Online Appendix

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

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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.

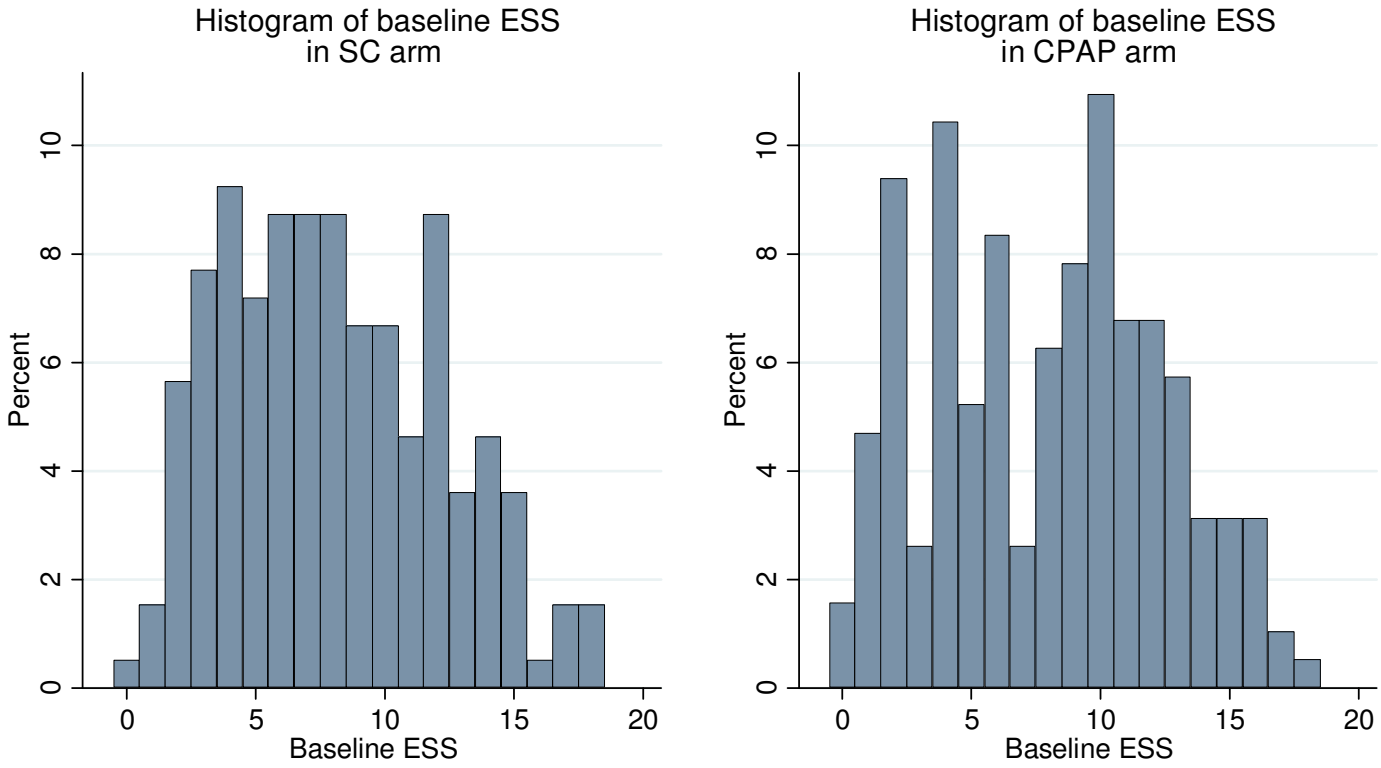
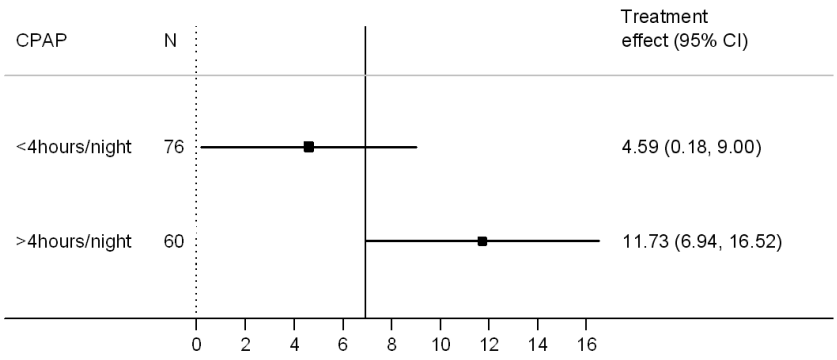
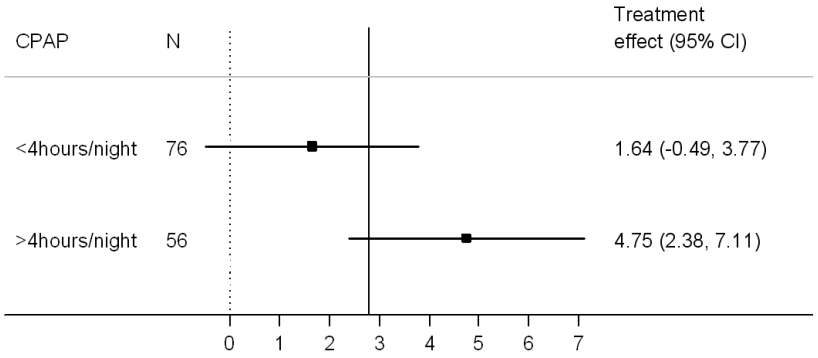


Figure a: Histogram showing the distribution of baseline ESS by treatment arm in the whole trial population.

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



SF36 – MCS
Test for interaction, p=0.02



SAQLI
Test for interaction, p=0.01

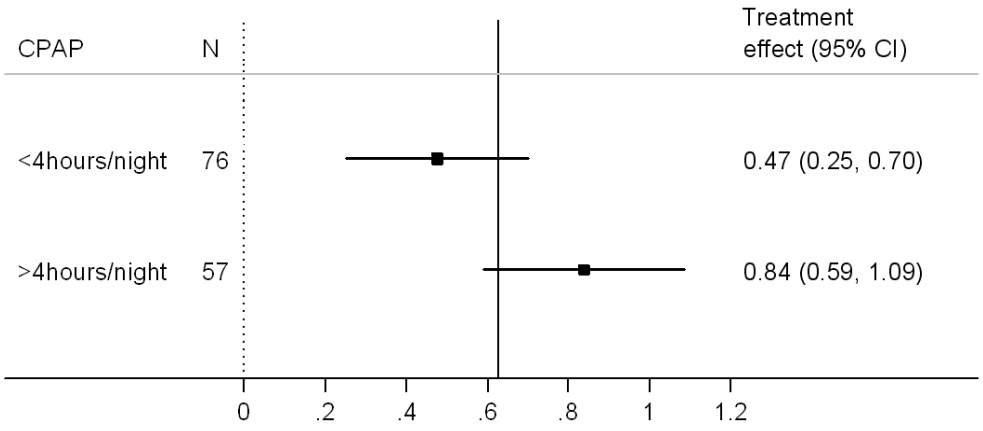
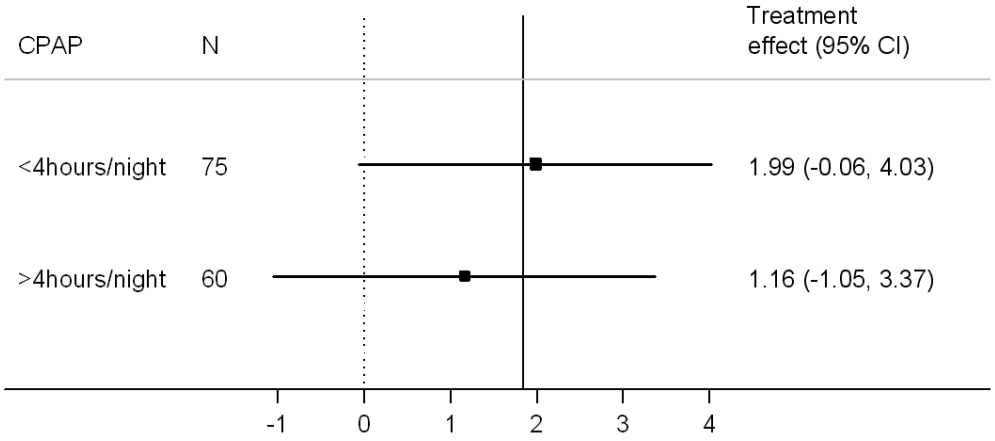


Figure b: Forest plots showing adjusted treatment effects, with tests for interaction, on SF-36 (energy and vitality dimension, mental component score) and SAQLI by CPAP compliance (<4 hours/night and >4 hours/night).

Systolic Blood Pressure
Test for interaction, p=0.52



HbA1c
Test for interaction, p=0.84

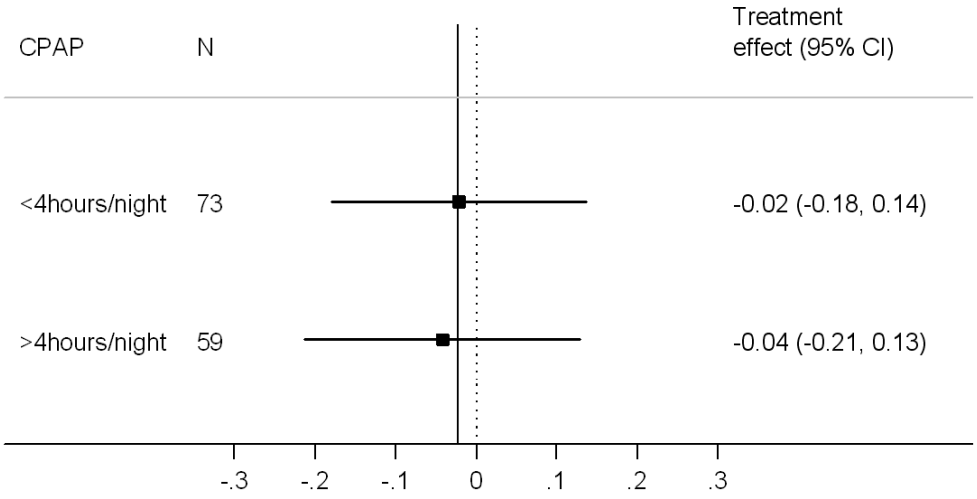


Figure c: Forest plots showing adjusted treatment effects, with test for interaction, on systolic blood and HbA1c by CPAP compliance (<4 hours/night and >4 hours/night).

Subgroup analysis on Systolic Blood pressure

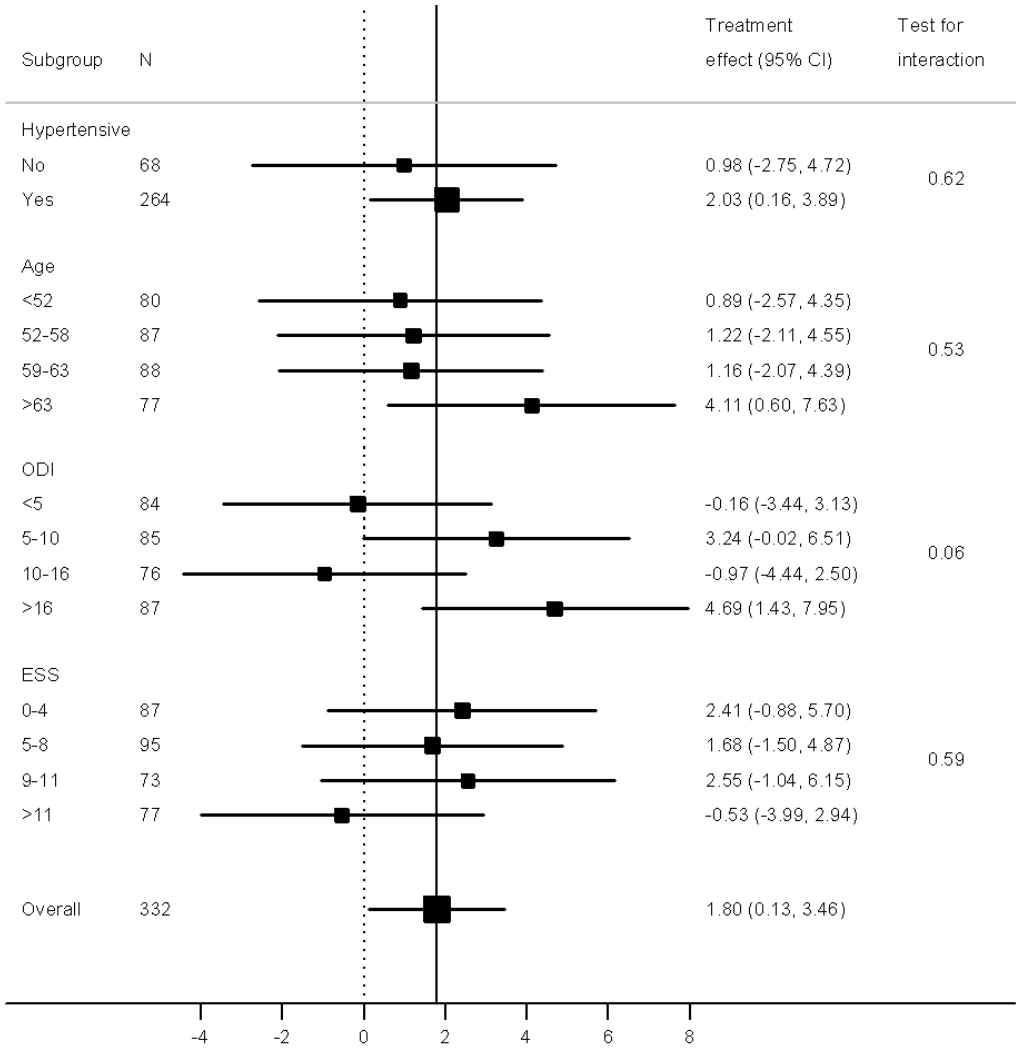


Figure d: Forest plots showing adjusted treatment effects, with tests for interaction in subgroup analyses, on Systolic Blood Pressure by hypertensive status, and quartiles of baseline age, ODI, and ESS.

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

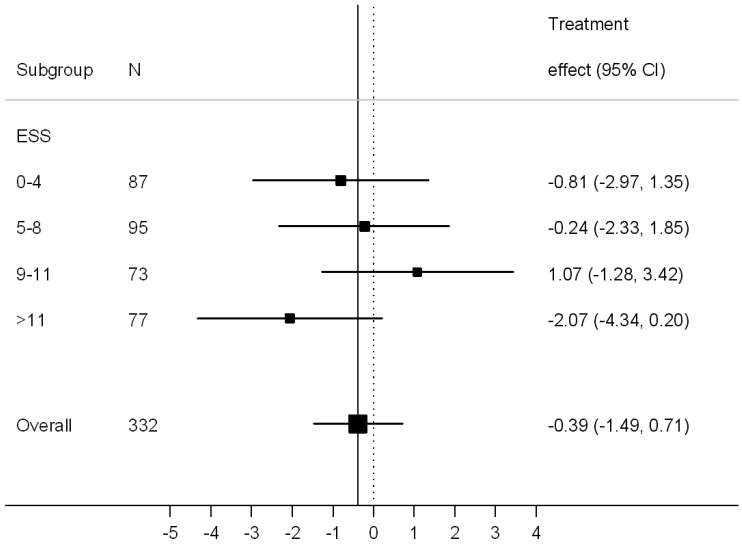


Figure e: Forest plots showing adjusted treatment effects, with tests for interaction, on Diastolic Blood Pressure by quartiles of baseline ESS.

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

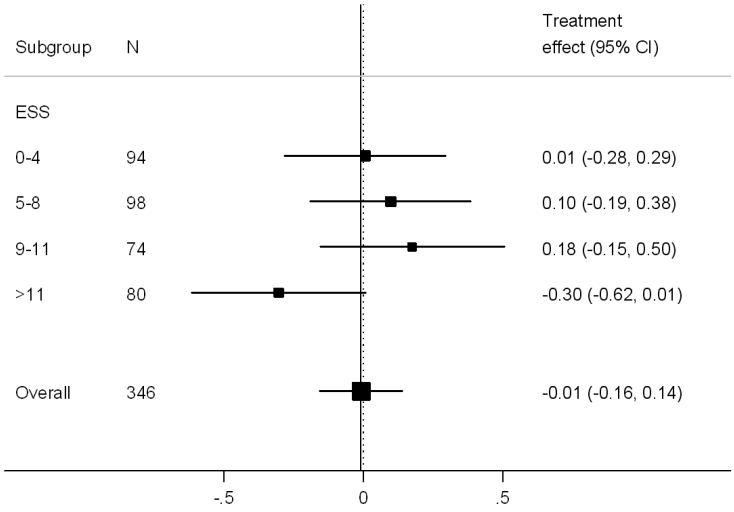


Figure f: Forest plots showing adjusted treatment effects, with test for interaction, on cholesterol by quartiles of baseline ESS.

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

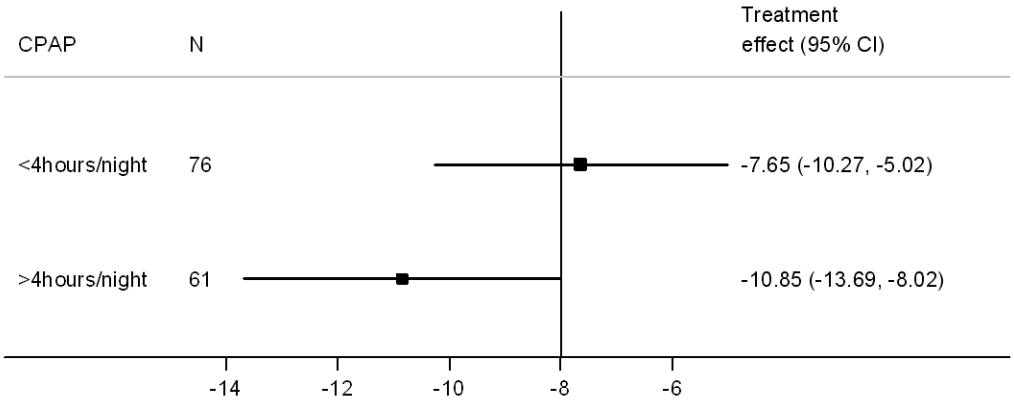


Figure g: Forest plots showing adjusted treatment effects, with test for interaction , on ODI by CPAP compliance (<4 hours/night and >4 hours/night).

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