EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Effects of suboptimal adherence of CPAP-therapy on symptoms of obstructive sleep apnea: a randomised, double-blind, controlled trial

Thomas Gaisl, Protazy Rejmer, Sira Thiel, Sarah R. Haile, Martin Osswald, Malgorzata Roos, Konrad E. Bloch, John R. Stradling, Malcolm Kohler

Please cite this article as: Gaisl T, Rejmer P, Thiel S, *et al*. Effects of suboptimal adherence of CPAP-therapy on symptoms of obstructive sleep apnea: a randomised, double-blind, controlled trial. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.01526-2019).

Effects of suboptimal adherence of CPAP-therapy on symptoms of obstructive sleep apnea: a randomized, double-blind, controlled trial

Thomas Gaisl, MD[1,*]; Protazy Rejmer[1,*]; Sira Thiel[1]; Sarah R. Haile, PhD[2]; Martin Osswald[1]; Malgorzata Roos, PhD[2]; Prof Konrad E. Bloch[1]; Prof John R. Stradling[3]; Prof Malcolm Kohler[1,4]

[1] Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland

[2] Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Zurich, Switzerland

[3] National Institute for Health Research (NIHR), Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Foundation Trust and University of Oxford, Oxford, United Kingdom

[4] Centre for Interdisciplinary Sleep Research, University of Zurich, Zurich, Switzerland

* Contributed equally

Corresponding author:

Professor Malcolm Kohler, Chair of Respiratory Medicine

University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland

E-mail: malcolm.kohler@usz.ch

Take home message:

Patients with obstructive sleep apnea and daytime sleepiness are still getting a substantial benefit from suboptimal CPAP adherence (i.e. 3 to 4 hours per night) albeit not as much as they might get if they adhered more.

Abstract

Introduction. Continuous positive airway pressure (CPAP) is currently the treatment of choice for sleepiness in patients with obstructive sleep apnea (OSA), however, adherence is often thought to be suboptimal. We investigated the effects of suboptimal CPAP-usage on objective and subjective sleepiness parameters in patients with OSA.

Material and Methods. In this 2-week, parallel, double-blind, randomized controlled trial we enrolled moderate-to-severe OSA patients with excessive pre-treatment daytime sleepiness (Epworth-Sleepiness-Scale [ESS] score >10 points) who had suboptimal CPAP adherence over at least 12 months (mean nightly usage time 3-4 hours). Patients were allocated through minimization to either subtherapeutic CPAP ("sham-CPAP") or continuation of CPAP (therapeutic-CPAP). A Bayesian analysis with historical priors calculated the posterior probability of superiority.

Results. Between May, 2016 and November, 2018, 57 patients (60±8 years, 79% men, 93% Caucasian) were allocated in total, and 52 who completed the study (50% in each arm) were included in the final analysis. The unadjusted ESS-score increase was +2.4 points (95% CI +0.6 to +4.2; p=0.01) in the sham-CPAP-group when compared to continuing therapeutic CPAP. The probability of superiority of therapeutic CPAP over sham CPAP was 90.4% for ESS, 90.1% for systolic, and 80.3% for diastolic blood pressure.

Conclusions. Patients with moderate-to-severe OSA and daytime sleepiness are still getting a substantial benefit from suboptimal CPAP adherence, albeit not as much as they might get if they adhered more. Whether a similar statement can be made for even lower adherence levels remains to be established in future trials.

Keywords: obstructive sleep apnea; suboptimal; continuous positive airway pressure; randomized controlled trial

Introduction

Symptomatic obstructive sleep apnea (OSA) affects 1–2% of females and 2–4% of males in the general population, while the prevalence of asymptomatic OSA is considerably higher.[1, 2] Untreated patients with OSA are at increased risk for all-cause and cardiovascular mortality, adverse medical outcomes, and poor neurocognitive performance.[3] Patients with OSA typically complain about non-restorative sleep, fatigue, insomnia and excessive daytime sleepiness. The latter finds its most commonly mentioned reflection in vehicle crashes being two to three times more common among patients with untreated OSA than in the general population.[4]

Population-based studies have demonstrated a directly proportional relationship between the severity of OSA and healthcare costs.[5] Excessive daytime sleepiness is arbitrarily defined as an Epworth Sleepiness Scale [ESS] score >10 and applies to 23% of the general population.[6] A score >10 seems to independently increase health care utilization.[7] Considering indirect costs of untreated OSA (e.g. due to lost productivity and illness-related accidents), its overall economic burden is likely to be far greater.[8]

According to current guidelines, the treatment of choice for OSA is continuous positive airway pressure (CPAP) therapy.[9] Data from randomized controlled trials (RCTs) have consistently shown that CPAP improves sleepiness, reduces the risk of comorbidities (e.g. high blood pressure (BP)) and improves quality of life (QoL).[10-12] However, its overall effectiveness seems to broadly correlate with the average nightly usage time[11], although there is no consensus on the definition of "non-adherence." A commonly held view is that a patient should use their CPAP device for at least 4 hours per night to experience an improvement of sleepiness and daily functioning.[13-18] However, a considerable proportion of CPAP users fail to achieve this threshold. Accordingly, 46-83% of the patients on CPAP

could be described as insufficiently treated, if optimal adherence were defined as >4 hours of nightly use.[19]

In contrast to the findings from observational data, indirect evidence from interventional trials does not support an apparent threshold of mean usage time necessary to reduce sleepiness in OSA. A recent meta-analysis could not find a dose-dependent response of ESS to CPAP adherence, which suggests that a broad spectrum of therapy usage time is beneficial for this outcome.[10] This is in opposition to what is known from studies on comorbidities, e.g. on high BP, where a dose-dependent reduction could be demonstrated.[11] Thus it remains unclear, if and how much suboptimally treated patients actually benefit from CPAP, or whether the treatment could be withdrawn altogether without any health-related consequences. Additionally, in some countries, reimbursement rules for CPAP devices depend on their average usage time (e.g. a threshold at 4 hours per night), however, interventional data is lacking.

In this study, we aimed to evaluate moderate-to-severe OSA patients with documented mean CPAP usage times between 3 and 4 hours per night for effects of therapy withdrawal on sleepiness. We hypothesized that two-weeks of CPAP withdrawal would result in the return of OSA and its sequelae despite apparent prior suboptimal use.

Methods

Trial design. This two-week, parallel, double-blind RCT investigated the effects of suboptimal continuous positive airway pressure (CPAP) treatment on subjective sleepiness and other parameters in patients with obstructive sleep apnea (OSA). We applied the previously described CPAP-withdrawal model[20, 21], where either a therapeutic or a sham-CPAP device is assigned. While identical in appearance, noise production, and operability, the sham CPAP device is not able to deliver a therapeutic pressure. This is achieved by 1) a

built-in flow-restrictor; 2) altered software settings; and 3) a leakage at the mask-end of the tubing intended to prevent rebreathing of CO_2. This design allows double-blinding and placebo effect without lessening the severity of OSA or improving the architecture of sleep.[22, 23]

Study population. To be included in our RCT, patients had to: 1) have a sleep-lab confirmed diagnosis of OSA with a 4%-Oxygen-Desaturation-Index ($ODI_{4\%}$) of at least 15/h and an Epworth Sleepiness Scale (ESS) score >10 points - both prior to commencing the CPAP therapy; 2) have been treated with CPAP for at least 12 months prior to inclusion in our study - as protocolled by the 1-year-statistics of the device showing a residual Apnoea-Hypopnea-Index (AHI) < 10/h and a mean usage time between three and four hours per night; 3) show at least a one-time re-emergence of $ODI_{4\%}$ ≥15/h during a four-night CPAP-withdrawal - as measured by ambulatory night-time pulse oximetry. The exclusion criteria were: 1) previously registered ventilatory failure (awake PaO_2 <9 kPa or arterial $PaCO_2$ >6 kPa); 2) unstable and/or untreated coronary or peripheral artery disease; 3) severe uncontrolled arterial hypertension (mean BP values >180/110mmHg in serial measurements); 4) previously diagnosed Cheyne-Stokes breathing pattern; 5) current professional driving; 6) age of <20 or >75 years at trial entry; 7) pregnancy. The trial was pre-registered at ClinicalTrials.gov (NCT02781740). All tests were conducted by the University Hospital Zurich and approved by the cantonal ethics committee of Zurich (KEK-ZH-Nr. 2016-00332). All patients provided written informed consent according to the Declaration of Helsinki. Data were obtained according to Good Clinical Practice (GCP) guidelines.

Procedures. Visits with clinical assessments were performed at 1) inclusion; 2) baseline inpatient respiratory polygraphy (RP) upon outpatient confirmation of persistence of relevant OSA; 3) follow-up inpatient RP after 2 weeks of intervention. A detailed description of the procedures can be found in the online supplement. The RPs were evaluated according to the

Guidelines by the American Association of Sleep Medicine from 2007 (AASM 2007 version B).[24] Regular controls of our RCT were performed by an external monitor who was otherwise not involved in the study.

Outcomes. The primary outcome was the change in ESS after two weeks. Secondary outcomes included 1) AHI and $ODI_{4\%}$ - as measured by RP; 2) test duration, number of missed signals and time to first 4 subsequently missed signals ("time to S4") – as measured by Oxford Sleep Resistance Tests (OSLER); 3) mean/average, minimal and maximal reaction time – as measured by Multiple Unprepared Reaction Time Test (MURT); 4) mean nightly CPAP usage over two weeks – as protocolled by the CPAP device; 5) systolic and diastolic BP and HR values over two weeks – as measured shortly before/after RP and protocolled in the patient diary; 6) self-assessed quality of life (QoL) – as represented by different parameters from the 36-Item Short Form Health Survey (SF-36) and Functional Outcomes of Sleep Questionnaire (FOSQ-10).

Statistical analysis. A sample size of 52 (26 per arm) was estimated to detect the minimal clinically important difference (MCID) with 80% power at the two-sided significance level of 0.05. This calculation assumed a standard deviation of 2.5 points for the change in ESS score between baseline and follow-up (based on our previous CPAP withdrawal trial[20]). A MCID of 2 points on the ESS was chosen based on three aspects: 1) pooled RCTs have confirmed this threshold to interpret the clinical relevance of changes in ESS[25]; 2) a 2 point decrease is considered economically viable by NICE[26], and 3) such a decrease is expected to improve work productivity by 2% and reduce sleep-related road accidents by about 9%.[27]

Comparison between baseline characteristics of the intervention group were performed using the Wilcoxon rank sum test with continuity correction (continuous variables) or Fisher`s exact test (categorical variables). A per protocol analysis was performed. For all outcomes, we considered a univariate linear regression analysis adjusting for treatment group and

baseline measurements of the outcome. A multivariate linear regression was performed as well, a two-sided significance level of <0.05 was used to determine statistical significance.

We also performed a Bayesian analysis because incorporation of historical data into current increases the probability of reproducibility.[28] Details on the Bayesian analysis including the systematic review can be found in the online supplement. The statistical analysis was performed with STATA Version 15 (StataCorp LP, College Station, TX) and R (R Core Team 2018, version 3.4.4 (2018-03-15)).

Results

Patient characteristics. From May 27, 2016 to November 10, 2018, 1035 patients from nine Swiss sleep laboratory centers (Kantonsspital Aarau, Kantonsspital Glarus, Kantonsspital Graubünden, Spital Horgen, Spital Männedorf, Kantonsspital Schaffhausen, Stadtspital Triemli, Universitätsspital Zürich, Zürcher RehaZentrum Wald) were identified as possibly eligible and contacted by mail. Fifty-seven patients (mean age 60.1 ± 8.0 years; 78.9% men; 93% Caucasian; 7% Asian) were randomized. Five patients discontinued the study, one of them due to a hypertensive serious adverse event possibly related to the study intervention (hypertensive crisis, Figure 1). The last patient completed the study on November 10, 2018. The final analysis encompassed 26 patients assigned to the sham- and 26 to the therapeutic CPAP-arm.

The trial profile can be seen in Figure 1, the baseline characteristics in Table 1. The additional information on study participants (comorbidities, medication) can be found in the online supplement. Subtherapeutic CPAP (i.e. the sham CPAP arm) was associated with re-emergence of OSA as evidenced by a significant increase in AHI from baseline (+33.4 /h [95% CI +23.3 to +43.6] p<0.001).

Primary outcome. In comparison to the control group, sham-CPAP led to an unadjusted increase in the ESS score by +2.4 points (95% CI +0.6 to +4.2), however a part of this effect might have been mediated by a higher than baseline CPAP-adherence in the control group. Although both study arms had a similar CPAP adherence during the two weeks prior to randomization (sham [mean ± standard deviation]: 3.5 ± 0.6 hours, therapy: 3.1 ± 0.8 hours), the adherence dropped to 2.1 ± 1.8 hours in the sham group and rose to 4.6 ± 1.8 hours in the control group (66% of all patients in this arm had a CPAP adherence above 4 hours at follow-up). The divergence in CPAP adherence was statistically significant (+1.9 hours [95% CI +0.4 to +3.6] p=0.017), but adjusting for this confirmed the primary outcome to still be statistically significant (adjusted ESS score increase of +2.0 points [95% CI +0.5 to +3.2], p=0.011). Additionally, in the isolated single arm analysis (i.e. only sham CPAP) the ESS score significantly increased by means of a paired t-test (+2.1 points [95% CI +0.5 to +3.2], p=0.020).

Secondary outcomes. Analogous to the ESS score, the FOSQ score worsened significantly in the sham intervention group (Table 2). Further baseline characteristics are reported in the online supplement, Table 2-3. The results of all secondary outcomes can be found in Table 2 and the online supplement, Table 4.

Objective sleepiness parameters. There was no effect on both independent ways to objectively assess sleepiness (i.e. the OSLER and MURT test). A non-significant trend which corresponded to the ESS change was mostly limited by a low sample size (Table 2).

Usage patterns. Twenty-eight (49%) participants reported their pre-trial suboptimal CPAP adherence was due to their lifestyle, 25 (44%) due to comorbidities, and 4 (7%) due to "technical issues." Further information regarding the categorization and the individual reasons can be found in the online supplement, Table 5. CPAP adherence patterns did not differ between these three groups (p-value for difference [global test] = 0.523).

Bayesian analysis. Based on a systematic review (Online supplement, Figure 1) historical data from four trials were included for ESS (2866 patients)[29-32], while only two provided historical data for BP (2376 patients)[29, 30]. In the current study data, we observed a difference in ESS between the treatment arms of about 2.4 points, while in the historical data there was a mean difference of about 1.3 points. Small differences in blood pressure were also observed in the current study data (see Table 2), and in the historical data (systolic BP: sham group +1.3 mmHg, therapeutic group -0.01 mmHg; diastolic BP: sham group -0.1 mmHg, therapeutic group -0.7 mmHg). Sampling from the posterior distributions, and computing the differences between the treatment arms, we obtained a median difference in delta ESS of 0.825 points (sham - therapeutic, positive favors therapeutic; 95% Credible Interval --0.41 to 2.05). The posterior probability of superiority for ESS and BP is 90.4% (Table 3).

Discussion

This is the first RCT to investigate explicitly pre-defined suboptimal CPAP usage and delineate individually reported reasons for lower adherence in a representative population. Our RCT demonstrated that suboptimal adherence to CPAP therapy improves subjective daytime sleepiness in patients with moderate-to-severe OSA, since withdrawal of therapeutic CPAP for two weeks resulted in a +2.4 points increase or 90.4% probability of superiority on the ESS. Large scale meta-analyses in this field have suggested that CPAP use in similar populations is associated with an even greater reduction in ESS score of 2.5 to 2.9 points.[10, 33] The effect of suboptimal CPAP-therapy on subjective daytime sleepiness was virtually the same as the one reported for usage times of four to seven hours per day.[10] However, approximately a third of our effect size might be due to improvements due to increases in CPAP adherence (see Result section). Whether similar statements can be made for lower

adherence remains to be established in future trials. In other words, this trial does not foreclose a non-existing dose-response effect of CPAP on subjective daytime sleepiness, the potential threshold might just be lower than 3 hours of usage time.

The effect of CPAP on the ESS score in our trial (per protocol analysis +2.4 points, adjusted: +2.0 points; single arm analysis: +2.1 points) was robust and confirmed our primary hypothesis (+2 points). Previous studies confirm that this 2-point change is not only statistically significant, but also clinically relevant.[25-27, 34] On the other hand, we were not able find objectively measurable correlates of sleepiness (i.e. significant effects for the OSLER and MURT test). Correspondingly, a previous meta-analysis indicated that the effect of CPAP on subjective sleepiness is generally larger than on objective measurements[33], which could provide partial explanation for our results. Since objective measures have always been less sensitive compared to subjective ones in this setting, one can hypothesize that objective measures (e.g. the OSLER or MURT test) do not fully characterize the symptoms of a patient.

In our study, participants of both arms diverged from their previously similar mean nightly CPAP times (therapy: 3.1 ± 0.8 hours, sham: 3.5 ± 0.6 hours) towards higher values in the therapeutic (4.6 ± 1.8 hours) and lower values in the sham group (2.1 ± 1.8 hours). This yielded a significant mean difference of 1.9 hours. The substantial impact of allocation to therapy adherence has already been reported in other interventional trials by other groups involving sham CPAP devices and seems to be a universal phenomenon across sex, race, and age-boundaries.[23, 35-37] In the literature, this phenomenon is also referred to as the "*Hawthorne effect*", where individuals modify an aspect of their behavior in response to their awareness of being observed. Interestingly, in multivariable analyses, the treatment allocation was the strongest predictor of CPAP adherence within RCTs.[35] Possible additional explanations for this include (subconscious) dissatisfaction with the current treatment in the

sham-CPAP arm, or simply unblinding.[36] Indeed, data from a meta-analysis suggests that a clinically significant proportion (approximately 30%) of the effectiveness of CPAP adherence in reducing sleepiness is probably caused by patient expectation of benefit.[38] In our study, we could rule out substantial unblinding, as only 59% of all study participants correctly guessed their allocation. This is in line with previous results by other groups using the CPAP withdrawal model, where 56% of participants could guess their true allocations correctly, which was only slightly higher than what one could expect by chance.[23] The fact, that the single arm analysis (i.e. only sham CPAP) also showed a clinically significant effect on the ESS, is reassuring. We suspect that the patients from the suboptimal collective might be more sensitive to any changes in their therapy regimens – for example on account of lifestyle circumstances and comorbidities having been classified as more than 90% of the reasons reported behind their generally lower adherence (Online supplement, Table 5). Considering other potential benefits of longer nightly CPAP usage (e.g. lower arterial blood pressure[11]), future trials should investigate different, focused ways of boosting adherence that might be efficiently incorporated in the clinical setting.

Although previous studies did not show a dose-dependent reaction of many objective surrogates of daytime sleepiness (e.g. maintenance of wakefulness test) to CPAP adherence, they were able to detect significant drops in proportions of patients with normalized or significantly improved ESS-, FOSQ- and SF-36 scores when CPAP was used less than four hours per night. [13, 15], [17, 18] Already compliant patients were also demonstrated to increase their mean usage times and relevant scores even further upon additional, intensive support.[39] These notions most probably led to the widely recommended threshold of 4 hours of mean usage time of CPAP therapy to be considered sufficient. Still, the meta-analysis comparing treatment effects of CPAP vs mandibular advancement devices,

encompassing 67 studies, noted no evidence of studies reporting higher CPAP adherence also reporting larger treatment effects (p=0.7).[10]

In lieu of our findings and pre-existing literature, the widely used four-hour-threshold for clinical benefit seems unjustified. We could think of several additional reasons to support that claim: 1) Sleep and sleepiness feature a great interpersonal variability, and a one-size-fits-all approach may not be adequate. 2) There seems to be a substantial subgroup of patients with OSA who, although sleeping for more than five hours per day, deliberately keep their CPAP intervals on levels which might be regarded as "suboptimal" (i.e. <4 hours per day) over a long period of time. When asked about their motivation, these patients often report being satisfactory treated at "their personal level." 3) Sleep itself is not uniform in its function and does exhibit a substantial variation in terms of restorability. CPAP therapy might therefore indeed have a lower time-threshold for countering excessive sleepiness, which would not necessarily be applicable to countering other sequelae of OSA (e.g. high BP). Apart from the possibility of the overall time-thresholds for countering sleepiness and other sequelae being different, it is also conceivable that other aspects play their roles as well. The thresholds of CPAP efficacy on different sequelae of OSA may not only be individual, but also composite – e.g. involving patterns of usage, adaptive pressures or varying air compositions.

The current trial population only consisted of a selected group of patients with excessive daytime sleepiness and moderate-to-severe OSA, thus the conclusions might not be generalizable to other populations with OSA. Another limitation of the current trial is the relatively short withdrawal period of two weeks, which might not feature the full effect of CPAP on daytime sleepiness. However, the ESS was primarily designed for a two week period and the test-retest reliability in this timeframe is sufficiently high.[40] Finally, the ESS score itself is prone to subjectivity and does represent an ordinal variable (and not an interval scale), thus conclusions regarding the effect size might be distorted.[41] Additionally,

potential unblinding might have contributed to CPAP adherence during the trial and thus affected the outcome. Nevertheless, the ESS score was chosen as the primary outcome, as it is the most widely used clinical instrument for evaluating sleepiness and most investigated marker for subjective daytime sleepiness.

We conclude, that patients with daytime sleepiness are still getting a substantial benefit from suboptimal CPAP adherence albeit not as much as they might get if they adhered more. Therefore, suboptimal CPAP usage between 3 and 4 hours/night in moderate-to-severe patients with OSA might not be a valid reason to stop treatment or not reimburse treatment at all. Whether a similar statement can be made lower adherence and/or very severe OSA remains to be established in future trials. Therefore, future trials should consider a larger spectrum of CPAP usage patterns (different mean usage times and their intervalled distributions) in a variety of OSA patients. Attention should be drawn to investigating different, focused ways of boosting adherence that might be efficiently incorporated in the clinical setting.

Acknowledgements

The authors would like to thank all colleagues which were involved in the recruitment process, especially Dr. Tsogyal Latshang (Kantonsspital Graubünden), Dr. Sarosh Irani (Kantonsspital Aarau), Dr. Yvonne Nussbuamer (Kantonsspital Schaffhausen), Prof. Robert Thurnheer (Kantonsspital Münsterlingen), Dr. Jean-Luc Kurzen (Spital Männedorf), Dr. Marc Spielmanns (Zürcher RehaZentrum Wald), Dr. Alexander Turk and Dr. Patrick Schihin (Spital Horgen), Lungenliga Glarus (Dr. Thomas Brack, Alice Odermatt) and Lunge Zürich (Dr. Michael Schlunegger, Dominic Karrer, Sylke Meier). We also thank the patients who committed to the study and often travelled long distances to participate. Without their effort, this project would not have been possible.

Author contributions

TG, MR and SRH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TG, KB, JRS, and MK. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: TG. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: TG, MR, and SRH. Administrative, technical, or material support: TG, MK. Study supervision: MK.

Conflicts of interest

This was an investigator-initiated trial and supported by the Swiss National Science Foundation (project no. 32003B_162534). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. No funds from the industry were received. JRS reports personal fees from Resmed UK, personal fees from Bayer Germany, outside the submitted work. MK reports grants from the University of Zurich, grants from Lunge Zurich, during the conduct of the study; grants from Bayer AG, outside the submitted work. TG reports personal fees from Bayer AG, outside the submitted work. All other authors report no conflict of interest.

References

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002; 165(9): 1217-1239.
2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015; 3(4): 310-318.
3. Molnar MZ, Mucsi I, Novak M, Szabo Z, Freire AX, Huch KM, et al. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax* 2015; 70(9): 888-895.
4. George CF. Sleep apnea, alertness, and motor vehicle crashes. *Am J Respir Crit Care Med* 2007; 176(10): 954-956.
5. Kapur V, Blough DK, Sandblom RE, Hert R, de Maine JB, Sullivan SD, et al. The medical cost of undiagnosed sleep apnea. *Sleep* 1999; 22(6): 749-755.
6. Sander C, Hegerl U, Wirkner K, Walter N, Kocalevent RD, Petrowski K, et al. Normative values of the Epworth Sleepiness Scale (ESS), derived from a large German sample. *Sleep Breath* 2016; 20(4): 1337-1345.
7. Ronksley PE, Hemmelgarn BR, Heitman SJ, Flemons WW, Ghali WA, Manns B, et al. Excessive daytime sleepiness is associated with increased health care utilization among patients referred for assessment of OSA. *Sleep* 2011; 34(3): 363-370.
8. Sassani A, Findley LJ, Kryger M, Goldlust E, George C, Davidson TM. Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. *Sleep* 2004; 27(3): 453-458.
9. Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009; 5(3): 263-276.
10. Bratton DJ, Gaisl T, Schlatzer C, Kohler M. Comparison of the effects of continuous positive airway pressure and mandibular advancement devices on sleepiness in patients with obstructive sleep apnoea: a network meta-analysis. *The Lancet Respiratory medicine* 2015; 3(11): 869-878.
11. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Jama* 2015; 314(21): 2280-2293.
12. Kuhn E, Schwarz EI, Bratton DJ, Rossi VA, Kohler M. Effects of CPAP and Mandibular Advancement Devices on Health-Related Quality of Life in OSA: A Systematic Review and Meta-analysis. *Chest* 2017; 151(4): 786-794.
13. Antic NA, Catcheside P, Buchan C, Hensley M, Naughton MT, Rowland S, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep* 2011; 34(1): 111-119.
14. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011; 15(6): 343-356.
15. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007; 30(6): 711-719.
16. Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS. Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. *Chest* 2006; 130(6): 1772-1778.
17. Weaver T. Adherence with continuous positive airway pressure (CPAP). UpToDate 2018 [cited 2018 Dec 18, 2018]; Available from: https://www.uptodate.com/contents/adherence-with-continuous-positive-airway-pressure-cpap
18. Masa JF, Corral-Peñafiel J. Should use of 4 hours continuous positive airway pressure per night be considered acceptable compliance? *European Respiratory Journal* 2014; 44(5): 1119-1120.
19. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008; 5(2): 173-178.
20. Kohler M, Stoewhas AC, Ayers L, Senn O, Bloch KE, Russi EW, et al. Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2011; 184(10): 1192-1199.

21. Schwarz EI, Martinez-Lozano Sinues P, Bregy L, Gaisl T, Garcia Gomez D, Gaugg MT, et al. Effects of CPAP therapy withdrawal on exhaled breath pattern in obstructive sleep apnoea. *Thorax* 2016; 71(2): 110-117.
22. Schwarz EI, Schlatzer C, Stehli J, Kaufmann PA, Bloch KE, Stradling JR, et al. Effect of CPAP Withdrawal on myocardial perfusion in OSA: A randomized controlled trial. *Respirology* 2016; 21(6): 1126-1133.
23. Chasens ER, Drumheller OJ, Strollo PJ, Jr. Success in blinding to group assignment with sham-CPAP. *Biol Res Nurs* 2013; 15(4): 465-469.
24. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012; 8(5): 597-619.
25. Crook S, Sievi NA, Bloch KE, Stradling JR, Frei A, Puhan MA, et al. Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. *Thorax* 2019; 74(4): 390-396.
26. Weatherly HL, Griffin SC, Mc Daid C, Duree KH, Davies RJ, Stradling JR, et al. An economic analysis of continuous positive airway pressure for the treatment of obstructive sleep apnea-hypopnea syndrome. *Int J Technol Assess Health Care* 2009; 25(1): 26-34.
27. Craig SE, Kohler M, Nicoll D, Bratton DJ, Nunn A, Davies R, et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. *Thorax* 2012; 67(12): 1090-1096.
28. McShane BB, Böckenholt U. Single-Paper Meta-Analysis: Benefits for Study Summary, Theory Testing, and Replicability. *Journal of Consumer Research* 2017; 43(6): 1048-1063.
29. Hoyos CM, Killick R, Yee BJ, Phillips CL, Grunstein RR, Liu PY. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. *Thorax* 2012; 67(12): 1081-1089.
30. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med* 2016; 375(10): 919-931.
31. Redline S, Adams N, Strauss ME, Roebuck T, Winters M, Rosenberg C. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. *Am J Respir Crit Care Med* 1998; 157(3 Pt 1): 858-865.
32. Weaver TE, Mancini C, Maislin G, Cater J, Staley B, Landis JR, et al. Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. *Am J Respir Crit Care Med* 2012; 186(7): 677-683.
33. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. *Arch Intern Med* 2003; 163(5): 565-571.
34. Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, et al. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. *Am J Respir Crit Care Med* 2018; 197(7): 961-963.
35. May AM, Gharibeh T, Wang L, Hurley A, Walia H, Strohl KP, et al. CPAP Adherence Predictors in a Randomized Trial of Moderate-to-Severe OSA Enriched With Women and Minorities. *Chest* 2018; 154(3): 567-578.
36. Budhiraja R, Kushida CA, Nichols DA, Walsh JK, Simon RD, Gottlieb DJ, et al. Impact of Randomization, Clinic Visits, and Medical and Psychiatric Cormorbidities on Continuous Positive Airway Pressure Adherence in Obstructive Sleep Apnea. *J Clin Sleep Med* 2016; 12(3): 333-341.
37. Paz YMHL, Hazen SL, Tracy RP, Strohl KP, Auckley D, Bena J, et al. Effect of Continuous Positive Airway Pressure on Cardiovascular Biomarkers: The Sleep Apnea Stress Randomized Controlled Trial. *Chest* 2016; 150(1): 80-90.
38. Crawford MR, Bartlett DJ, Coughlin SR, Phillips CL, Neill AM, Espie CA, et al. The effect of continuous positive airway pressure usage on sleepiness in obstructive sleep apnoea: real effects or expectation of benefit? *Thorax* 2012; 67(10): 920-924.
39. Bouloukaki I, Giannadaki K, Mermigkis C, Tzanakis N, Mauroudi E, Moniaki V, et al. Intensive versus standard follow-up to improve continuous positive airway pressure compliance. *Eur Respir J* 2014; 44(5): 1262-1274.
40. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep* 1992; 15(4): 376-381.
41. Campbell AJ, Neill AM, Scott DAR. Clinical Reproducibility of the Epworth Sleepiness Scale for Patients With Suspected Sleep Apnea. *J Clin Sleep Med* 2018; 14(5): 791-795.

Tables

Table 1. Baseline characteristics of the intention-to-treat population.

	Subtherapeutic CPAP (sham) n=29	**Therapeutic CPAP (real)** n=28
Anthropometrics		
Age, years	61.5 ± 6.5	60.1 ± 8.7
Sex, male	21 (81%)	21 (81%)
BMI, kg/m^2	32.2 ± 4.4	33.0 ± 4.9
Height, cm	172.1 ± 9.7	174.6 ± 7.5
Weight, kg	95.6 ± 16.0	100.1 ± 13.3
Neck circumference, cm	42.2 ± 3.6	43.5 ± 3.5
Waist circumference, cm	113 ± 14	115 ± 14
Hip circumference, cm	108 ± 11	108 ± 11
Mallampati score, class	2.7 ± 1.0	2.4 ± 1.0
CPAP adherence data		
CPAP adherence (over 365 days), hr/day*	3.5 ± 0.4	3.3 ± 0.4
Leakage (over 365 days), l/min*	1 (0 to 6)	0 (0 to 2.5)
Obstructive sleep apnea		
Time since diagnosis of OSA, years	5.4 ± 3.3	5.4 ± 3.2
Apnea-hypopnea index at diagnosis, hr^{-1}	46.7 ± 21.8	38.8 ± 17.9
Apnea-hypopnea index during CPAP, hr^{-1}*	3.3 ± 2.5	2.2 ± 2.5
Epworth Sleepiness Scale at diagnosis, points	12.3 ± 2.6	12.1 ± 2.4
Epworth Sleepiness Scale at study inclusion, points**	8.5 ± 3.9	9.5 ± 4.7
Apnea-hypopnea index during CPAP, hr^{-1}*	3.3 ± 2.5	2.2 ± 2.5

Data are n (%), median (interquartile range), or mean ± SD as appropriate. BMI, body mass index; OSA, obstructive sleep apnea. * data downloaded from CPAP device ** before pulse oximetry

Table 2. Per protocol analysis on primary and secondary outcomes.

	Subtherapeutic CPAP (sham) n=26		**Therapeutic CPAP (real)** n=26		**Treatment effect**		
	Baseline	Follow-up	Baseline	Follow-up	**Change***	95% CI	p-value
Trial outcomes							
Epworth Sleepiness Scale, points	8.3 ± 4.8	10.3 ± 5.6	8.7 ± 4.0	8.2 ± 3.7	**+2.4**	+0.6 to +4.2	**0.010**
OSLER: time to 4 missed signals, minutes	7 (4 to 19)	18 (3 to 23)	7 (2 to 24)	6 (2 to 39)	**+8**	-12 to +28	0.435
OSLER: total signals missed	7 (4 to 19)	17.5 (18 to 33)	7 (2 to 24)	6 (2 to 39)	**+17**	-15 to +49	0.289
MURT: mean reaction time, milliseconds	268 ± 54	300 ± 73	312 ± 87	318 ± 101	**+21**	-21 to +65	0.317
Systolic blood pressure (office), mmHg	132.8 ± 14.7	132.5 ± 15.6	133.6 ± 16.4	129.3 ± 14.7	**+2.9**	-3.8 to +9.6	0.384
Diastolic blood pressure (office), mmHg	82.3 ± 8.3	84.3 ± 11.6	83.5 ± 11.2	82.2 ± 10.6	**+2.4**	-3.1 to +7.9	0.388
Quality of life (SF-36 standardized scores)							
FOSQ, points	17.9 ± 1.9	17.9 ± 2.0	17.8 ± 2.9	17.0 ± 2.0	**+1.1**	0.1 to +2.4	**0.044**
Physical Role	66 ± 39	59 ± 41	63 ± 39	62 ± 39	**-9**	+5 to -24	0.223
Physical Functioning	76 ± 22	72 ± 25	72 ± 28	72 ± 26	**-3**	-11 to +5	0.445
Emotional Role	65 ± 41	63 ± 42	71 ± 41	77 ± 31	**-10**	-25 to +5	0.173
Social Functioning	74 ± 25	78 ± 26	77 ± 24	77 ± 22	**+4**	-3 to +12	0.242
Vitality	51 ± 19	47 ± 21	55 ± 18	54 ± 21	**-2**	-5 to +9	0.544
Bolidy Pain	68 ± 28	68 ± 25	60 ± 31	58 ± 32	**-2**	-11 to +6	0.575
Mental Health	68 ± 20	68 ± 20	74 ± 20	73 ±19	**0**	-6 to +6	0.985
General Health	66 ± 23	60 ± 20	58 ± 20	61 ± 18	**-6**	-12 to +1	0.094
Health Transition	40 ± 24	47 ± 25	47 ± 25	48 ± 21	**+3**	-7 to 13	0.614
Sleep variables							
Apnea-Hypopnea Index, hr^{-1}	4.9 (2.5 to 10.9)	34.3 (23.1 to 51.7)	4.1 (2.5 to 7.1)	3.6 (2.2 to 5.7)	**+33.4**	+23.3 to +43.6	**<0.001**
Oxygen-Desaturation Index 4%, hr^{-1}	4.9 (2.5 to 9.9)	35.1 (17.5 to 61.6)	4.0 (2.5 to 7.1)	4.0 (1.9 to 6.8)	**+33.1**	+21.7 to +44.4	**<0.001**
Sleep time, hours	6.2 (5.5 to 7.2)	6.3 (5.3 – 7.5)	6.4 (5.4 – 7.8)	6.5 (5.4 to 7.6)	**+0.1**	-10.1 to +19.5	0.445

Data are in mean ± standard deviation (mean±SD) or median (IQR). FOSQ= Functional Outcomes of Sleep Questionnaire 10; MURT= Multiple Unprepared Reaction Time Test; OSLER= Oxford Sleep Resistance Test; SF36= Short Form 36 Questionnaire.

* adjusted for baseline. In in the isolated single arm analysis the primary outcome significantly increased by +2.2 points ([95% CI +0.7 to +3.8], p=0.005) in the sham CPAP arm.

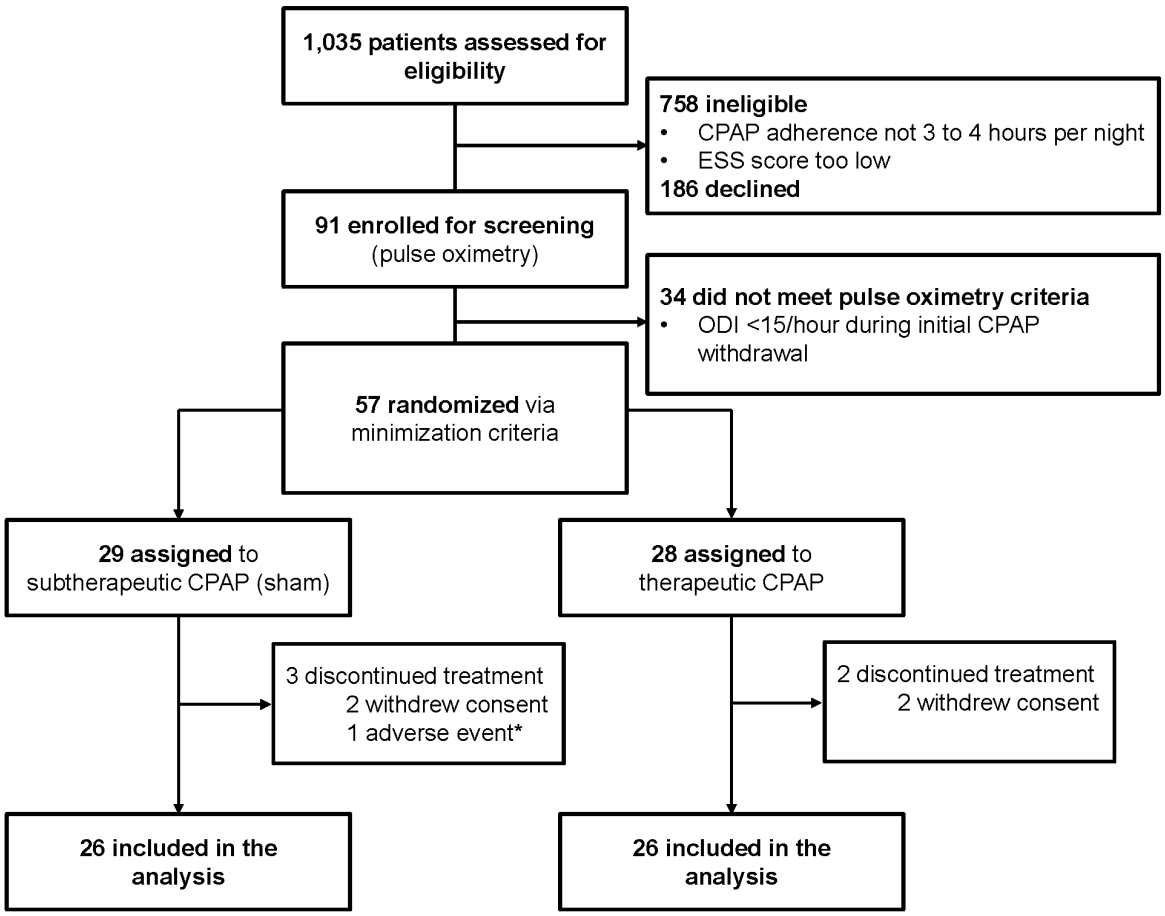
Table 3. Primary and secondary endpoint Bayesian analysis using historical data from four RCTs[29-32] with a CPAP adherence between 3 and 4 hours. A detailed description of the analysis and the systematic review behind this method can be found in the online supplement.

Endpoint	Sample size*, n	Lower boundary	Median	Upper boundary	Monte Carlo error	Probability of superiority
Epworth Sleepiness Scale	52 + 2866	-0.4128	0.8248	2.051	0.0009	**90.41 %**
Systolic blood pressure	52 + 2376	-0.8241	1.6045	4.043	0.0009	**90.17 %**
Diastolic blood pressure	52 + 2376	-1.0352	0.8044	2.662	0.0013	**80.27 %**

* current data + historical priors (four RCTs[29-32])

Figures

Figure 1. Trial profile.



* one patient was unblinded and consequently withdrawn from the trial due to a hypertensive urgency.

CPAP= Continuous Positive Airway Pressure, ESS= Epworth Sleepiness Scale, ODI = Oxygen Desaturation Index.

ONLINE SUPPLEMENT

Effects of suboptimal adherence of CPAP-therapy on symptoms of obstructive sleep apnea: a randomized, double-blind, controlled trial.

Thomas Gaisl, MD[1]; Rejmer Protazy[1]; Sira Thiel[1]; Sarah R. Haile, PhD[2]; Martin Osswald[1], Malgorzata Roos, PhD[2]; Prof Konrad Bloch[1]; Prof John R. Stradling[3]; Prof Malcolm Kohler[1,4]

[1] Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland

[2] Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Zurich, Switzerland

[3] National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Foundation Trust and University of Oxford, Oxford, United Kingdom

[4] Centre for Interdisciplinary Sleep Research, University of Zurich, Zurich, Switzerland

Methods

Screening

Patients were screened at the following institutions: 1) University Hospital Zurich (internal search performed by us); 2) Independent association of "Lunge Zürich" (who, on our behalf, provided a pre-selection of potential participants derived from their data base after written permissions from the following referring hospitals had been obtained: Spital Männedorf, Zürcher RehaZentrum Wald, Spital Triemli and Spital Horgen); 4) Kantonsspital Aarau, Kantonsspital Graubünden, Kantonsspital Schaffhausen, Kantonsspital Münsterlingen and "Lunge Glarus" (external search performed by us after written permissions had been obtained within the scope of trans-regional collaborations).

Confirmation of relevant OSA

The patients had to wear wrist pulse oximeters (Pulsox-300i, Konica Minolta Sensing Inc., Osaka, Japan) at home during each night of the four-night period off CPAP. Regular CPAP therapies had to be resumed for at least two weeks prior to minimization/allocation.

Randomization and masking. The MS-DOS program MINIM (London, UK) was used to allocate participants by two minimization criteria: maximal off-CPAP $ODI_{4\%}$ </> 30/h (from four consecutive CPAP withdrawal nights) and body mass index (BMI) </> 30 kg/m^2. After random allocation, every participant received the same model of CPAP-machine. Each device was marked with a random 5-digit code (generated via random.com) masking the allocation for patients and investigators throughout the whole trial. Regular controls of our RCT were performed by an external monitor who was otherwise not involved in the study.

Respiratory polygraphies (RPs)

Baseline inpatient RPs were performed under therapeutic CPAP in both arms. Follow-up RPs were performed after two weeks under either therapeutic (control arm) or subtherapeutic CPAP (intervention arm) settings. Inpatient RPs were recorded by Alice 6 Diagnostic System (Philips Respironics, PA, USA), scored with validated Somnolzyer 24x7 software (Philips Respironics, PA, USA)[1] and reviewed manually. The recommendations of the American

Academy of Sleep Medicine from 2007 were applied (AASM 2007 Version B)[2] with quantification of OSA-severity by AHI and $ODI_{4\%}$.

CPAP device

For this trial we used AirSense AutoSet S10 by ResMed (San Diego, CA, USA). All patients were trained to operate the study CPAP-device and explicitly advised to continue their usual CPAP routines. Participants, as well as outcome assessors, remained blinded to the arm-assignment until completion of the data analysis.

Patient diaries

During the two weeks of intervention, the patients had to keep a diary to record their systolic and diastolic blood pressure (BP) and heart rate (HR) values three times a day (morning, midday, evening) with three subsequent measurements at a time, as well as note special occurrences (if any). For measuring BP and HR, each participant was provided with the same, clinically validated device (OMR-M7-IT, HEM-7322T, Omron, Advance AG, Switzerland) and trained in its use.

Vigilance tests

Immediately after each RP (at baseline and on the follow-up visit) a one-time Oxford Sleep Latency Test (OSLER) and a one-time Multiple Unprepared Reaction Time (MURT) test were performed. The clinical circumstances of those tests were controlled to ensure low external stimulation: 1) Performance in the same, darkened room with sound insulation and observation via infra-red camera; 2) Confiscation of cell phones, smart devices and watches prior to testing; 3) Testing prior to breakfast, morning medication or the habitual use of stimulants in the morning (e.g. tobacco, caffeine). The participants were allowed to freely change their bodily positions for the duration of the tests.

Sleepiness and QoL questionnaires

After each RP, the participants had to fill out the same bundle of three questionnaires: the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ-

10) and the 36-Item Short Form Health Survey (SF-36) to retrospectively assess their previous two weeks.

Bayesian analysis

To supplement the classical analysis, we also considered historical data. Historical trials were identified via a systematic review of the literature.

Eligibility criteria of randomized controlled trials

- Aged ≥18 years
- Diagnosis of obstructive sleep apnea (OSA) defined by an apnoea–hypopnoea index (AHI) ≥5/h
- Random assignment to any combination of continuous positive airway pressure (CPAP, fixed or autotitrating), or an inactive control (sham-CPAP, any other type of placebo [e.g. placebo tablet], no treatment, or usual or standard care)
- RCTs of patients with a concurrent disease (eg, heart failure and stroke) were eligible for inclusion
- Assessment of Epworth Sleepiness Scale (ESS), or Short Form (36) Health Survey (SF-36), or arterial blood pressure (ambulatory, office measurements) at baseline and a follow-up visit and reported with some measure of variability (eg, standard deviation or error) either the average number (i.e. points, standardized score, or mmHg) at each visit, the average change in each group at follow-up compared with baseline, or a treatment effect for the difference in the change of the number between groups
- Parallel or crossover randomized controlled trial design

Comment: If two eligible trials contained a significant overlap in patients, the larger of the two trials was used in the analysis.

Databases

- MEDLINE (from inception to December 1, 2018)
- Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3 (from inception to December 1, 2018)
- Bibliographies of eligible trials

Search terms used for MEDLINE and Cochrane library

MEDLINE:

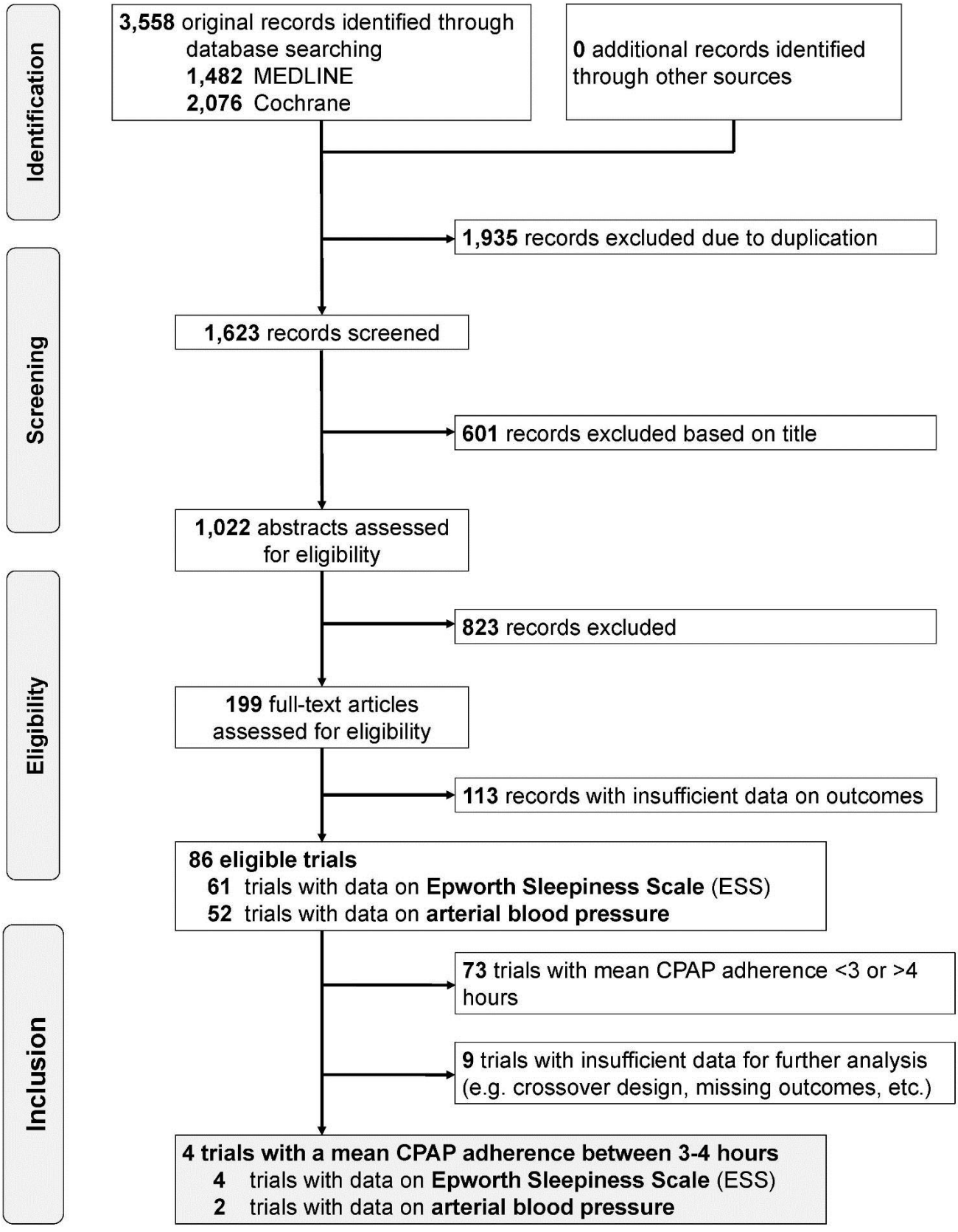
1. 1.(apn* or OSA* or SAHS or hypopn*).af.
2. 2.(randomized controlled trial or controlled clinical trial).pt. or randomized.ab,ti. or placebo.ab,ti. ortrial.ti. or clinical trials as topic.sh. or randomly.ab,ti.
3. 3.(*CPAP or positive airway pressure).af
4. 1 and 2 and 3

Cochrane Library:

1. Apn* or OSA* or SAHS or hypopn*
2. randomized or placebo or randomly or trial
3. *CPAP or positive airway pressure
4. 1 and 2 and 3

Key: af = all fields, pt = publication type, ab = abstract, ti = title, sh = MeSH subject heading, OSA = obstructive sleep apnoea, SAHS = sleep apnoea/hypopnoea syndrome, CPAP = continuous positive airway pressure.

Figure 1. Detailed PRISMA study flow-chart.



Statistical methods

We combined data from the current study and the historical trials with a Bayesian analysis. We followed the idea of Baeten et al.[3], but modified it in two major ways. First, we applied the *bayesmeta* R package for Bayesian random-effects meta-analysis[4] instead of using MCMC sampling. Second, we considered both the control arm and the CPAP arm individually to compute priors based on historical data. We then calculated posterior probability of superiority of therapeutic CPAP versus sham CPAP. In addition, we quantified the probability of improvement in each of the treatment arms separately. Since Hoyos[5] did not report standard deviations for change from baseline, we estimated these from pooled standard deviations for the treatment estimates. Data were analyzed with R (R Core Team (2018), R version 3.4.4 (2018-03-15)).

Data from four trials were included for ESS[5-8], while only two provided historical data for BP[5,6]. Standard errors for the Hoyos trial[5] were estimated from the confidence intervals reported for the treatment estimates, otherwise data were used as reported. In the current study data, we observed a difference in ESS between the treatment arms of about 3 (mean sham CPAP 2.2, therapeutic CPAP -0.9), while in the historical data, there was a mean difference about about 1 (sham -0.8, CPAP -2.1). Small differences in blood pressure were also observed in the current study data (SBP: mean sham -0.3, CPAP -2.9; DBP: sham 2.1, CPAP -0.5), and in the historical data (SBP: sham 1.3, CPAP -0.01; DBP: sham -0.1, CPAP -0.7). The posterior mean [variance] ESS for the CPAP arm was -1.1 [0.17], and for the sham CPAP arm 0.06 [0.15]. The posterior mean systolic (diastolic) BP for the CPAP arm was -0.5 [0.92] (-0.7 [0.45]), and for the sham CPAP arm 1.2 [0.62] (0.1 [0.44]). Sampling from the posterior distributions, and computing the differences between the treatment arms, we obtained a median difference in delta ESS of 0.825 (sham - CPAP, positive favors CPAP) (95% Credible Interval -0.41 to 2.05). The posterior probability of superiority of therapeutic CPAP vs sham CPAP was 90.4% with a Monte Carlo error of 0.0009. Similarly for systolic

(diastolic) BP, the median difference in change was 1.6 [-0.8 to 4.0] (0.8 [-1.0 to 2.7]). The posterior probability of superiority of therapeutic CPAP vs sham CPAP for systolic (diastolic) BP was 90.2% (80.3%) with a MC error of 0.0009 (0.0013). Based on the posterior distributions, we also calculated the probability for each treatment arm that the mean difference was less than 0 (that is, that the outcome at follow-up was less than at baseline). With sham CPAP, the probability of a lower ESS score was only 44%, while with real CPAP, the probability was 99%. For systolic (diastolic) BP, the probability of a lower BP was 7% (44%) with sham, and 68% (86%) with real CPAP.

We amended the approach of Baeten et al.[3] for the two following reasons: 1) when applying *bayesmeta*, we do not need to consider burn-in or convergence diagnostics as *bayesmeta* is a numerical approach to Bayesian analysis, and 2) we use historical knowledge not only in the control group, but also in the treatment group. Baeten et al.[3] planned the trial to include the historical data, while we performed a post-hoc analysis of a conventionally planned study. The choice of the half-normal heterogeneity prior with scale 0.5 was suggested by Friede et al.[6] They also provided satisfactory robustness analysis for this choice of prior. In our study however, we provided a robustness check, by computing the results with and without the Hoyos trial[5]. Incorporation of historical data into current increases the probability of reproducibility.[7]

Table 1. Studies for the Bayes analysis (historical data)

Author	**Design**	**Follow-up** (months)	**Mean CPAP adherence** (hours)	**N*** (overall)	**N*** (CPAP)	**N*** (Sham)	**ESS data**	**BP data**
Hoyos et al. 2012[5]	Parallel	3.0	3.6	65/52	34/28	31/24	Yes	Yes
McEvoy et al. 2016[8]	Parallel	44.4	3.3	2409/2324	1221/1166	1188/1158	Yes	Yes
Redline et al. 1998[9]	Parallel	2.0	3.1	111	59	52	Yes	No
Weaver et al. 2012[10]	Parallel	2.0	4±2	281/223	141/113	140/110	Yes	Yes

* depending on the outcome (ESS data / BP data)

Results

Table 2. Comorbidities of patients included in the final analysis.

	Subtherapeutic CPAP (sham) n=26	**Therapeutic CPAP (real)** n=26
Active smokers	6 (23.1%)	4 (15.4%)
Ex-smokers	10 (43.5%)	11 (52.4%)
Smoking start, age	24.1 ± 12.6	18.1 ± 4.4
Smoking stop, age	42.8 ± 16.2	40.9 ± 10.9
Pack years of smoking	16.6 ± 19.5	15.8 ± 14.9
More than one alcoholic standard drink per day	16 (61.5%)	18 (69.2%)
Obesity	17 (65.4%)	20 (76.9%)
Arterial hypertension	17 (65.4%)	18 (69.2%)
Dyslipidemia	9 (34.6%)	11 (42.3%)
Diabetes	22 (84.6%)	22 (84.6%)
Metabolic syndome	2 (7.7%)	3 (11.5%)
Cerebrovascular event	3 (11.5%)	2 (7.7%)
Atrial fibrillation	3 (11.5%)	4 (15.4%)
Coronary artery disease	4 (15.4%)	2 (7.7%)
Heart failure	1 (3.8%)	0 (0.0%)
Aneurysm	2 (7.7%)	1 (3.8%)
Chronic obstructive pulmonary disease	2 (7.7%)	1 (3.8%)
Asthma	2 (7.7%)	2 (7.7%)
Cancer *(for more details see Table 7)*	4 (15.4%)	2 (7.7%)
Depression *(for more details see Table 8)*	2 (7.7%)	3 (11.5%)
Schizophrenia *(for more details see Table 8)*	1 (3.8%)	0 (0%)
Dementia *(for more details see Table 9)*	0 (0%)	1 (3.8%)
Narcolepsy (treated)	0 (0%)	1 (3.8%)
Miscellaneous		
Shift workers *(for more details see Table 10)*	1 (3.8%)	1 (3.8%)

Data are n (%), or mean (SD) as appropriate.

Table 3. Medication of patients included in the final analysis.

	Subtherapeutic CPAP (sham) n=26	**Therapeutic CPAP (real)** n=26
Beta blocker	7 (26.9%)	5 (19.2%)
Alpha blocker	1 (3.8%)	1 (3.8%)
Angiotensin-converting-enzyme inhibitor	6 (23.1%)	4 (16.0%)
Calcium channel blocker	2 (7.7%)	10 (38.5%)
Angiotensin II receptor blocker	5 (19.2%)	6 (23.1%)
Aldosteroneantagonist	0 (0.0%)	1 (3.8%)
Diuretics	4 (16.0%)	6 (23.1%)
Statins	7 (26.9%)	10 (38.5%)
Insulin	2 (7.7%)	2 (7.7%)
Oral antitiabetics	5 (19.2%)	4 (15.4%)
Oral anticoagulation	4 (15.4%)	4 (15.4%)
Aspirin	6 (23.1%)	6 (23.1%)
Sodium oxybate	0 (0%)	0 (0%)

Data are n (%)

Table 4. Blood pressure profiles by study arms.

		Subtherapeutic CPAP (sham) n=26	**Therapeutic CPAP (real)** n=26	**p-value**
Morning	Systolic blood pressure, mmHg	133.2 ± 16.2	130.2 ± 13.0	0.477
	Diastolic blood pressure, mmHg	81.5 ± 7.4	81.7 ± 9.4	0.941
	Heart rate, bpm	72.6 ± 9.1	71.9 ± 11.5	0.827
Noon	Systolic blood pressure, mmHg	130.2 ± 12.1	130.8 ± 12.5	0.850
	Diastolic blood pressure, mmHg	79.8 ± 7.6	81.0 ± 8.2	0.592
	Heart rate, bpm	75.4 ± 9.1	75.5 ± 11.8	0.974
Evening	Systolic blood pressure, mmHg	134.6 ± 15.0	132.0 ± 16.1	0.709
	Diastolic blood pressure, mmHg	79.2 ± 8.3	80.1 ± 8.1	0.687
	Heart rate, bpm	78.3 ± 10.9	76.6 ± 9.5	0.550

Table 5. Suboptimal CPAP-adherence profiles of all study participants.

Profile	n (%)	Examples
Lifestyle	28 (49%)	Shift workers with unregular sleep cycles, falling asleep while watching TV, decision to use CPAP only "*on demand (… when symptomatic)*"; "*seasonal*"; or "*… at the beginning of the night*", social restrictions (bed-partner, children, etc.), frequent traveling (to places without electricity)
Comorbidities	25 (44%)	Sleep-related neurological disorders (e.g. narcolepsy), cognitive disabilities (incl. dementia, depression, claustrophobia, etc.), airway-related diseases (e.g. chronic sinusitis, chronic cough), nocturia, craniofacial abnormalities (operations etc.), gastroesophageal reflux disease, substance abuse (alcohol, drugs, etc.), schizophrenia, untreatable cancer, etc.
Technical	4 (7%)	Mask-related issues (leakages), suboptimal pressure settings, skin irritation, beards, CPAP not working properly

Table 6. Recruitment details on average CPAP adherence by center. Ultimately, 1,035 patients from nine Swiss sleep laboratory centers were recruited by the investigators at the study site in Zurich.

Recruiting site	**Subjects screened**	**Average CPAP adherence**
Kantonsspital Aarau	294	2.7 ± 1.4
Kantonsspital Glarus	37	2.8 ± 1.1
Kantonsspital Graubünden	131	2.8 ± 1.2
Spital Horgen	16	2.9 ± 1.7
Spital Männedorf	10	2.8 ± 1.6
Kantonsspital Schaffhausen	8	3.6 ± 1.3
Stadtspital Triemli	151	3.2 ± 1.2
Universitätsspital Zürich*	268	3.2 ± 1.4
Zürcher RehaZentrum Wald	120	2.9 ± 1.3
	Sum: 1035	**Average all centers: 3.0 ± 1.4**

* study site

Table 7. Additional information on the subgroup population with cancer (12%, n=6).

Case	Cancer (Type)	Date of first diagnosis	Stage	Treatment	Follow up?	Involvement of the CNS	Cancer related medication during the trial	Insomnia, sleeping pills
1	Urothelial carcinoma of the bladder	May 2012	pT1 G3	Transurethral resection (May 2012) and epirubicin in May 2012.	Confirmed complete remission in June 2016.	No.	None.	No insomnia. Depression diagnosed in 2010 treated with SNRI.
5	Breast cancer	1993	pT2 pN0 (0/3) M0 L1 Pn0 R0 G2 HR+ Herz2- Ki67 20%	Mastectomy 1993, chemotherapy (unclear) 1993, radiotherapy (unclear) 1993 and hormonal therapy (Tamoxifen) since 1993	Confirmed complete remission in November 2014.	No.	Tamoxifen	No.
13	Testicular cancer	1993	Stage I	Inguinal orchiectomy	Confirmed complete remission in 2010.	No.	No.	No.
27	Breast cancer	July 2011	pT1c(m) pN2a(5/15) G3 / ER 100% / PR 100% / HER2(IHC) 1+, MIB1 20%	Mastectomy 2011, chemotherapy (Sparano-Regime) 2011-2012, radiotherapy (27x2=54Gy) 2012 and hormonal therapy (Tamoxifen) since 2012	Confirmed complete remission in December 2015.	No.	Tamoxifen.	No.
32	Prostate cancer	January 2017	T1 No M0	Transurethral resection 2017	No follow-up due to recent diagnosis	No.	No.	No.
43	Breast cancer	November 1996	pT1, pN0, M0, G1	Quadrantectomy 1996, chemotherapy	Confirmed complete remission in 2013.	No.	No.	No insomnia. Depression diagnosed in 2009 treated with SSRI.

Table 8. Additional information on the subgroup population with depression (10%, n=5) and schizophrenia (2%, n=1).

Case	Diagnosis	Date of first diagnosis	Treatment	Use of hypnotics
1	Depression	unclear	SSRI	No
2	Depression	2011	SNRI, psychotherapy	No
3	Depression	2009	SSRI	No
4	Depression	2005	SSRI, psychotherapy	No
12	Depression	2010	NDRI, psychotherapy	No
20	Schizophrenia	>20 years ago	Psychotherapy, no pharmacotherapy	No

NDRI, Norepinephrine-dopamine reuptake inhibitor
SSRI, Selective serotonin reuptake inhibitor
SNRI, Serotonin–norepinephrine reuptake inhibitor

Table 9. Additional information on the subgroup population with dementia (2%, n=1).

Case	Diagnosis	Diagnostics	Pharmacotherapy	Use of hypnotics
4	Mild cognitive impairment	Mini–Mental State Examination	Gingko leaves	No

Table 10. Additional information on the subgroup population of shift workers (4%, n=2).

Case	Profession	In this profession	Type of shifts	Use of hypnotics
17	Postal employee	Since >10 years	Permanent night shifts (1 AM to 9 AM)	No
52	Nurse	For >10 years	Alternating day and night shifts during the trial, no changes to usual habits	No

Table 11. Additional information on the subgroup population (29%, n=15) with central nervous system (CNS) medications.

Case	Substance	Dosage	Administration	Indication	Changes*
1	Escitalopram	10 mg	1x daily, oral	Depression	No
2	Duloxetine	60 mg	1x daily, oral	Depression	No
3	Escitalopram	10 mg	1x daily, oral	Depression	No
3	Valproate	300 mg	1x daily, oral	Epilepsy	No
4	Escitalopram	20 mg	1x daily, oral	Depression	No
4	Ginkgo biloba	unclear	1x daily, oral	Mild cognitive impairment	No
6	Cetirizine	10 mg	1x daily, oral	Rhinitis	No
10	Quetiapine	25 mg	1x daily, oral	Bipolar disorder	No
12	Trazodone	25 mg	1x daily, oral	Insomnia	No
19	Levetiracetam	100 mg	2x daily, oral	Epilepsy	Dose increase to 3x daily at V4
19	Fentanyl	2 mg	1x daily, dermal	Pain	No
19	Trazodone	25 mg	1x daily, oral	Insomnia	No
25	Escitalopram	20 mg	1x daily, oral	Obsessive-compulsive disorder	No
29	Bupropion	150 mg	1x daily, oral	Depression	No
31	Oxycodon	10 mg	2x daily, oral	Pain	No
33	Venlafaxine	150 mg	1x daily, oral	Anxiety disorder	No
40	Escitalopram	10 mg	1x daily, oral	Obsessive-compulsive disorder	No
46	Amitriptyline	25 mg	2x daily, oral	Migraine	No
46	Pregabalin	300 mg	1x daily, oral	Pain	No
46	Lorazepam	1 mg	1x daily, oral (on demand)	Insomnia	No
46	Pramipexole	0.125 mg	1x daily, oral	Parkinson	No
47	Trazodone	150 mg	1x daily, oral (on demand)	Insomnia	No

* Changes during the trial (V1 to V4) as noted on CRF

References

1. Punjabi NM, Shifa N, Dorffner G, Patil S, Pien G, Aurora RN. Computer-Assisted Automated Scoring of Polysomnograms Using the Somnolyzer System. *Sleep.* 2015;38(10):1555-1566.
2. Iber C A-IS, Chesson AL, Qaun SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications (1st edn). *Westchester: American Academy of Sleep Medicine.* 2007.
3. Baeten D, Baraliakos X, Braun J, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2013;382(9906):1705-1713.
4. Röver C. Bayesian random-effects meta-analysis using the bayesmeta R package. 2017; https://arxiv.org/abs/1711.08683. Accessed 10.04.2019, 2019.
5. Hoyos CM, Killick R, Yee BJ, Phillips CL, Grunstein RR, Liu PY. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. *Thorax.* 2012;67(12):1081-1089.
6. Friede T, Rover C, Wandel S, Neuenschwander B. Meta-analysis of two studies in the presence of heterogeneity with applications in rare diseases. *Biom J.* 2017;59(4):658-671.
7. McShane BB, Böckenholt U. Single-Paper Meta-Analysis: Benefits for Study Summary, Theory Testing, and Replicability. *Journal of Consumer Research.* 2017;43(6):1048-1063.
8. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *The New England journal of medicine.* 2016;375(10):919-931.
9. Redline S, Adams N, Strauss ME, Roebuck T, Winters M, Rosenberg C. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. *American journal of respiratory and critical care medicine.* 1998;157(3 Pt 1):858-865.
10. Weaver TE, Mancini C, Maislin G, et al. Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. *American journal of respiratory and critical care medicine.* 2012;186(7):677-683.