ORIGINAL ARTICLE

Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial

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ABSTRACT

Background Continuous positive airway pressure (CPAP) for symptomatic obstructive sleep apnoea (OSA) improves sleepiness and reduces vascular risk, but such treatment for the more prevalent, minimally symptomatic disease is contentious.

Methods This multicentre, randomised controlled, parallel, hospital-based trial across the UK and Canada, recruited 391 patients with confirmed OSA (oxygen desaturation index >7.5/h) but insufficient symptoms to warrant CPAP therapy. Patients were randomised to 6 months of auto-adjusting CPAP therapy, or standard care. Coprimary endpoints were change in Epworth Sleepiness Score (ESS) and predicted 5-year mortality using a cardiovascular risk score (components: age, sex, height, systolic blood pressure, smoking, diabetes, cholesterol, creatinine, left ventricular hypertrophy, previous myocardial infarction or stroke). Secondary endpoints included some of the individual components of the vascular risk score, objectively measured sleepiness and self-assessed health status.

Results Of 391 patients randomised, 14 withdrew, 347 attended for their follow-up visit at 6 months within the predefined time window, of which 341 had complete ESS data (baseline mean 8.0, SD 4.3) and 310 had complete risk score data. 22% of patients in the CPAP group reported stopping treatment and overall median CPAP use was 2 : 39 h per night. CPAP significantly improved subjective daytime sleepiness (adjusted treatment effect on ESS −2.0 (95% CI −2.6 to −1.4), p<0.0001), objectively measured sleepiness and self-assessed health status. CPAP did not improve the 5-year calculated vascular risk or any of its components.

Conclusions In patients with minimally symptomatic OSA, CPAP can reduce subjective and objective daytime sleepiness, and improve self-assessed health status, but does not appear to improve calculated vascular risk.

INTRODUCTION

Obstructive sleep apnoea (OSA) leads to recurrent hypoxic episodes, repeated arousals, surges in blood pressure (BP) and, in some patients, excessive daytime sleepiness and raised diurnal BP. Approximately 20–30% of the middle-aged population has some degree of OSA, most with few or no symptoms.[1 2] Severity of sleepiness from OSA correlates poorly with sleep study severity of OSA.[3] This is likely due to inter-individual variation in the degree of brain arousal from apnoeas,[4] the effect these arousals have on daytime function[5] and an individual's lifestyle. The UK National Institute for Health and Clinical Excellence (NICE) concluded that only two papers, with conflicting results, looked at the benefit of continuous positive airway pressure (CPAP) at low levels of OSA symptom severity.[6–8] Thus one aim of the current study was to identify any symptomatic benefit from CPAP in sleep clinic patients with apparently minimal symptoms.

During each apnoea there are often recurrent hypoxic dips and surges in BP.[9] These events may provoke sustained hypertension and several other potentially adverse cardiovascular consequences.[10–16] While the acute effects of OSA on BP are abolished by CPAP,[9] any beneficial effects on sustained hypertension appear to be limited mainly to the more severe and symptomatic patients, with little benefit observed in non-sleepy patients in short-term randomised trials.[6–8] Thus the second aim of this study was to assess the effect of 6 months of CPAP therapy on several potentially adverse vascular consequences, combined in an established calculated vascular risk algorithm in minimally symptomatic patients with OSA.

METHODS

Study design

The Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular trial (MOSAIC) was a randomised, parallel, 6-month controlled trial that was conducted between May 2006 and February 2010. There were 10 recruiting centres in the UK and Canada, with Oxford as the coordinating centre. All centres are designated sleep units with facilities for diagnosis, treatment and follow-up of patients with OSA, and have healthcare professionals specifically trained in CPAP set-up and usage. The trial was approved by the ethics committees of all the centres (REC No: 05/Q1604/159) and registered (ISRCTN 34164388).

Patients

Patients referred to sleep clinics, usually due to snoring, witnessed apnoeas or daytime sleepiness,

were assessed for eligibility and a screening log was kept. All patients were diagnosed with OSA using overnight respiratory polygraphy as standard in the participating centres. Patients were eligible if they were aged between 45 and 75 years, had proven OSA on the diagnostic sleep study, with >7.5 per hour oxygen desaturations of >4% (oxygen desaturation index, ODI), but had insufficient daytime symptoms associated with OSA to warrant CPAP therapy. This decision followed a detailed discussion between physician and patient about the evidence for possible benefits of CPAP versus the potentially lifelong nightly usage of a physical therapy. Thus patients with Epworth Sleepiness Scores (ESS) above the conventional upper normal limit (9) were included, when this was not accompanied by patient concerns. In addition, to ensure technical uniformity of the ODI across centres, a second domiciliary, overnight, pulse-oximetry recording (Konica-Minolta Inc, Osaka, Japan) was performed in all patients at baseline and at 6 months. This was used as the trial ODI value, which could therefore be different from the entry ODI. All patients who gave informed consent did so in accordance with Good Clinical Practice standards.

Continuous positive airway pressure

Patients assigned to CPAP were instructed in the use of an auto-adjusting CPAP machine (Autoset S8, ResMed, Abingdon, UK). Induction was by trained staff who were not involved in outcome assessments or data analysis. Humidification and interface choices were made on an individual basis. All patients had one or more follow-up visits to download compliance data, check for residual apnoea/hypopnoeas and mask leakage, and to make any necessary adjustments. There were routine telephone calls at 2 and 4 months, and telephone advice and replacement parts if requested by the patient.

Standard care

The standard care (SC) group had an identical planned visit schedule to the CPAP group. Both groups were asked to continue on their normal medication and not given any specific advice regarding diet and exercise.

Outcomes

The joint primary outcomes at 6 months (predefined time window 5–8 months) were change in ESS, and change in a composite vascular risk endpoint, the 5-year risk of a fatal cardiovascular event calculated using a cardiovascular risk score. Secondary outcomes at 6 months were change in objective sleepiness, self-assessed health status, BP, lipids, glucose metabolism, obesity measures, vascular events and sleep apnoea severity (ODI).

Assessments of sleepiness

Subjective sleepiness was determined using the ESS,[17] which assesses the tendency to fall asleep during eight typical daytime scenarios. Objective sleepiness was assessed using one Oxford Sleep Resistance (OSLER) test administered at the same time of day (Stowood Scientific Instruments Oxford, UK), a sleep resistance challenge which tests the ability to stay awake for 40 min in a quiet, darkened room.[18 19]

Self-assessed health status

The Medical Outcome Study, the 36-item Short-Form health survey (SF-36),[20] the Calgary Sleep Apnoea Quality-of-Life Index (SAQLI)[21] and the two-part Euroqol (EQ-5D) questionnaires[22] were administered by trial staff and are described in the online supplementary appendix.

BP measurements and blood tests are also given in the online supplementary appendix.

Cardiovascular risk score

To avoid the problem of multiple comparisons, a calculated vascular risk score was used as a composite endpoint, thus allowing the inclusion of relevant factors with their correct relative weightings (only some of which could potentially be affected by OSA or its treatment). The algorithm proposed by Pocock *et al*[23] is similar to the Framingham risk score but estimates the probability of a fatal cardiovascular event within 5 years from 11 factors: age (at baseline), sex, height, systolic BP (median of a 7-day period), total cholesterol, creatinine, cigarette smoking (current smoker if smoked in the previous month), diabetes (either on treatment, previously diagnosed and in general practice records, or fasting glucose ≥7 mmol/litre and haemoglobin A1c (HbA1c) >6.5%), left ventricular hypertrophy (Sokolov-Lyon method on ECG), history of cerebrovascular incident and/or myocardial infarction (from general practice records and verified from hospital case records if equivocal). Although some of these factors clearly could not change during follow-up (thus representing a 'fixed offset'), their inclusion is necessary to derive a valid single risk score with the correct weightings.

Sample size calculation, randomisation data and statistical methods are given in the online supplementary appendix.

RESULTS

Flow diagram of trial allocation, implementation of intervention and baseline data

Figure 1 shows the trial profile. The trial was stopped nine patients short of the target of 400 because the number not attending for follow-up (4%) was lower than predicted (10%). Baseline data by group assignment are shown in table 1, and the baseline distribution of ESS scores by group assignment is shown in the online supplementary appendix (figure a).

Primary outcomes

Table 2 shows a summary of the adjusted treatment effects for the primary outcomes, including the results of the imputation and sensitivity analyses (further described in the online supplementary appendix). CPAP improved subjective sleepiness by a two-point reduction in the ESS scale compared with the SC group (95% CI −2.6 to −1.4; p<0.0001). There was a small, clinically insignificant, absolute increase of 0.1% in the 5-year risk of a fatal vascular event in the CPAP arm, relative to SC (95% CI 0.0% to +0.2%; p=0.070). The analyses of the components of the risk score in patients included in the primary risk score analysis are shown in table 3.

Secondary outcomes

Objective sleepiness

The proportion of patients falling asleep during the 40 min OSLER test was similar in the two groups at baseline (39% and 35% in the SC and CPAP group, respectively). At 6 months, the odds of falling asleep during the OSLER test were 44% lower in the CPAP treatment group compared with SC (95% CI −1 to −68%), p=0.045 (logistic regression). A 'time to event' (falling asleep) Kaplan–Meier plot of these data is shown in figure 2.

Indices of self-assessed health status

Most components of the SF-36 (except bodily pain, mental health and role physical) showed evidence of improvement following CPAP (tables 4 and 5, figure 3). The largest treatment effect was in energy/vitality, +6.6 (95% CI +3.1 to +10.1),

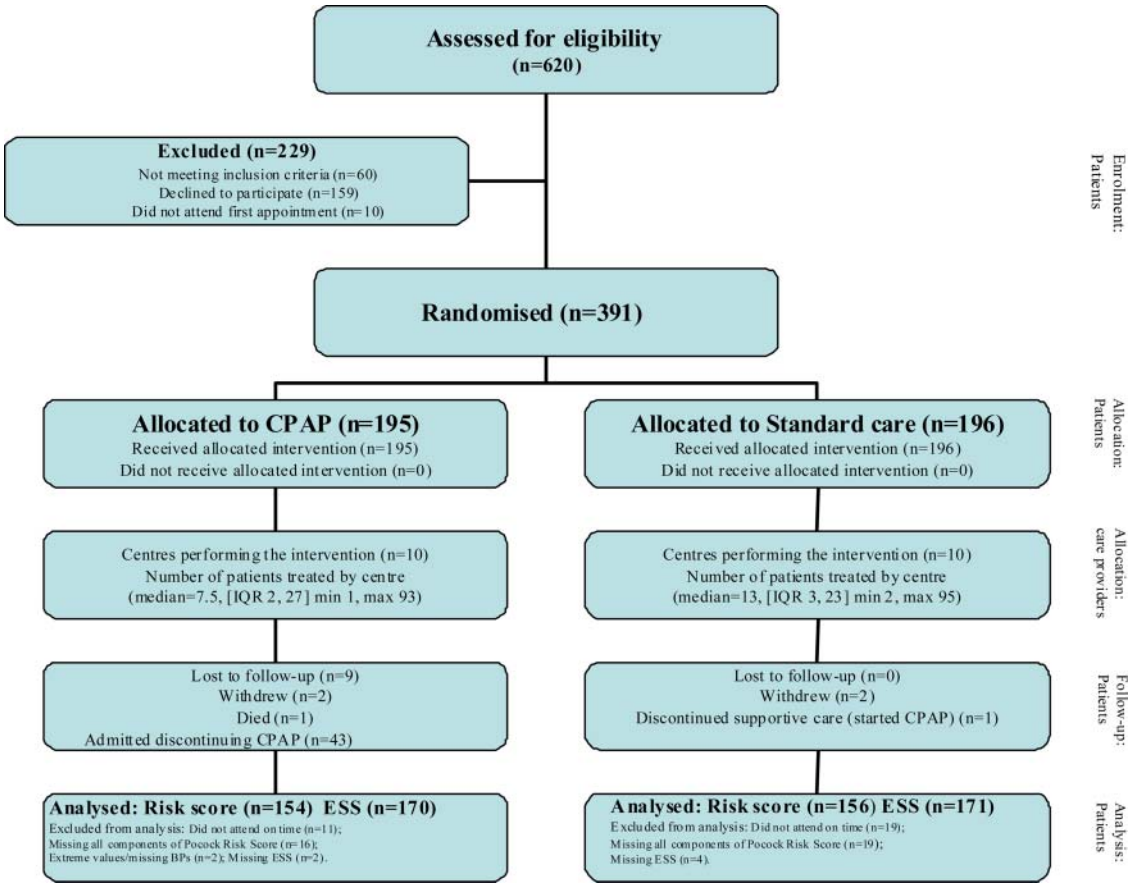

Figure 1 Flow diagram showing the trial allocation. BP, blood pressure; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Score. This figure is only reproduced in colour in the online version.

p<0.0001. The mental component score improved by 2.6 points (95% CI +0.9 to +4.2), p=0.003. The SAQLI also showed a statistically significant improvement, but the small improvement in the Euroqol was not statistically significant (see online supplementary appendix tables a and b).

Other metabolic and vascular outcomes

CPAP usage

Forty-three (22%) of the 195 patients randomised to CPAP reported stopping treatment during follow-up (see online supplementary appendix, tables c and d). Of the 172 patients on CPAP who attended their 6-month visit 'on time' (predefined time window 5–8 months), 150 (87%) had compliance data at 6 months. Median CPAP usage was 2 : 39 h/night (IQR 0 : 36 to 4 : 59), with compliance in non-users with missing data set to zero. Including all the patients on CPAP in the analysis did not substantially alter this result (median 2 : 27 h/night (IQR 0 : 28 to 4 : 55)). Age, sex, study centre and baseline ODI, ESS, body mass index, neck circumference and OSLER result were not predictive of CPAP compliance. Following the end of the 6-month trial, 71% of patients randomised to CPAP expressed a wish to continue CPAP.

Effect of CPAP usage on outcomes

Figure 4A shows the effect of <4 h/night and ≥4 h/night of CPAP usage on change in ESS compared with SC. There was a statistically significant improvement in ESS with greater CPAP compliance (p=0.0001). The effect of CPAP usage on self-assessed health status outcomes are detailed in the online supplementary appendix (figure b). Figure 4B shows the effect of CPAP usage on change in 5-year vascular risk compared with SC. There is no evidence to suggest that good compliance (≥4 h/night) improved vascular risk compared with poor compliance (<4 h/night, p=0.49). The effect of CPAP usage on systolic BP and HbA1c are detailed in the online supplementary appendix (figure c). The effect of CPAP usage on ODI is also shown in the online supplementary appendix (table c and figure g).

Association of age, sex, ODI, baseline ESS and hypertensive status with outcomes

The effect of CPAP therapy on ESS was largely independent of baseline ODI, age or sex (figure 5). There was some evidence that patients with ESS scores in the two quartiles above the median at baseline benefitted more than those below the median. However, there was still a significant treatment effect even in those in the lowest ESS quartile at baseline. The effect of CPAP therapy on 5-year vascular risk was independent of baseline ESS, ODI, age, sex and hypertensive status (figure 5). The effect of the above factors on systolic BP is detailed in the online supplementary appendix (figure d). The association between baseline ESS and change in diastolic BP and cholesterol are detailed in the online supplementary appendix (figures e and f).

DISCUSSION

This study has shown that in minimally symptomatic patients with OSA, 6 months of CPAP therapy improves daytime

Table 1 Baseline characteristics and minimisation variables in all MOSAIC patients

	Standard care (N=196)	CPAP (N=195)
Epworth Sleepiness Score	8.0 (4.2)	7.9 (4.4)
Vascular risk score	35.7 (7.6)	35.5 (7.7)
Vascular risk score components		
Sex (men)	152 (77.6%)	153 (78.5%)
Age (years)	57.6 (7.5)	57.9 (7.2)
Height (cm)	174.8 (8.8)	174.0 (9.1)
Total cholesterol (mmol/l)	5.2 (1.2)	5.3 (1.2)
Systolic BP (mm Hg)	129.6 (13.6)	129.7 (11.6)
Creatinine (μmol/litre)	95.5 (18.8)	92.0 (14.9)
Left ventricular hypertrophy	3 (1.6%)	2 (1.1%)
Previous myocardial infarction	14 (7.1%)	9 (4.6%)
Previous stroke	1 (0.5%)	4 (2.1%)
Diabetic	40 (20.4%)	23 (11.8%)
Smoking status		
Current smoker	28 (14.3%)	17 (8.7%)
Ex-smoker	97 (49.5%)	102 (52.3%)
Hypertensive	149 (76.0%)	151 (77.4%)
Oxygen desaturation index (>4% dips/h)	9.4 (5.2, 15.0)	10.2 (4.7, 17.5)
Resting O_2 saturation (%)	96.0 (1.4)	96.0 (1.3)
OSLER (min)	40·0 (25·8, 40·0)	40·0 (27·0, 40·0)
Waist circumference (cm)	109.4 (12.9)	108.1 (12.6)
BMI (kg/m^2)	32.5 (5.6)	32.2 (5.6)
Neck circumference (cm)	43.0 (4.0)	42.5 (3.9)
Diastolic BP (mm Hg)	81.3 (8.0)	81.3 (7.7)

Data are presented as mean (SD), median (25th, 75th percentiles) or number of patients (%).
BMI, body mass index; BP, blood pressure; CPAP, continuous positive airway pressure; MOSAIC, Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular trial; OSLER, Oxford Sleep Resistance test.

Table 2 Primary outcome results. Adjusted treatment effects (CPAP change minus standard care change) for ESS, and percentage risk of fatal cardiovascular event within 5 years

	Standard care/ CPAP (N)	Adjusted treatment effect (95% CI)	p Value
ESS	171/170	−2.0 (−2.6 to −1.4)	<0.0001
5-year risk of fatal vascular event (%)			
Primary analysis	156/154	+0.1 (0.0 to +0.2)	0.070
Sensitivity analysis (ignoring smoking changes)	156/154	+0.1 (0.0 to +0.1)	0.19
Imputation analysis	175/172	+0.1 (0.0 to +0.2)	0.028

CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Score.

sleepiness and self-assessed health status, but does not improve the calculated 5-year risk of a fatal cardiovascular event, or any of its component parts.

The individuals in this study were less sleepy than in the majority of previous randomised controlled studies on CPAP. In two of our previous comparable trials the mean baseline ESS of 16, and the median baseline OSLER of 21 min, compares to about 8 and 40 min, respectively.[24 25] The ESS improvement was seen across almost the whole spectrum of baseline ESS severity. Compared with SC, the number needed to treat for at least a two-point ESS improvement is about four (online supplementary appendix, table e). The fall in ESS of two points, relative to control, compares to a fall of about five points observed in one of our previous studies mentioned above.[24] Because the ESS scale is an ordinal, rather than a linear, measure of sleepiness, it is difficult to compare changes at different points across the spectrum. However, in the NICE economic model,[26] a drop of 2.3 in ESS in patients treated with CPAP incurred a cost of £9331 and was considered economically viable. This drop of two in ESS would be expected in theory to improve work productivity by about 2%[27] and reduce sleep-related road accident rates by about 9%,[28] further adding to the cost efficacy of treatment.

This effect of CPAP on sleepiness was also observed almost equally across the whole ODI spectrum, confirming previous findings that the correlation between symptoms and apnoea-hypopnoea index (AHI), or ODI, is very poor. Nearly a quarter of patients started on CPAP in the current study admitted stopping therapy as they did not perceive benefits to outweigh inconvenience. However, 71% stated at the 6-month appointment that they wished to continue CPAP long term. This is similar to long-term CPAP take-up rates for patients with moderate OSA in many centres, including our own.[29 30] From the baseline data we collected, there were no clear ways to predict in advance which individuals will benefit from treatment (figure 5).

We have also shown that self-assessed health status, as measured by SF-36 and SAQLI, improves with CPAP in patients with minimally symptomatic OSA. A previous randomised controlled trial of self-assessed health status in severely sleepy subjects with OSA showed treatment effects of 0.9 in the SAQLI,[31] and 14.5 in the Energy/Vitality component of SF-36, compared with the current trial of 0.6 and 6.6, respectively. This suggests that CPAP therapy in patients with minimally symptomatic OSA produces an improvement in self-assessed health status of 45–70% of that seen in severely sleepy patients.

Despite the clear symptomatic response to CPAP there was, if anything, weak evidence that vascular risk slightly worsened

Table 3 Baseline and follow-up means (SD) and adjusted treatment effects for the components of the vascular risk score

	Standard care, N=156		CPAP therapy, N=154			
Outcome measure	Baseline	Follow-up	Baseline	Follow-up	Adjusted treatment effect (95%CI)	p Value
Systolic BP (mmHg)	130.1 (13.0)	129.8 (12.0)	129.7 (11.6)	131.1 (13.4)	+1.8 (0.0 to +3.5)	0.049
Cholesterol (mmol/litre)	5.2 (1.1)	5.1 (1.2)	5.3 (1.2)	5.1 (1.1)	0.0 (−0.2 to +0.1)	0.68
Creatinine (μmol/litre)	96.3 (19.2)	94.8 (19.9)	93.9 (14.3)	92.8 (15.5)	+0.2 (−1.8 to +2.2)	0.82
Current smoker (%)	22 (14.1)	19 (12.2)	10 (6.5)	12 (7.8)		
Diabetic (%)	30 (19.2)	33 (21.2)	19 (12.3)	20 (13.0)		
Left ventricular hypertrophy (%)	2 (1.3)	1 (0.6)	2 (1.3)	4 (2.6)		
Myocardial infarction (%)	9 (5.8)	9 (5.8)	9 (5.8)	9 (5.8)		
Stroke (%)	1 (0.6)	1 (0.6)	2 (1.3)	2 (1.3)		

BP, blood pressure; CPAP, continuous positive airway pressure.

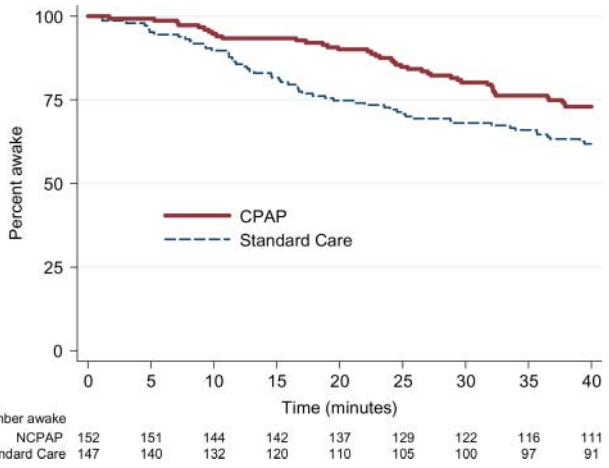

Figure 2 Kaplan–Meier plot showing the percent (and number) of subjects remaining awake during the Oxford Sleep Resistance (OSLER) test, for the standard care group and continuous positive airway pressure (CPAP) group at the 6-month follow-up visit.This figure is only reproduced in colour in the online version.

compared with SC, although the effect was clinically insignificant. This unimportant adverse effect was largely explained by small statistically non-significant differential changes in both smoking status and BP (and its medication) over the 6 months (table 2). Change in vascular risk did not seem to be related to initial OSA severity, or CPAP compliance, implying that we probably did not miss an effect, simply because overall compliance with CPAP was low. However, in the subgroup of patients with higher baseline ESS values (>11), there was a trend towards an improvement in vascular risk with CPAP (figure 5). Similarly systolic and diastolic BP, and cholesterol did fall in the CPAP arm relative to the SC arm in patients with higher ESS (>11), although these interactions were not statistically significant (online supplementary appendix, figures d–f). The drop in cholesterol of 0.30 mmol/litre in our most sleepy patients was similar to the findings of a previous study showing a fall in cholesterol of 0.28 mmol/litre in a more severely affected and sleepy population (mean ESS 16) treated for 1 month with CPAP.[11] This suggests that patients with greater sleepiness benefit more than non-sleepy patients and supports previous findings.[7 8 25] A randomised controlled 12-month study by Barbe *et al*[32] in a hypertensive non-sleepy population showed a small reduction in systolic and diastolic BP (1.9 and 2.2 mm Hg, p=0.07 and p=0.0008, respectively), but a larger effect (3.7 and 3.5 mm Hg, p=0.007 and p=0.0001, respectively) in patients with the highest CPAP compliance (>5.6 h/night) who also had the largest improvement in sleepiness. More recently, the same group[33] studied non-sleepy patients without prior cardiovascular events (some with hypertension) over a median of 4 years. Although there was no significant overall reduction in new events (predominantly new onset hypertension) in the CPAP group, the subgroup of patients prepared to use CPAP for >4 h/night did experience a reduction in vascular events. Interestingly, in both these trials the baseline AHI of the study population was higher (mean 45 and 39) than the ODI in our study (median 10), and thus these patients probably had worse OSA.

As no sham CPAP was used in our control group, our results might merely be due to a placebo effect of CPAP, observed in previous short trials.[24 25] However, as this was a 6-month trial, the placebo effect is likely to have diminished with time. In addition, previous studies employing sham CPAP did not generate placebo effects with the OSLER test;[24] yet we have demonstrated a significant treatment effect on this objective measure of sleepiness.

We adopted a clinical approach to setting up CPAP therapy, without overnight CPAP titration, which has become standard in many UK and European based sleep centres.[34] We obtained relatively low CPAP compliance, probably representing the likely usage when such non-sleepy patients are offered CPAP, which may have lessened the chance of demonstrating an effect on vascular risk, although there was no benefit in the sizeable subgroup of higher compliers. Similar to the current trial, CPAP compliance has been reported to be relatively low (2.9 h/night) in a study using overnight CPAP titration to establish an optimal pressure to abolish breathing irregularities in patients with mild OSA.[35] However, the Spanish group has managed to achieve higher compliance levels in their trials on non-sleepy patients (defined as ESS<10).[32 33]

Table 4 SF-36 questionnaire

Energy/vitality	Standard care, N=168	CPAP, N=171
Baseline mean score (SD)	49.7 (23.7)	49.8 (22.4)
6-month mean score (SD)	53.9 (22.5)	60.6 (20.9)
Mean change (SE)	+4.2 (1.4)	+10.8 (1.3)
Adjusted treatment effect (95% CI), p value	+6.6 (+3.1 to +10.1), p<0.0001	

Mean baseline and 6-month energy/vitality scores with adjusted treatment effect. An increase in the energy and vitality subscore indicates an improvement in health status. CPAP, continuous positive airway pressure; SF-36, 36-item Short-Form health survey.

Table 5 SF-36 questionnaire

Mental component score	Standard care, N=158	CPAP, N=165
Baseline mean score (SD)	46.6 (11.3)	48.2 (10.4)
6-month mean score (SD)	48.5 (11.0)	52.0 (9.8)
Mean change (SE)	+1.9 (0.7)	+3.8 (0.6)
Adjusted treatment effect (95% CI), p value	+2.6 (+0.9 to +4.2), p=0.003	

Mean baseline and 6-month mental component scores with adjusted treatment effect. An increase in mental component score indicates an improvement in health status. CPAP, continuous positive airway pressure.

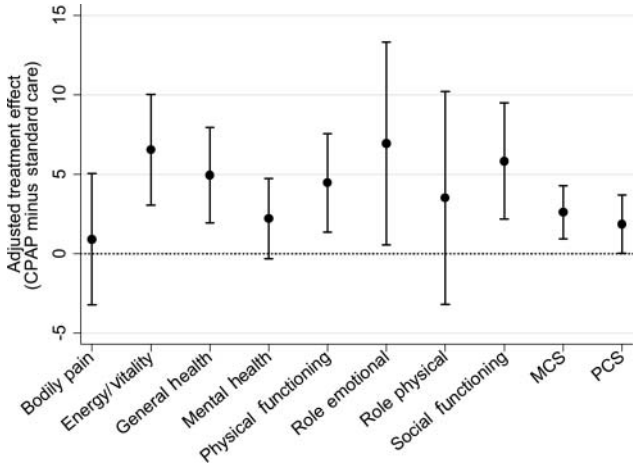

Figure 3 36-item Short-Form health survey (SF-36). Adjusted treatment effects and their 95% CIs on the mental component score (MCS), physical component score (PCS) and their eight individual components. Higher scores indicate improved self-assessed health status. CPAP, continuous positive airway pressure.

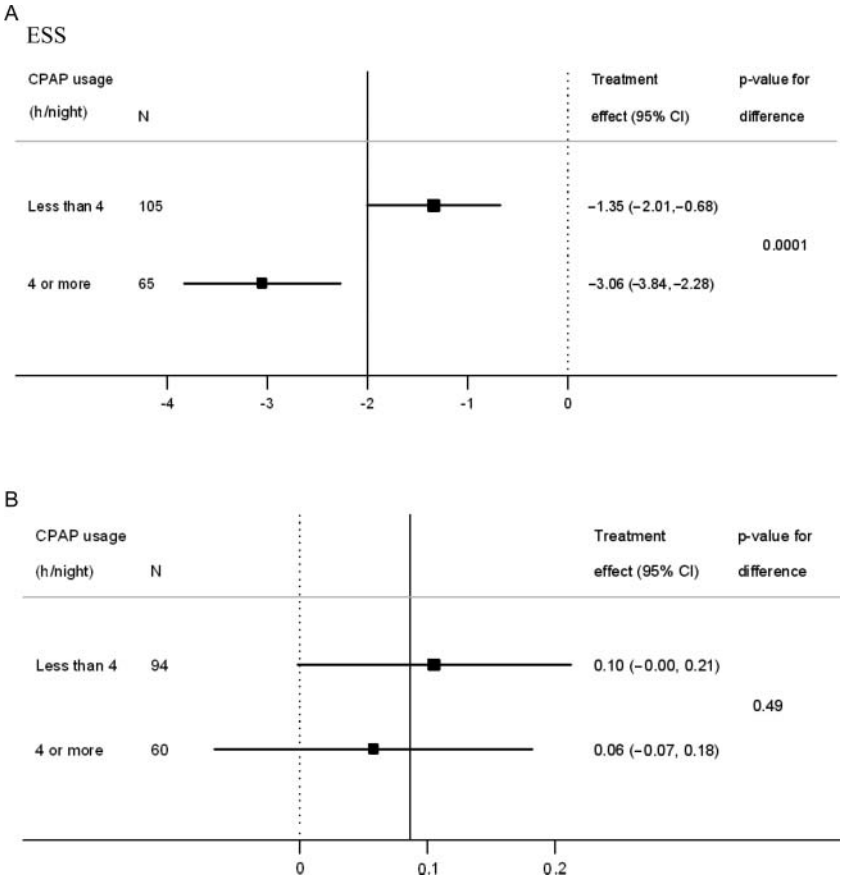

Figure 4 Forest plots showing the adjusted treatment effects by continuous positive airway pressure (CPAP) compliance (<4 h/night and ≥4 h/night), with tests for interactions, on (A) Epworth Sleepiness Score (ESS) and (B) vascular risk (%).

It may be that the markers of cardiovascular risk included in the risk score are either too insensitive or unlikely to change in a 6-month period, and other markers such as endothelial function, sympathetic activity levels or circulating inflammatory markers may more sensitively reflect any risk reduction. However, short trials of 1-month duration in more severely affected patients have shown clear reductions in BP.[25]

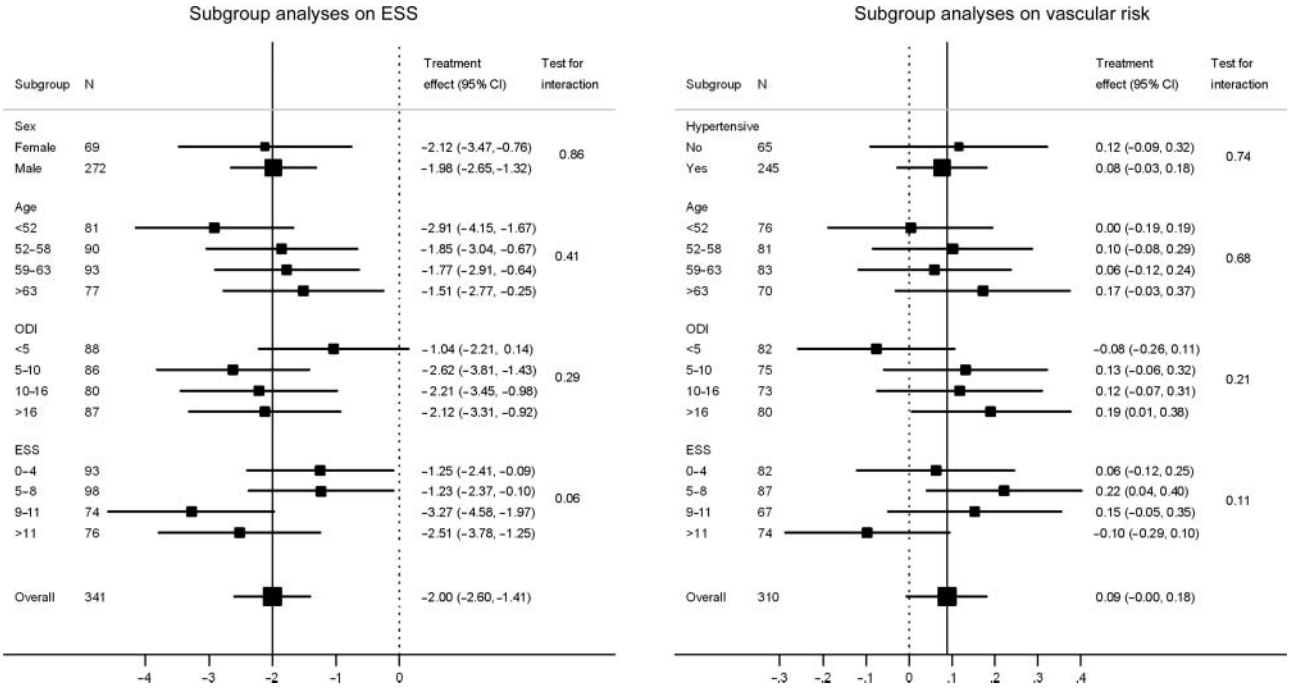

Figure 5 Forest plots showing the adjusted treatment effects, with tests for interaction, on Epworth Sleepiness Score (ESS) (left panel, by sex and quartiles of age, baseline oxygen desaturation index (ODI) and baseline ESS), and on vascular risk (%) (right panel, by baseline hypertensive status and quartiles of age, baseline ODI, baseline ESS).

In conclusion, our findings show that even when there is little enthusiasm for CPAP by patient and physician, because of an apparent paucity of symptoms, nearly half of patients on CPAP experienced at least a two-point improvement in ESS. This positive treatment effect extends further down the spectrum of OSA symptom severity than was previously thought, but it is difficult to predict, at an individual level, which patients will benefit. However, this positive treatment effect on symptoms was not accompanied by a reduction in calculated vascular risk or BP. Thus CPAP should be offered to patients with OSA, despite minimal daytime symptoms, on a trial basis, but with the expectation that some will decide that the benefits do not justify the inconvenience and thus will return their equipment. Because this study was carried out in a general sleep clinic setting, it is therefore only applicable to mainstream sleep practice; the sleepiness and self-assessed health status benefits should not be extrapolated to subjects with undiagnosed OSA in the general population who have not had cause to present to a sleep clinic.

Contributors The authors fulfilled the criteria for authorship, had full access to all data in the study, and had final responsibility for the decision to submit for publication.

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Competing interest None.

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Correction

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Online Appendix

CPAP improves sleepiness but not calculated vascular risk in patients with minimally symptomatic OSA; the MOSAIC randomised controlled trial.

Table of Contents

METHODS

Trial schedule

There were four planned visits during the trial:

1. Enrolment; anthropometric measures (weight, waist, hip and neck circumference) were carried out in addition to the tests described in the main paper. A drug and smoking history were obtained. The oximeter and BP machine were supplied for home use.

2. Randomisation visit; usually one week later, oximetry and BP data were downloaded and the patient allocated to their trial group. CPAP was set up at this visit if allocated.

3. Third visit; three weeks later, a routine CPAP follow-up visit was scheduled. However, all patients were reviewed so that both trial groups had an equal number of visits.

4. Final visit; at six months, a repeat of the enrolment visit.

General practice health records were obtained at baseline and six months to confirm past medical history and current medication.

Exclusion criteria

Patients were excluded from the trial if they had any of the following: ventilatory failure, Cheyne-Stokes breathing, previous exposure to CPAP, systolic blood pressure (BP) >180 or diastolic BP >110 mmHg on three successive measurements during the eligibility assessment, a heavy goods or public service vehicle driver's licence, previous sleep-related accident, or a disability precluding either informed consent or compliance with the protocol.

CPAP compliance

CPAP compliance over the six month follow up was determined by downloading usage data from the machine and defined as total hours used, divided by days between the set-up visit and the six month follow-up visit. Non-users were defined as those who admitted stopping CPAP therapy at least one month prior to their six month follow-up appointment. Compliance was set to 0 hours/night in those non-users who had no compliance data available at six months, usually due to the patient having returned their machine some while before their six month visit.

Self-assessed health status questionnaires

The SF-36 has been widely used to assess quality of life and self assessed health status in a number of different disorders,[1] including OSA.[2] The SAQLI was designed as a disease-specific instrument to evaluate health-related quality of life in OSA patients in clinical trials of CPAP and is well validated.[3] It contains questions related to CPAP use where appropriate, any adverse effects of CPAP will reduce the score. The EuroQol-5 Dimensions (EQ-5D) is a generic questionnaire for the evaluation of quality of life encompassing five dimensions but contains no questions related to sleep or sleepiness,[4] and in populations with OSA[5] has not captured response to CPAP to the extent other questionnaires have.[6] There is one question for each dimension which can be answered by three levels of impairment. The scores for the five domains are computed and the EQ-5D utility index derived according to evaluations in a British population. In addition, the subjects rate health status on a visual analogue scale, 0 (worst health imaginable) to 100 (best health imaginable), providing a second measure.

Blood pressure measurements

Home BP measurements were carried out using a digital automatic monitor with internal memory (M7, Omron Healthcare, Kyoto, Japan). Home measurements of BP have been shown to be as good, or nearly as good, as 24hr measurements in predicting adverse consequences. [7] Patients were given verbal and written instructions on using the machine, and a diary to record readings. Readings were taken in triplicate in the seated position, following five minutes rest, on three separate occasions across the day, and on seven consecutive days. This was done at baseline (prior to randomisation) and repeated in the week prior to the six months visit. Data were extracted from the monitor's memory, and the median value of all the seven days values (systolic and diastolic BP) was used in the analysis.

Blood tests

Participants were asked to fast from midnight prior to both their enrolment visit and the six months visit. Samples were taken for glucose, lipids, creatinine, HbA1c, and insulin. The homeostatic model assessment (HOMA)[8] of beta cell function and insulin sensitivity was calculated.

Blinding

Sham CPAP was not used in the control arm and therefore patients were not blinded. It was not possible to blind all trial staff, although the assessments were done blind wherever possible. Therefore, the observed effects on sleepiness might be considered due to bias or the 'placebo effect' of CPAP.

However, in a six month trial, any placebo effect is likely to have diminished with time. In addition, in previous studies, sham CPAP, although producing placebo effects on the ESS, did not generate placebo effects on the OSLER test;[9] yet we have demonstrated a significant treatment effect on this objective measure of sleepiness. Finally, the observation of a therapeutic dose response (figure 4a, main paper) argues against a placebo effect of CPAP.

Sample size calculation

A sample size calculation to ensure we did not miss a difference of one point on the ESS scale with 90% power indicated 220 patients should be randomised; this was based on a similar but smaller study of relatively asymptomatic patients with OSA treated with CPAP.[10] However, it was not possible to calculate a sample size for the risk score because of the absence of any appropriate data. Therefore, because BP and cholesterol were judged to be the dominant components likely to change in the risk score, these were used. Data from our previous studies in more severe patients[11;12] indicated that approximately 360 patients should be randomised to ensure that we did not miss a 3mmHg change in BP, or a 0·3mmol/l change in cholesterol, with 80% power. We assumed 10% of patients would fail to attend their six month visit and thus the trial was designed to recruit a total of 400 patients.

Randomisation

Randomisation was carried out by telephoning the Medical Research Council Clinical Trials Unit (MRC CTU), using minimisation with a random element of 80%; the minimisation factors were OSA severity (ODI, above or below 20/h), risk score (above or below 40) and participating centre.

Data and Statistical methods

Data were held in a central database (MRC CTU) and primary endpoint data subjected to a 100% check by the co-ordinating centre. Prior to the analysis, a statistical analysis plan, incorporating all analyses reported (apart from the subgroup analyses by baseline ESS and ODI, and all subgroup analyses on secondary outcomes), was written in agreement with the trial coordinators and statisticians. Data were analysed on an intention-to-treat basis but excluded those with missing data and those who attended their final six month follow-up visit either more than four weeks earlier, or eight weeks later, than the expected date of that visit, whatever the reason, in order to more accurately determine the effect of CPAP at six months. Furthermore, one patient with renal failure was excluded due to a creatinine value

outside the range used in the original derivation of the risk score, as was a patient who did not obtain BP readings prior to randomisation.

All data were analyzed using multivariable regression models with adjustment for the minimisation variables and baseline value of the corresponding variable being analyzed. In addition a backwards elimination procedure was applied to baseline body mass index (BMI), neck circumference, resting oxygen saturation, and medication usage (whether using antihypertensives, statins, hypoglycaemics or insulin at enrolment) using a p-value ≥0·1 for removal of variables in order to adjust for strong predictors of outcome. Data were initially planned to be analysed unadjusted using t-tests, however, this is an inappropriate method of analysis for trials using minimisation in the randomisation process and was therefore not used.[13] Subgroup analyses were performed using interaction tests. A post-hoc sensitivity analysis, whereby smoking status was assumed not to have changed from baseline, was performed on the risk score to determine its influence on the results.

Baseline and six month values are presented as means (SD), medians (25^{th} & 75^{th} percentiles), or percentages, as appropriate. All statistical analyses were performed using STATA Version 11 for Windows (Stata Corporation, TX, USA).

The data are reported in accordance with the CONSORT criteria.[14]

Imputation analysis

In addition to the above analysis, an imputation analysis of the risk score was also performed, as just over 10% of the study population had one or more components of the risk score missing. The missing at random assumption seemed plausible and so multiple imputation, using chained equations, was used to impute missing baseline and follow-up data.[15] The imputation model included all baseline and follow-up risk score components along with all covariates which were planned to be adjusted for in the analysis. Twenty imputed datasets were created from the model which matched on all continuous variables.

Role of the funding source

Funders of the trial had no role in study design, data collection, data analysis or interpretation, or writing of the report. Authors fulfilled the criteria for authorship, had full access to all data in the study, and had final responsibility for the decision to submit for publication. There are no conflicts of interests.

RESULTS

Primary outcomes – sensitivity and imputation analysis

The missing at random assumption for the multiple imputation analysis seemed plausible since participants at three centres were much more likely to have missing risk scores than others. In particular, all patients in one centre had missing risk scores due to the centre not measuring LVH status. The majority of the remaining missing risk scores were due to six month blood pressures not being taken because patients omitted to take them.

There were two patients in the CPAP arm and one on SC who started smoking during the six month follow-up, and four patients on SC who stopped smoking. In a sensitivity analysis, ignoring these changes, the treatment effect was +0.1% (95% CI 0.0% to +0.1%; p=0.19). The imputation analysis made little difference to the original adjusted treatment effect (+0·1%, 95% CI 0·0% to +0.2%; p=0·028, n=347). Although this effect is slightly stronger than the treatment effect observed in the complete case analysis, this is due to the uneven changes in smoking between the treatment arms being amplified by the imputation.

Secondary outcomes – EQ-5D

In contrast to the SF-36 and SAQLI, we did not see a significant improvement in general health status as assessed by the EQ-5D. Similar results with this questionnaire have been found in severely sleepy patients.[6] It appears, therefore, that the EQ-5D is not sensitive to the emotional and self-assessed health status changes observed with CPAP, probably due to the absence of a sleep and fatigue dimension (as present in the SF-36). Thus its recommended use by NICE for cost-effectiveness calculations may not be universally applicable.[16]

Other vascular and metabolic outcomes

Table c shows the treatment effect of CPAP on diastolic BP, lipids, glucose control and indices of obesity. The only significant effect was a small fall in obesity indices (BMI, waist circumference) favouring SC. The small number of vascular events occurring during the trial are shown in table d .

CPAP effect on ODI

CPAP therapy reduced ODI by 7·9 dips/h from baseline compared to SC, (95% CI -5·9 to -10·0), p<0·0001, (table c); a greater reduction in ODI was associated with higher CPAP compliance (figure g).

TABLES AND FIGURES

SAQLI questionnaire

SAQLI	**Standard Care (N=163)**	**CPAP (N=167)**
Baseline mean score (SD)	4.8 (1.2)	4.9 (1.1)
6m mean score (SD)	5.0 (1.3)	5.6 (1.0)
Mean change (SE)	+0.2 (0.1)	+0.7 (0.1)
Adjusted effect, 95% CI, p-value	+0.6 (+0.4 to +0.8) p<0.0001	

Table a: Mean baseline and six month SAQLI scores with adjusted treatment effect. An increase in SAQLI score indicates an improvement in health status.

EQ-5D questionnaire

Health Status (Visual Analogue Score)	**Standard Care N=108**	**CPAP N=110**
Baseline mean (SD)	67.5 (17.9)	71.0 (17.3)
6m mean (SD)	70.3 (17.6)	75.5 (16.4)
Mean change (SE)	+2.7 (1.5)	+4.4 (1.3)
Adjusted difference, 95% CI, p-value	+3.0 (-0.5 to +6.5) p=0.095	
EQ5D score	**N=107**	**N=110**
Baseline mean (SD)	0.75 (0.24)	0.80 (0.17)
6m mean (SD)	0.80 (0.22)	0.83 (0.19)
Mean change (SE)	+0.04 (0.02)	+0.03 (0.02)
Adjusted difference, 95% CI, p-value	+0.02 (-0.03 to +0.06) p=0.43	

Table b: Mean baseline and six month EQ-5D and health status scores (Visual Analogue Score) with adjusted treatment effects. An increase in scores indicates an improvement in health status.

Vascular and Metabolic Outcomes

	Standard Care			CPAP			Adjusted treatment effect (95% CI)	P value
	N	Baseline	Follow up	N	Baseline	Follow up		
DBP (mmHg)	166	81·4 (8·1)	81·3 (8·0)	166	81·2 (7·7)	80·8 (8·3)	-0·4 (-1·5 to +0·7)	0·46
HDL (mmol/l)	169	1·28 (0·32)	1·26 (0·33)	170	1·32 (0·39)	1·28 (0·35)	-0·01 (-0·05 to +0·02)	0·50
LDL (mmol/L)	166	3·09 (1·0)	2·99 (1·1)	166	3·18 (0·99)	3·07 (0·97)	0·00 (-0·13 to +0·13)	0·97
Trig (mmol/L)	171	1·69 (0·9)	1·71 (0·9)	168	1·68 (1·00)	1·67 (0·88)	-0·04 (-0·16 to +0·07)	0·46
HbA1c (%)	163	6·03 (0·95)	6·07 (1·01)	166	5·99 (0·89)	6·03 (1·12)	-0·01 (-0·14 to +0·12)	0·91
Glucose (mmol/L)	166	5·77 (1·34)	5·89 (1·67)	167	5·67 (1·52)	5·81 (1·85)	0·00 (-0·23 to +0·23)	0·99
Insulin (mU/l)	128	101·4 (62·8)	107·1 (85·0)	136	95·2 (76·3)	95·7 (83·3)	-6·6 (-21·6 to +8·3)	0·38
%B	127	123·5 (55·8)	122·5 (59·2)	133	121·4 (55·4)	124·0 (64·6)	+2·7 (-8·0 to +13·5)	0·62
%S	127	68·3 (52·6)	65·8 (48·2)	133	82·3 (79·9)	84·9 (130·8)	+3·0 (-12·8 to +18·7)	0·71
IR	127	2·24 (1·4)	2·37 (1·78)	133	2·03 (1·49)	2·09 (1·86)	-0·09 (-0·40 to +0·22)	0·58
BMI (kg/m^2)	174	32·5 (5·6)	32·3 (5·6)	172	32·2 (5·6)	32·3 (5·6)	+0·4 (+0·1 to +0·7)	0·019
Waist circum-ference (cm)	174	109·7 (12·9)	108·9 (13·1)	172	108·1 (12·6)	108·6 (13·1)	+1·1 (+0·1 to +2·2)	0·034
Neck circum-ference (cm)	174	43·1 (4·1)	42·9 (4·0)	172	42·7 (3·9)	42·7 (3·8)	+0·2 (-0·1 to +0·5)	0·20
ODI	170	12·9 (11·3)	12·6 (13·6)	171	13·9 (13·1)	5·2 (9·0)	-7·9 (-10·0 to -5·9)	<0·0001

Table c. Baseline and follow-up means (SD) and adjusted treatment effects for the secondary endpoints. DBP=diastolic blood pressure, HDL=high-density lipoprotein, LDL=low-density lipoprotein, Trig=triglycerides, %HbA1c=%haemoglobin A1c, %B=%beta cell function, %S=%insulin sensitivity, IR=insulin resistance ((glucose (mmol/l) x insulin (mU/l))/22·5), BMI=body mass index, ODI=4% oxygen desaturation index (per hour).

Vascular events

Vascular Event	**Standard Care**	**CPAP**
N (%)	**(N=173)**	**(N=172)**
Angina	3 (1·7%)	1 (0·6%)
Myocardial Infarction	0	0
Peripheral Vascular Disease	1 (0·6%)	2 (1·2%)
Atrial Fibrillation	7 (4·1%)	6 (3·5%)
Transient Ischaemic Attack	0	1 (0·6%)
Stroke	0	0
Total no. of new vascular events	11	10
No. of patients	11 (6·4%)	9 (5·2%)

Table d: Number of patients experiencing a vascular event during six month follow-up period (one patient had two events).

Number needed to treat

Event	**% Standard care**	**% CPAP**	**NNT**
≥2 point reduction	25.1	47.7	4.4
≥3 point reduction	12.0	36.1	4.2
≥4 point reduction	6.9	25.6	5.3

Table e: Percent achieving a certain reduction in ESS (Epworth Sleepiness score) in each group, and therefore the number needed to treat overall for one person to achieve that reduction or more compared to standard care (NNT).

Baseline variables according to recruitment centre

	Oxford (N=188)	**Reading (N=50)**	**Taunton (N=65)**	**Vancouver (N=40)**	**Leeds (N=21)**	**Global p-value**
ESS	8.4 (4.1)	7.7 (4.1)	9.2 (4.4)	4.0 (3.0)	8.6 (3.8)	<0.0001
ODI	10.5 (5.1-17.6)	6.1 (2.9-14.7)	8.7 (3.8-13.2)	9.3 (7.0-15.6)	10.3 (7.6-20.1)	0.43
Risk score	35.9 (6.8)	32.2 (8.7)	35.0 (8.3)	32.5 (7.6)	32.1 (9.8)	0.006
BMI	32.5 (5.5)	30.3 (5.2)	33.3 (5.4)	33.7 (7.1)	32.5 (5.3)	0.036

Table f: Numbers of subjects randomised and baseline characteristics by centre. Also presented are global p-values testing for heterogeneity between centres.

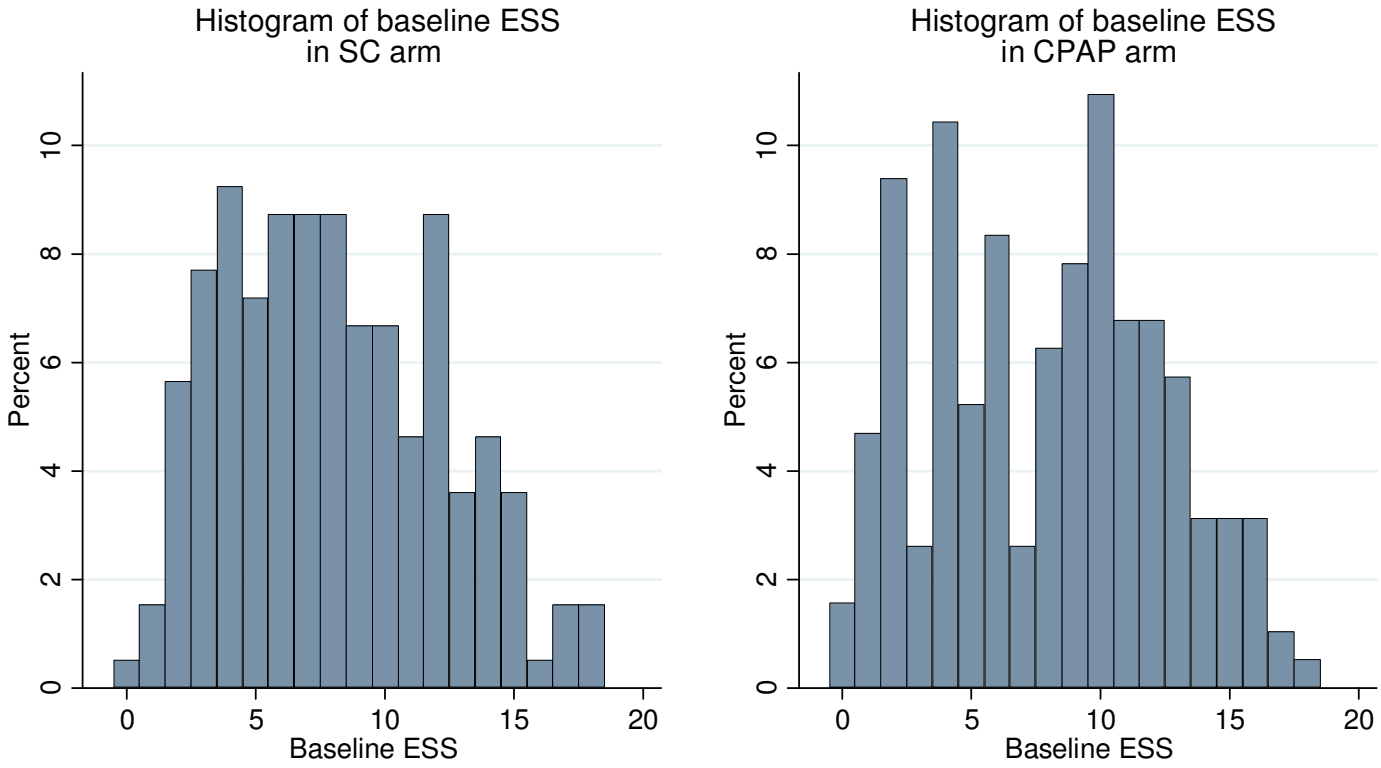
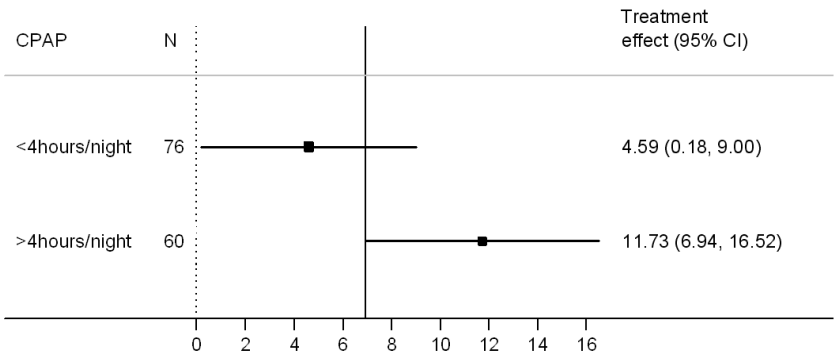
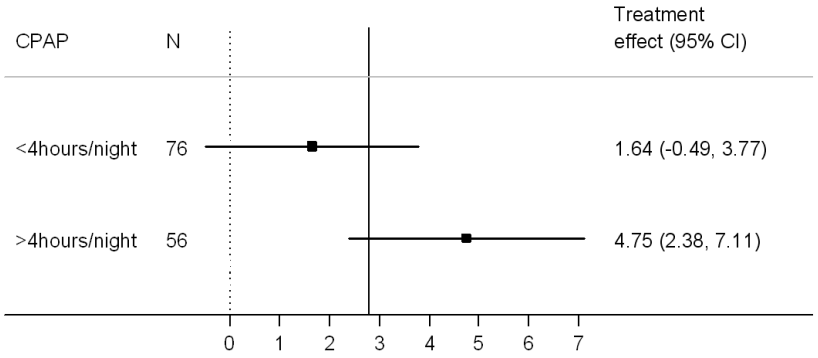


Figure a: Histogram showing the distribution of baseline ESS by treatment arm in the whole trial population.

SF36 – Energy/Vitality
Test for interaction, p=0.01



SF36 – MCS
Test for interaction, p=0.02



SAQLI
Test for interaction, p=0.01

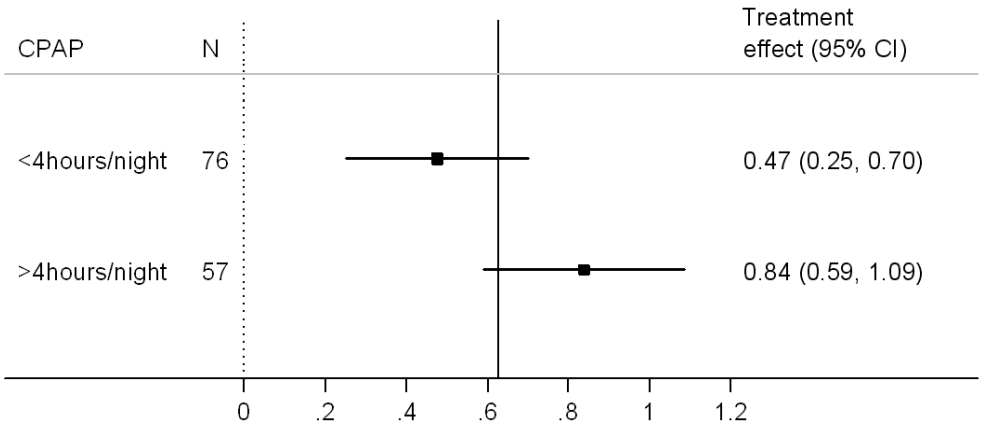
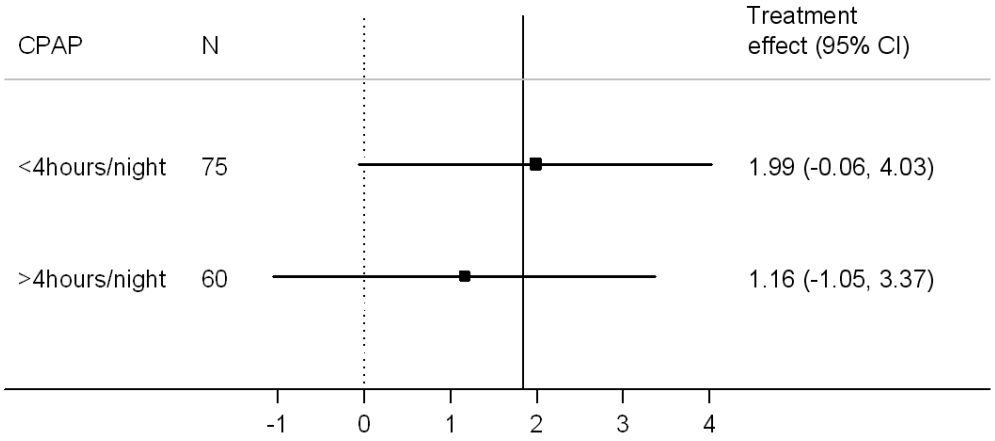


Figure b: Forest plots showing adjusted treatment effects, with tests for interaction, on SF-36 (energy and vitality dimension, mental component score) and SAQLI by CPAP compliance (<4 hours/night and >4 hours/night).

Systolic Blood Pressure
Test for interaction, p=0.52



HbA1c
Test for interaction, p=0.84

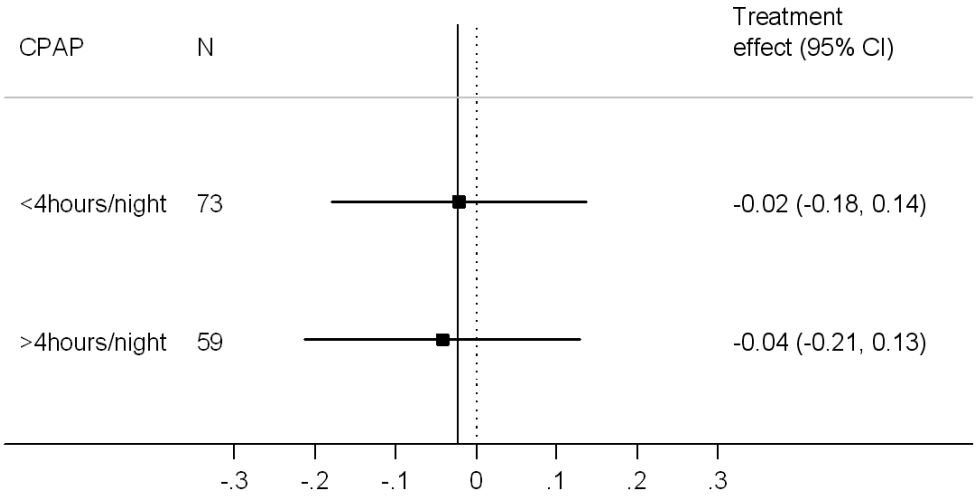


Figure c: Forest plots showing adjusted treatment effects, with test for interaction, on systolic blood and HbA1c by CPAP compliance (<4 hours/night and >4 hours/night).

Subgroup analysis on Systolic Blood pressure

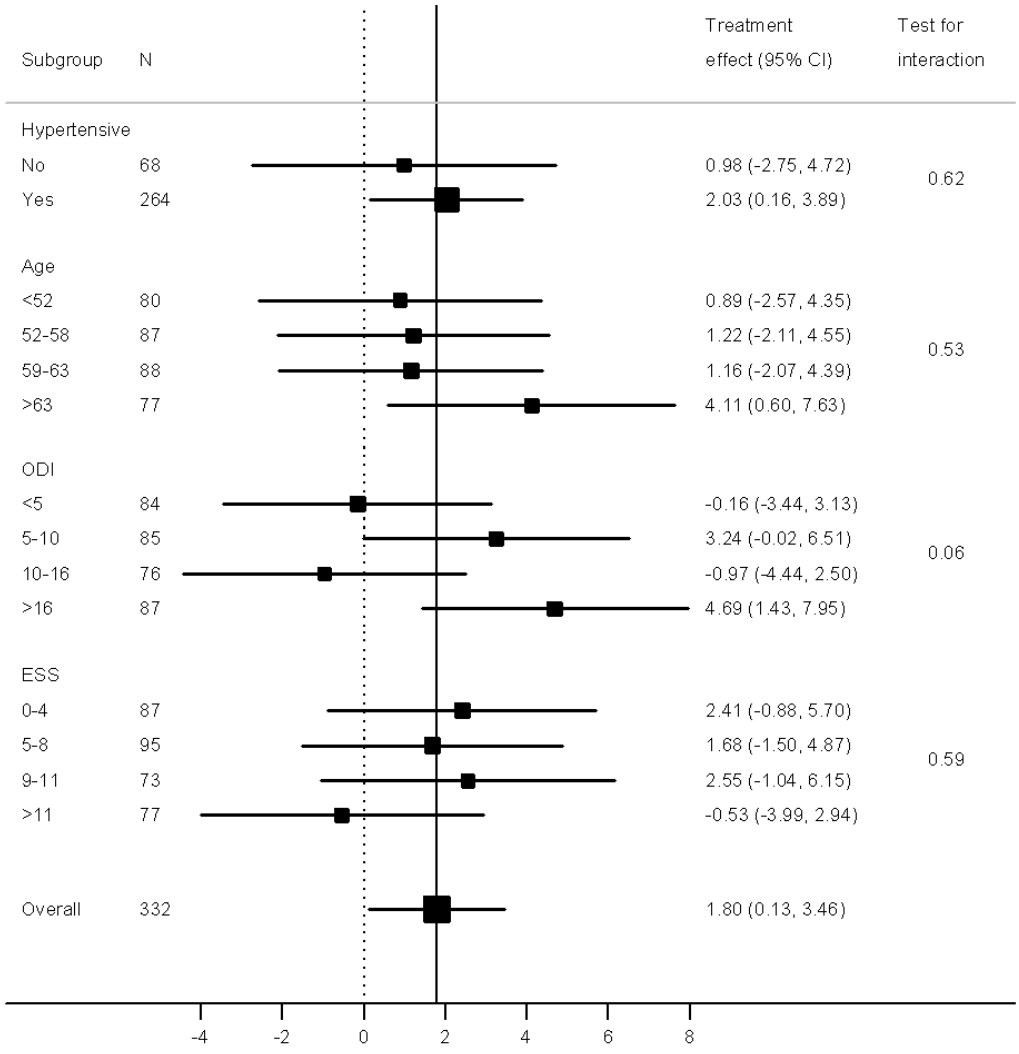


Figure d: Forest plots showing adjusted treatment effects, with tests for interaction in subgroup analyses, on Systolic Blood Pressure by hypertensive status, and quartiles of baseline age, ODI, and ESS.

Subgroup analysis on Diastolic Blood Pressure by ESS
Test for interaction, p=0.30

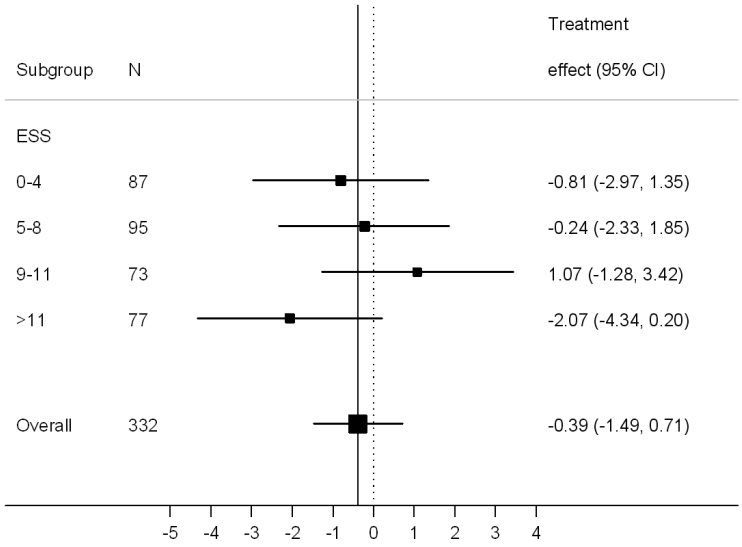


Figure e: Forest plots showing adjusted treatment effects, with tests for interaction, on Diastolic Blood Pressure by quartiles of baseline ESS.

Subgroup analysis on Cholesterol by ESS
Test for interaction, p=0.16

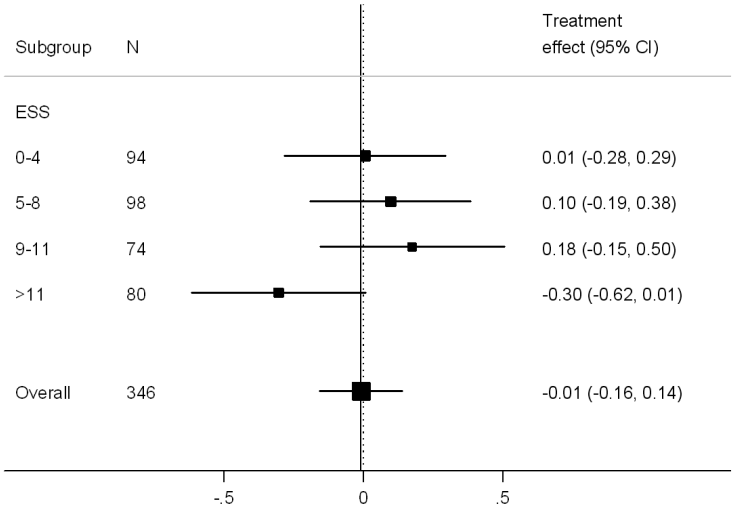


Figure f: Forest plots showing adjusted treatment effects, with test for interaction, on cholesterol by quartiles of baseline ESS.

Subgroup analysis on ODI by compliance
Test for interaction, p=0.05

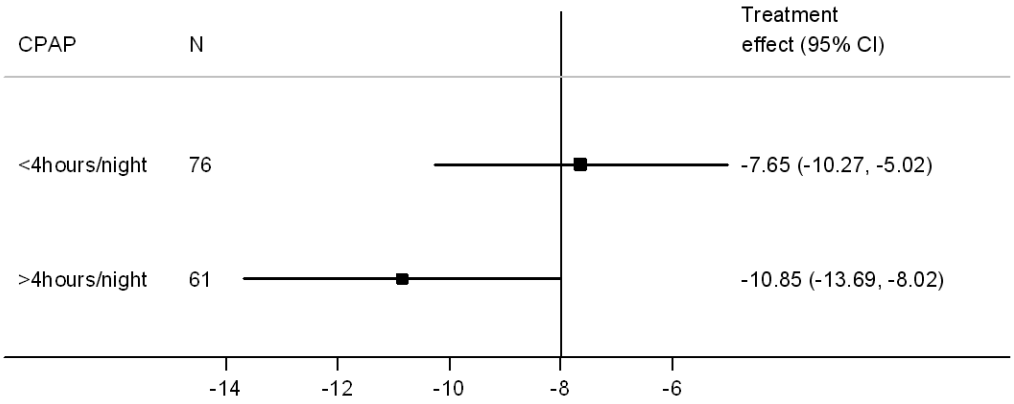


Figure g: Forest plots showing adjusted treatment effects, with test for interaction , on ODI by CPAP compliance (<4 hours/night and >4 hours/night).

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