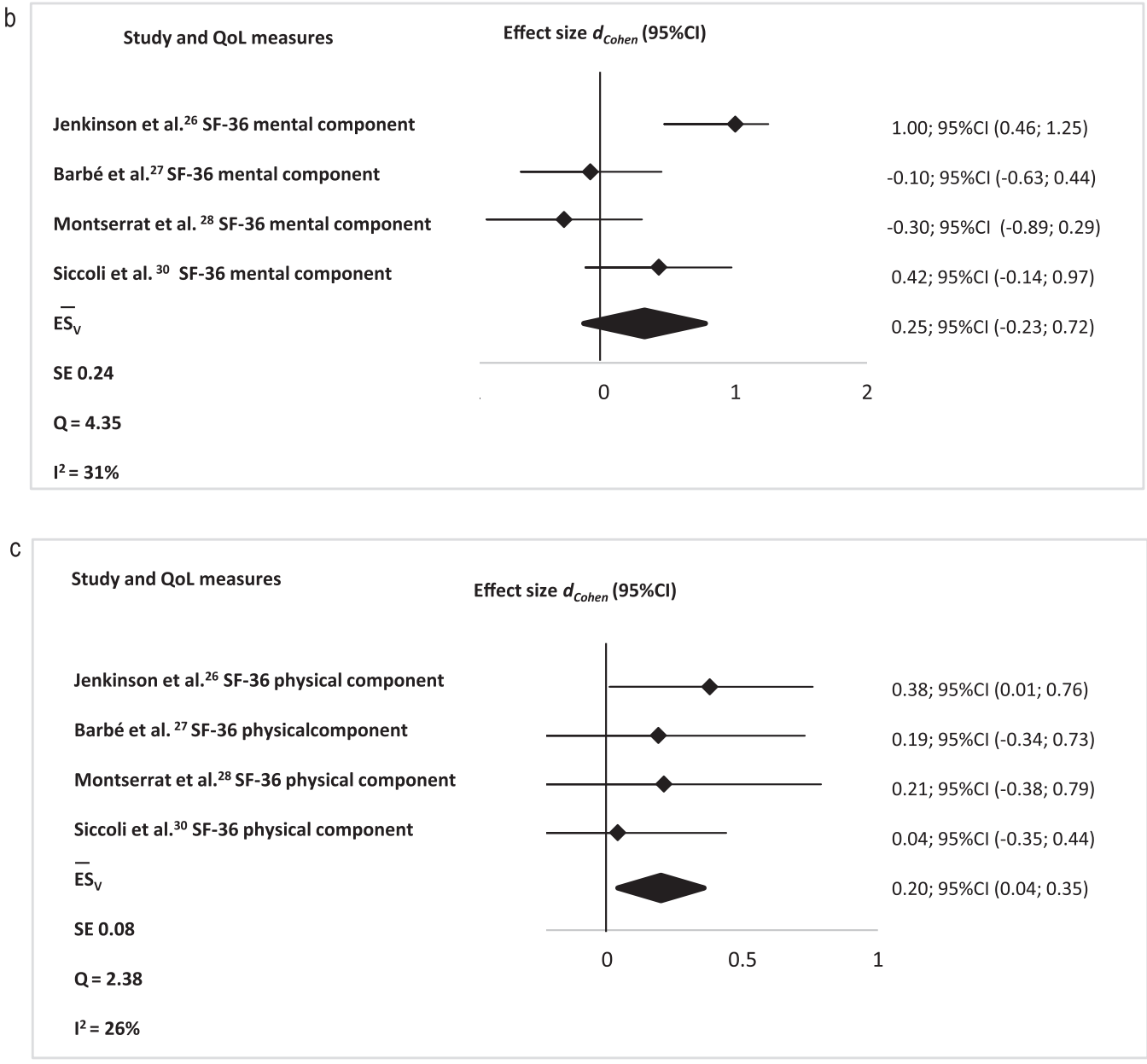

Fig. 4. Continued.

to sham CPAP, placebo pills, and conservative treatment. We found no significant differences in overall and psychological QoL between CPAP treated patients and controls. However, physical QoL improved in CPAP treated patients compared with control treatments. Furthermore, subgroup analyses and sensitivity analyses showed that the type of control group, the study design, OSA severity, and risk of bias (RoB) may be relevant in capturing the effect of CPAP on QoL.

We found that patients undergoing CPAP treatment reported significantly higher physical QoL compared to controls. This result provided additional support for the effect of CPAP on physical QoL revealed in an earlier meta-analysis.[21] These findings may be of clinical importance, as physical QoL was found to be related to nocturnal parameters indicating sleep disruption.[21,59] However, no treatment effect of CPAP compared to controls was found for psychological QoL. This finding may be explained by the low severity of psychological symptoms at baseline. As we excluded studies with focus on major comorbidities, it is possible that the occurrence or severity of some confounders related to comorbid medical illnesses that could negatively affect psychological QoL in OSA patients may have been low. Furthermore, meta-analysis by Huang et al.[60] demonstrated the significant alterations of brain structural and functional response in OSA patients possibly explaining psychic disorders. Patients with OSA showed both decreased grey matter volume and functional response in orbital frontal cortex compared to healthy controls, while the cerebellum VI bilateral anterior (para)cingulate gyri and the amygdala/hippocampus exhibited atrophy of grey matter volume but increased activity. These changes suggest that early diagnosis and treatment are crucial.[60] However, recent histopathological investigations of autopsy of brain tissue from OSA patients further indicate that myelin in OSA patients is impacted and not protected by CPAP treatment.[61] Therefore, the suboptimal effect of CPAP treatment on psychological QoL may also be explained by the irreversible OSA-related brain injuries, that may further contribute to the development of the psychological symptomatology in OSA patients.[60,61]

Subgroup analyses showed non-significant improvements in overall QoL with CPAP treatment when controlled for type of QoL measures. The results of the subgroup comparisons are not

particularly surprising given the fact that disease-specific and generic QoL measures in OSA patients were found to be highly correlated.[62,63] However, recent meta-analysis by Patil et al.[22] identified significant effect of CPAP treatment on QoL using disease specific measures. The explanation for this inconsistence in results may be that Patil et al.[22] included only studies with longer duration of CPAP treatment (6 weeks), while we used cut-off of 2 weeks.

We found a significant improvement in overall QoL when controlled for OSA severity. This result may be surprising as self-reported health outcomes are usually discordant with polysomnography (PSG) measures of OSA severity.[20] Issues such as abbreviated PSG monitoring, night-to-night variability, or the "first-night effect" of the PSG may partly explain the variability of OSA severity across different studies.[64] Nevertheless, the significant effect of CPAP treatment on QoL in patients with mild OSA may also be caused by the low RoB in two[35,38] of the four studies included in subgroup analysis.

In line with the meta-analysis by Jing et al.[21] we found only a negligible CPAP treatment effect on overall QoL scores in studies with a crossover design compared to a small but significant effect revealed in studies with a parallel design. This result is consistent with previous research, as long-term parallel-group trials were found to be more efficient at capturing the important information regarding the benefits of CPAP treatment.[21,65] Furthermore, the crossover study design was found to be less effective in assessment of CPAP treatment effects, as the washout period is usually too short to eliminate the effects of first treatment.[65] The washout period in crossover studies included in our meta-analysis ranged from 0 to 2 weeks.[33–38] Consequently, it is understandable that these short washout periods could not eliminate CPAP treatment effects.

Subgroup analyses also showed that CPAP led to a small but significant improvement in overall QoL in studies with controls receiving sham CPAP compared to the negligible improvement revealed in controls using placebo pills. This result is surprising, as sham CPAP is supposed to worsen both sleep and gas exchange.[35,66] An explanation may be that most of the studies that used placebo pills as a control condition also had a very low number of participants.[33–35] Furthermore, all studies with placebo pills as a control condition had a crossover design, identified as less sensitive in capturing the effect of CPAP treatment.[65]

Sensitivity analyses that controlled for the number of included participants, duration of intervention, and compliance level showed only small, non-significant effects of CPAP treatment on overall QoL scores. The results of our meta-analysis may be explained by the relatively small sample sizes, the short durations of the interventions, and the relatively low CPAP compliance level (with the highest value of 5.0 h per night) in the included studies. For example, a compliance of $\geq$4 h per night has been considered acceptable (e.g. Masa and Corral-Peñafiel[67]). However, the adequate use of CPAP treatment may vary for different outcomes. For instance, to obtain an improvement in daytime sleepiness, at least 4 h per night of compliance with CPAP are required[68]; 6 h per night are needed for memory improvement[69] and 7.5 h per night is considered to be adequate for improvement in sleep-related quality of life.[68] But, there are individuals who are not able to achieve normal functional status or remain excessively sleepy despite optimal CPAP treatment of more than 7 h per night.[68,70,71]As adherence with CPAP treatment appears to be associated with positive changes in QoL,[72] future research and clinical practice should examine strategies for its improvement. More attention should be given to educational and behavioural intervention strategies that were found to be efficient in improving adherence with CPAP,[73] while device improvements were found to have only modest impact on adherence with CPAP treatment.[74]

Finally, we found a small, non-significant effect of CPAP treatment when controlled for the number of included participants. This result is not surprising as cut-offs based on study size introduce an extra element of subjectivity and thus may not ameliorate bias if the large studies are insufficiently critiqued.[75] Although we stated the cut-off value of 100 participants following previous recommendations,[48,49] the concept of single threshold to distinguish small trials from large trials in the area of medical interventions is not straightforward. A solution may therefore be to make a separate exclusion of studies with high and unclear RoB. In line with this assumption, we found a small but significant CPAP treatment effect on QoL in studies with low RoB.[35,36,38]

Strengths and limitations

The strength of this review and meta-analysis is that randomised controlled trials (RCTs) were conducted in different countries, which adds to the generalizability of our results. The results of our study are applicable to adult patients of both genders with mild to severe OSA. We tried to avoid meta-bias by searching in multiple databases. As most of the participants in the included studies were diagnosed by PSG in the same way, misclassification based on differences in sensitivity and specificity of diagnostic measures can be excluded. All studies included in our review and meta-analysis used the SF-36 to measure psychological and physical QoL. Despite some limitations, the mental health component of the SF-36, and in particular the "vitality" domain, is still considered to be the most suitable generic health-related QoL measure for OSA patients.[76] However, a potential drawback may be that the questions of the SF-36 related to daily activities or social functioning are assessed by asking about limitations due to "emotional problems" or "physical health". Moreover, neither of these categories is considered to clearly cover the main reasons for impaired functioning that OSA patients experience (i.e., fatigue, sleepiness, or poor sleep quality).[76] One of the eligible studies was excluded from our MA, as we did not receive the missing, additional information. However, the results of the excluded study were consistent with our findings, i.e. QoL improvement was found only in the physical QoL domain and not in the psychological QoL domain.[57] We also have to be careful in the interpretation of the results, as many studies had a high or unclear RoB. Next, the studies in our review consistently rated poorly on allocation concealment and blinding. Because inadequately concealed trials and lack of proper blinding may show even more favourable treatment effects than adequately blinded and concealed studies,[24,77] careful attention must be paid when interpreting CPAP treatment effect on QoL in OSA patients. We also tried to avoid biases in the assessment of CPAP treatment effect on QoL by exclusion of studies with full samples of OSA patients with major comorbidities that may affect QoL; i.e. heart failure, stroke, or comorbid sleep disorders. However, the limitation of our study may be that comorbidities may not be fully eliminated as the exclusion criteria in analysed studies varied from not specified,[37] to less strict[26,28–30,33–36]; or led to exclusion of all chronic conditions.[27,31,32] Finally, since the reported treatment duration ranged from three weeks to six months, this review cannot conclude on the long-term effects of CPAP treatment.

Implications and recommendations for practice and future research

More high-quality RCTs with larger samples are needed to learn more about the effectiveness of CPAP treatment on QoL improvement. Most of the studies included in our review had a moderate duration of CPAP treatment; thus, repetitions with longer treatment duration are recommended. Future RCTs should also consider evaluating secondary outcome measures, such as sleep-related problems.

Conclusion

In conclusion, when comparing CPAP with control treatment, our meta-analysis showed no significant impact of CPAP on overall and psychological QOL. However, CPAP was found to improve physical

QoL compared with control treatments. Moreover, we found that CPAP may significantly affect overall QoL in studies with sham CPAP controls, parallel design, low risk of bias, and mild OSA patients. More high-quality trials are needed for further investigation of the effects of CPAP treatment on QoL improvement.

Declaration of Competing Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Appendix A. Search strings

Web of Knowledge: ("Sleep apnea" OR "sleep apnoea" OR OSA) AND ("quality of life" OR "health status" OR "functional status" OR "self-perceived health" OR "self-perceived health" OR "self-rated health" OR "self-rated health") AND (CPAP OR "continuous positive airway pressure").

Pubmed: ("Sleep Apnea Syndromes"(Mesh) OR sleep apnea (tiab) OR sleep apnoea(tiab) OR OSA(tiab)) AND ("Continuous Positive Airway Pressure"(Mesh) OR CPAP(tiab) OR continuous positive airway pressure(tiab)) AND ("Quality of Life"(Mesh) OR "Health Status"(Mesh) OR quality of life(tiab) OR health status (tiab) OR functional status(tiab) OR self-rated health(tiab) OR self-perceived health(tiab)).

PsycINFO: (DE "Sleep Apnea" OR TI ("sleep apnea" OR "sleep apnoea" OR OSA) OR AB ("sleep apnea" OR "sleep apnoea" OR OSA)) AND (TI ("continuous positive airway pressure" OR CPAP) OR AB ("continuous positive airway pressure" OR CPAP)) AND (DE "Quality of Life" OR TI ("quality of life" OR "health status" OR "functional status" OR "self-rated health" OR "self-perceived health") OR AB ("quality of life" OR "health status" OR "functional status" OR "self-rated health" OR "self-perceived health")).

The Cochrane Library: ("sleep apnea" or "sleep apnoea" or OSA:ti, ab,kw) and ("continuous positive airway pressure" or CPAP:ti,ab,kw) and ("quality of life" or "health status" or "functional status" or "self-rated health" or "self-perceived health":ti,ab,kw).

EMBASE: ((('sleep apnea':ti,ab,kw OR 'sleep apnoea':ti,ab,kw OR 'osa':ti,ab,kw) AND 'continuous positive airway pressure':ti,ab,kw OR 'cpap':ti,ab,kw) AND 'quality of life':ti,ab,kw OR 'health status':ti,ab, kw OR 'self-rated health':ti,ab,kw OR 'self-perceived health':ti,ab,kw OR 'functional status':ti,ab,kw)).

CINAHL: "sleep apnea OR sleep apnoea OR OSA AND continuous positive airway pressure OR CPAP AND quality of life OR health status OR functional status OR self-rated health OR self-perceived health on 2019-03-03 09:15 AM".

Appendix B. Overview of the included studies: exclusion criteria, sociodemographic and clinical data, level of compliance with CPAP

Table B.1
Overview of the included studies.

Study	Exclusion criteria	Sociodemographic and clinical data Mean (SD/SE, range)	CPAP compliance, Mean (SD/SE, range)
Engleman et al.[33] Scotland	Neurological disorder; co-existing sleep disorder	Age: 52 ± 2.0 years Gender: 12 men, 4 women AHI: 12.5 ± 0.5 events/h BMI: 29.8 ± 1.8 kg/m^2 ESS: 14 ± 1.0	8 patients: 5.0 ± 0.6 h/per night
Engleman et al.[34] Scotland	Lung disease; neurological disorder; co-existing sleep disorder	Age: 47 ± 12.0 years Gender: 21 men, 2 women AHI: 43.0 ± 12.0 events/h BMI: 30.0 ± 7.0 kg/m^2 ESS: 12.0 ± 4.0	2.8 ± 2.0 h/per night
Engleman et al.[35] Scotland	Shift workers; co-existing sleep disorder; neurological disease; lung disease	Age: 44.0 ± 8.0 years Gender: 21 men, 13 women AHI: 10.0 ± 3.0 events/h BMI: 30.0 ± 5 kg/m^2 ESS: 13.0 ± 3.0	2.8 ± 2.1 h/per night
Jenkinson et al.[26] UK	Mental impairment; major psychoses; alcohol dependence; learning difficulties	Age: real CPAP: 50.0 (33–71) years Age: sham CPAP: 48.0 (36–68) years Gender: 101 men, 0 women AHI: NA Oximeter: >4% SaO2 (dips/h) Sham CPAP: 28·5 (10.7–68.7) Real CPAP: 32·9 (15.5–63.4) BMI: real CPAP: 35.1 (25.8–44.3) kg/m^2 BMI: sham CPAP: 35.0 (26.9–51.4) kg/m^2 ESS: real CPAP: 16.0 ESS: Sham CPAP: 17.0	Controls: 4.6 h/per night real CPAP: 5.4 h/per night

(*continued*)

Table B.1 (*Continued*)

Study	Exclusion criteria	Sociodemographic and clinical data Mean (SD/SE, range)	CPAP compliance, Mean (SD/SE, range)
Barbé et al.[27] Spain	Cognitive deterioration; cardiac disease; less than 8 years of formal education; Illicit drugs; alcohol abuse; any chronic disease that may affect QoL	Age: real CPAP: 54 ± 2.0 years Age: sham CPAP: 52 ± 2.0 years Gender: 5 female, 49 male AHI: real CPAP: 54 ± 2.0 events/h AHI: sham CPAP: 52 ± 2.0 events/h BMI: 29.0±1.0 (26.9–51.4) kg/m^2 BMI: sham CPAP: (29 ± 0.4) kg/m^2 ESS: real CPAP: 7.0 ± 0.4 ESS: sham CPAP: 7.0 ± 0.4 multicentre; 6 hospitals	Controls: 4.0 ± 0.5 h/per night Real CPAP: 5.0 ± 0.4 h/per night
Faccenda et al.[36] UK	Shift workers; diabetes; taking medication which may alter blood pressure	Age: 50.0 (29–72) years Gender: 55 males, 13 females AHI: 35.0 (15–129) events/h BMI: 30.0 (21–53) kg/m^2 ESS: 15.0 (16–24)	3.3 ± 0.8 h/per night
Montserrat et al.[28] Spain	Severe cardiovascular disease; hazardous job coincidentally with OSA	Age: 54.0 ± 10.0 years Gender: 41 male, 4 female AHI: 54.0 ± 19.0 events/h BMI: 32.0 ± 6.0 kg/m^2 ESS: 16.0 ± 5.0	Not specified
Chakravorty et al.[29] UK	Neuromuscular disorders; hypothyroidism; associated respiratory diseases; acute abdomen; chest infection; visual impairment, cancer	Age: 50.0 ± 11.0 years Gender: not specified AHI: 49.0 ± 28.0 events/h BMI: 37.0 ± 12.0 kg/m^2 ESS: 14.0 ± 5.0	Not specified
Barnes et al.[37] Australia	Not specified	Age: 46.6 ± 1.1 years Gender: 64 male, 16 female AHI: 5–30 events/h BMI: 31.0 ± 0.6 kg/m^2 ESS: 10.0 ± 0.5	3.6 ± 0.3 h/per night
Marshall et al.[38] New Zealand	History of somnolence requiring immediate treatment; shift work; chronic sleep restriction; currently taking sedatives, antidepressants, psychotropics or stimulants; an alcohol intake of 0.3 standard units/24 h or caffeine dependency (unable to forego caffeine on testing days); had undergone upper airway surgery; or had any clinically significant co-existing disease or additional sleep disorders	Age: 50.5 (25–67) years Gender: 23 male, 6 female AHI: 21.6 ± 7.5 events/h BMI: 3.5 (6.0) kg/m^2 ESS: 12.5 (0.8)	4.9 (0–8.4) h/per night
Siccoli et al.[30] UK	Respiratory failure	Age: real CPAP: 48.1 ± 9.5 years Age: sham CPAP: 48.7 ± 10.6 years Gender: 102 male; 0 female BMI: real CPAP: 35.8 ± 7.3 kg/m^2 BMI: sham CPAP: 34.5 ± 5.0 kg/m^2 ESS: real CPAP: 15.8 ± 4.0 ESS: sham CPAP: 15.2 ± 4.0	Controls: 3.9 ± 2.5 h/per night Real CPAP: 4.7 ± 2.1 h/per night
Weaver et al.[31] USA	Unstable medical condition in the past 3 months; greater than fifth grade reading level; and no history of other sleep disorder, current pregnancy, substance abuse, sleepiness-related driving accident, or sleepiness-sensitive occupation	Age: real CPAP: 49.5 ± 10.9 years Age: sham CPAP: 51.7 ± 11.9 years Gender: 223 patients; 140 male; 122 female Black: 79.3%; whites: 76.3% AHI: real CPAP: 12.8 ± 6.4 events/h AHI: sham CPAP: 12.5 ± 6.5 events/h BMI: real CPAP: 33.2 ± 6.3 kg/m^2 BMI: sham CPAP: 34.2 ± 7.8 kg/m^2 ESS: real CPAP: 15.0 ± 3.4 ESS: sham CPAP: 14.7 ± 3.0	Controls: 3.1 ± 2.1 h/per night Real CPAP: 4.0 ± 2.0 h/per night
Bartool-Anwar et al.[32] USA	Chronic medical conditions, previous treatment for OSA with CPAP or surgery, oxygen saturation on baseline PSG <75% for >10% of the recording time, history of motor vehicle accident related to sleepiness within the past 12 months, use of various medications known to affect sleep or neurocognitive function, health and social factors that may impact testing procedures (e.g. shift work)	Age: real CPAP: 52.0 ± 12.0 years Age: sham CPAP: 51.0±12.0 years Gender: male; female AHI: real CPAP: 40.0 ± 24.0 events/h AHI: sham CPAP: 41.0 ± 25.0 events/h BMI: real CPAP: NA BMI: sham CPAP: NA ESS: real CPAP: 10.3 ± 4.5 ESS: sham CPAP: 14.7 ± 3.0 Multi-centre study	Controls: 2.92 ± 2.92 h/per night Real CPAP: 3.69 ± 3.10 h/per night

CPAP: continuous positive airway pressure.

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