Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): a 12-month, multicentre, randomised trial

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Summary

Background The therapeutic and economic benefits of continuous positive airway pressure (CPAP) for moderate to severe obstructive sleep apnoea (OSA) syndrome have been established in middle-aged people; however, the benefits in older people are unknown. This trial was designed to address this evidence gap.

Methods This 12-month, multicentre, randomised trial enrolled patients across 14 National Health Service sleep centres in the UK. Consecutive patients aged 65 years or older with newly diagnosed OSA syndrome were eligible to join the trial. Patients were randomly assigned (1:1) into parallel groups to receive either CPAP with best supportive care (BSC) or BSC alone for 12 months. Randomisation was done by the Medical Research Council Clinical Trials Unit with computer-generated randomisation. The main investigator at each centre was masked to the trial randomisation. Coprimary endpoints were Epworth sleepiness score (ESS) at 3 months and cost-effectiveness over the 12-month trial period. Secondary outcomes were subjective sleepiness at 12 months, plus objective sleepiness, quality of life, mood, functionality, nocturia, mobility, accidents, cognitive function, and cardiovascular risk factors and events at 3 months and 12 months. The analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN90464927.

Findings Between Feb 24, 2010, and May 30, 2012, 278 patients were randomly assigned to the trial, of whom 231 (83%) completed the trial. 140 patients were allocated to and received CPAP plus BSC and 138 were allocated to and received BSC only. CPAP reduced ESS by 2·1 points (95% CI –3·0 to –1·3; p<0·0001) at 3 months for 124 (89%) of 140 patients compared with 124 (90%) of 138 patients given BSC, and by 2·0 points (–2·8 to –1·2; p<0·0001) at 12 months for 116 patients compared with 122 patients given BSC. The effect was greater in patients with higher CPAP usage or higher baseline ESS. Quality-adjusted life-years were similar between the groups (treatment effect 0·01 (95% CI –0·03 to 0·04; p=0·787) and health-care costs were marginally reduced with CPAP (–£35, –390 to 321; p=0·847). CPAP improved objective sleepiness (p=0·024), mobility (p=0·029), total cholesterol (p=0·048), and LDL cholesterol (p=0·042) at 3 months, but these were not sustained at 12 months. Measures of mood, functionality, nocturia, accidents, cognitive function, and cardiovascular events remained unchanged. Systolic blood pressure fell in the BSC group. 37 serious adverse events occurred in the CPAP group, and 22 in BSC group; all were independently classified as being unrelated to the trial and no significant harm was attributed to CPAP use.

Interpretation In older people with OSA syndrome, CPAP reduces sleepiness and is marginally more cost effective over 12 months than is BSC alone. On the basis of these results, we recommend that CPAP treatment should be offered routinely to older patients with OSA syndrome.

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Introduction

Obstructive sleep apnoea (OSA) is one of the commonest respiratory disorders affecting up to 20% of the general population.[1] When OSA leads to sleep disruption resulting in excessive daytime sleepiness it is known as OSA syndrome. OSA syndrome is thought to affect up to 4% of the middle-aged population (30–60 years);[1,2] however, with the current obesity epidemic, the proportion of affected patients might require upward revision[3] because obesity is the strongest risk factor for

OSA. The long-term consequences of OSA syndrome include reduced social functioning and quality of life; neurocognitive impairment; increased risk of road traffic accidents; cerebrovascular, cardiovascular, and metabolic morbidity; and higher mortality.[4] Continuous positive airway pressure (CPAP) therapy is established as an efficacious and cost-effective treatment for middle-aged patients with moderate to severe OSA syndrome.[5]

In older people (older than 60 years), the prevalence of OSA syndrome is increased and the symptoms can be

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conflated with the functional impairments of ageing.[6] Thus, reversing the OSA syndrome component of any functional impairment could increase independence and reduce health-care costs in ageing populations. However, the magnitude of the treatment and economic benefits of CPAP shown in middle-aged people cannot be extrapolated to older populations. The daytime sleepiness associated with OSA could be less debilitating in older people who have more flexible schedules allowing for extra sleep opportunities. Conversely, both the prevalence of morbidities leading to polypharmacy and the detrimental effect on sleep of the illnesses themselves increase with age.[7] Furthermore, different perceptions of quality of life, higher overall health-care use, and shorter life expectancy could modify the economic benefits of CPAP in this population. This trial was designed to assess the efficacy of CPAP to reduce daytime sleepiness in older people with OSA syndrome and to determine its cost-effectiveness.

Methods

Study design and participants

The PREDICT trial was a multicentre, investigator-masked, randomised, parallel controlled trial done in 14 National Health Service (NHS) sleep centres in the UK.

Consecutive patients aged 65 years or older with newly diagnosed OSA syndrome were invited to join the trial. A diagnosis of OSA syndrome was based on the clinical practice in each centre; the criteria that needed to be fulfilled for a diagnosis were 4% or greater oxygen desaturation index (ODI) with more than 7·5 events per h, and Epworth sleepiness score (ESS) of 9 or greater. ODI and ESS were assessed again at enrolment and the (standardised) enrolment measures were used in the primary analysis (as opposed to the measures made during clinical diagnosis). Exclusion criteria were previous exposure to CPAP, awake oxygen saturation (SpO$_2$) less than 90% on air, ratio of forced expiratory volume in 1 s to forced vital capacity of less than 60%, being a professional driver, reporting sleepiness while driving, shift work, or any severe symptom of OSA syndrome for which the referring physician felt CPAP was mandatory. The number of patients assessed for eligibility was documented in screening logs.

This trial was approved by a central research ethics committee (REC 09/H0708/33) and all patients gave written informed consent. Further details of the trial management and any changes to the protocol are provided in the appendix pp 4, 5.

Randomisation and masking

Patients were randomly assigned (1:1) centrally by the Medical Research Council Clinical Trials Unit (MRC CTU) by computer-generated randomisation, with minimisation by ESS at enrolment (>13 vs ≤13), functionality (Townsend Disability Scale [TDS] >1 vs ≤1), and recruitment centre. The allocation group was revealed by telephone to the (unmasked) investigator initiating the intervention, once baseline data collection was complete.

Treatment allocation was concealed from the individual completing follow-up assessments. Patients were discouraged from discussing their treatment allocation with the masked research staff and the importance of maintaining blinding was emphasised in the patient information sheets. The case report forms were designed to collect blinded and unblinded data separately. Masking of all trial staff was not possible, although the assessments were done blind wherever possible. The trial manager and trial support staff at the coordinating centres in Oxford and London did not have contact with the patients. The trial statisticians analysed the results using an analysis plan that had been finalised before the database was locked and before the blinded data were analysed.

Procedures

All recruitment centres had expertise in the treatment of OSA syndrome and were provided with auto-titrating CPAP devices (S9 Autoset, ResMed [UK] Ltd, Oxfordshire, UK), humidifiers, and a range of interfaces. CPAP treatment (auto-titrating with default minimum and maximum pressure settings at 4–20 cm H$_2$O) was initiated using the standard practice in each centre, by appropriately qualified staff not involved in trial outcomes. Humidification and choice of interface were made on an individual patient basis. At every follow-up visit (3 months and 12 months), the hours of use of CPAP were downloaded from the CPAP machine.

BSC was comprised of advice on minimising daytime sleepiness through sleep hygiene, naps, caffeine, and weight loss, as appropriate to each patient. A standard information booklet was given to all patients. Both groups had identical visit schedules, and were asked to continue with their usual drugs and medical care during the trial. Further details of the visit schedules are outlined in the appendix p 4.

Structured assessments were done at baseline, 3 months, and 12 months. Additionally, all patients received a telephone call at 1 week, 1 month, and 6 months to record symptoms and side-effects and to optimise CPAP adherence. Patients also completed monthly diaries recording symptoms, side-effects, use of health care, change in medication, functionality, and quality-of-life questionnaires. All enrolled patients completed a domiciliary overnight respiratory polygraphy study (Embletta Gold, Embla, Amsterdam, Netherlands) before initiation of CPAP, the results of which were scored centrally. Domiciliary overnight pulse-oximetry (Konica-Minolta, Osaka, Japan) was done at 3 months and 12 months.

Outcomes

The coprimary outcomes were subjective sleepiness at 3 months measured by the ESS[8] (mean ESS of months 3 and 4) and cost-effectiveness of provision of

CPAP over the 12 months measured by quality-adjusted life-years (QALYs) calculated with the European Quality of Life-5 Dimensions (EQ-5D) and use of health-care resources, which was collected monthly from patient diaries.[9]

Secondary outcomes were subjective sleepiness at 12 months (mean ESS of months 10, 11, and 12), objective sleepiness (Oxford Sleep Resistance test [OSLER]; Stowood Scientific Instruments, Oxford, UK),[10] quality of life (Short-Form 36 [SF-36]),[11] Sleep Apnea Quality of Life Index (SAQLI),[12] mood (Hospital Anxiety and Depression Scale),[13] functionality (TDS),[14] nocturia, mobility (Timed Up and Go test),[15] accidents (domestic and driving),

cognitive function (Mini Mental State Examination,[16] Trail Making Test B,[17] Digit Symbol Substitution Test,[18] simple and four-choice reaction time[19]), cardiovascular risk factors (systolic and diastolic blood pressures, fasting blood profile), and cardiovascular events at 3 months and 12 months. SF-36 was also used to derive short-form six dimensions (SF-6D). Treatment compliance was a tertiary outcome measured objectively by download of the CPAP smart card at every visit.

Statistical analysis

The study was designed to detect a minimally clinically important change of one point in the ESS, with 90% power at the two-sided 5% significance level. Assuming a 10% loss to follow-up and a standard deviation for the change in ESS in each group of 2·4,[5] 270 patients were required. Data were held in a central database at MRC CTU. All analyses were prespecified in the analysis plans.

Analysis was by intention-to-treat with adjustment for treatment allocation, minimisation factors, and the corresponding baseline variable of the outcome. Multivariable linear regression models were used for continuous outcomes and logistic regression used for binary outcomes. Data obtained outside the prespecified time period of 2–5 months (primary ESS outcome) and patients with missing data were excluded from the relevant analysis. Multiple imputation with chained equations was used to assess the effect of missing data on the primary outcomes,[20] initially under the missing at random assumption. This was followed with several sensitivity analyses in which missing outcomes were assumed to be better or worse on average than those noted in the trial. Exploratory analyses were done to investigate the effect of age, ODI, body-mass index, and baseline ESS on the primary treatment effect with fractional polynomials.[21] The effect of use of CPAP on the primary ESS outcome was also explored. Additionally, a sensitivity analysis of the primary efficacy outcome was done excluding the patients who switched from BSC to CPAP before 3 months.

The cost-effectiveness of CPAP was analysed from the perspective of the UK NHS. Health outcomes were expressed as QALYs with EQ-5D (primary) and SF-6D (secondary). Costs were evaluated in UK pounds sterling (2012 price base) and included the costs associated with general practitioner and nurse visits, phone calls to the general practitioner and NHS Direct, ambulance use, visits to accident and emergency, outpatient appointments, hospital overnight admissions, emergency admissions, and total number of nights in hospital, as recorded in the monthly diaries, plus the cost of CPAP treatment. The unit costs applied to every item to calculate the total cost per patient are given in appendix p 11. The base-case analysis was done in the intention-to-treat groups after multiple imputation with chained equations of missing data and adjustment for imbalances in baseline EQ-5D (or SF-6D) and in the
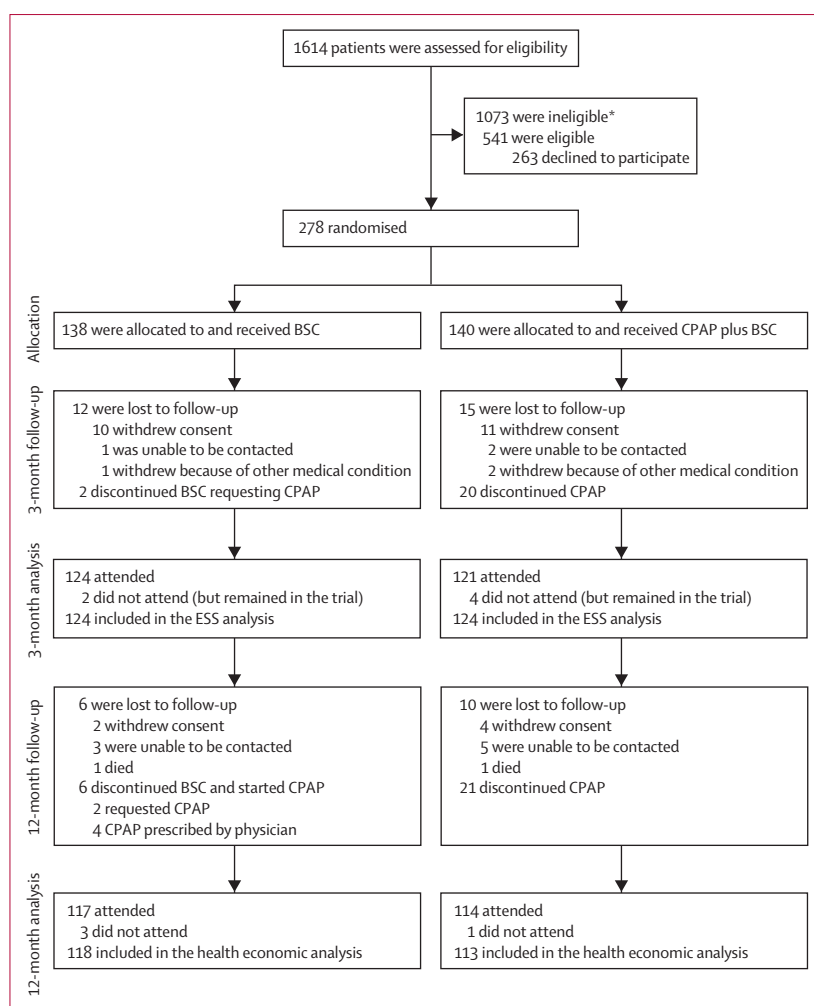

Figure 1: Trial profile
1614 patients were assessed for eligibility, of these 541 (34%) were eligible. The number of patients included in the ESS and health economic analysis included data obtained from monthly diaries (when available) for those who did not attend the 3 month and/or 12 month visits, but remained in the trial. Information about recruitment is also given in the appendix p 3. BSC=best supportive care. CPAP=continuous positive airway pressure. ESS=Epworth sleepiness score. *The 1073 ineligible patients were grouped into the following categories: 442 (41%) did not meet inclusion oxygen desaturation index or ESS criteria; 79 (7%) had previous exposure to CPAP; 171 (16%) had awake oxygen saturations less than 90% on air or forced expiratory volume in 1 s/forced vital capacity ratio less than 60%; 216 (20%) for being a professional driver, reporting sleepiness whilst driving, shift work, or any severe symptom of OSA syndrome for which the referring physician felt CPAP was mandatory; and 165 (15%) for no information or incomplete data.

health-care costs in the month before enrolment.[22] The probability of CPAP being cost effective under the conventional UK NHS thresholds was calculated with semi-parametric bootstrapping.[23] The sensitivity analysis tested five scenarios: (1) the assumption that the CPAP device was replaced every 3 years, the masks replaced every 3 months, and the filters replaced monthly; (2) the assumption that the CPAP device was used for 1 year and discarded (no annuitisation of costs); (3) complete case analysis in which patients with missing data were removed from the analysis; (4) missing data imputed with mean interpolation between follow-up points; and (5) the assumption that individuals with missing data had 25% greater costs or had 25% lower health-related quality of life than what otherwise would be predicted from the multiple imputation model. All analyses were done with Stata version 12.0 (StataCorp LP, College Station, TX, USA).

The trial is registered with International Standard Randomised Controlled Trial number ISRCTN90464927.

Role of the funding source

The National Institute of Health Research Health Technology Assessment Programme funded this trial (08/56/02) and the views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, National Institute of Health Research, National Health Service, or the Department of Health. Neither the funder nor the company (RedMed UK) had any role in the trial design, data collection, data analysis, data interpretation, or writing of the report. The raw data were accessible by DJB, AJN, and the Independent Data Monitoring Committee only during the trial, and on completion to AM, RF, SG, JRS, RLR, and MJM. The corresponding author had full access to all of the data on completion of the trial and the final responsibility to submit for publication.

Results

Between Feb 24, 2010, and May 30, 2012, 278 patients were randomised. 138 patients were allocated to and received BSC and 140 were allocated to and received CPAP plus BSC. Follow-up visits were done for 245 (88%) of 278 patients at 3 months and 231 (83%) of 278 patients at 12 months (figure 1). The main reason for loss to follow-up was withdrawal of consent; 21 (8%) patients at 3 months and 27 (10%) patients at 12 months. The table and appendix (pp 12, 13) show the baseline characteristics and overnight domiciliary respiratory polygraphy measurements of the enrolled patients. The mean age across both treatment groups was 71·1 (SD 4·6) years, ODI 28·7 (19·1) events per h, and ESS 11·6 (3·7). The baseline characteristics were broadly similar between the two groups, although by chance the BSC group seemed to have a slightly higher incidence of comorbidities than did the CPAP group.

	BSC group (N=138)	CPAP group (N=140)
Age (years)	71·3 (4·6)	70·9 (4·7)
Male sex	109 (79)	120 (86)
Ethnic origin		
White	134 (97)	133 (95)
Asian	3 (2)	5 (4)
Other	1 (1)	2 (1)
Body-mass index (kg/m²)	33·6 (6·4)	33·9 (5·7)
Neck circumference (cm)	42·6 (4·0)	44·0 (4·4)
Systolic blood pressure (mm Hg)	140·4 (20·0)	137·7 (17·7)
Diastolic blood pressure (mm Hg)	77·6 (12·4)	77·7 (10·2)
Current drivers	111 (80)	117 (84)
Oxygen desaturation index (>4% dips per h)	27·9 (18·5)	29·4 (19·7)
Time SpO₂ <90% (min)	33·2 (13·9–84·4)	38·5 (14·6–91·0)
Epworth sleepiness score	11·6 (3·9)	11·6 (3·4)
Oxford Sleep Resistance Test (min)	20·3 (9·4–37·5)	22·4 (13·3–40·0)
European Quality of Life-5 dimensions	69·2 (18·2)	69·2 (17·1)
Sleep Apnea Quality of Life Index	4·7 (1·2)	4·8 (1·2)
Townsend Disability Scale	2·5 (1–7)	2·5 (1–5)
Mini Mental State Examination	29 (28–30)	29 (27–30)
Comorbidity		
Ischaemic heart disease	49 (36)	42 (30)
Hypertension	104 (75)	98 (70)
Diabetes	43 (31)	40 (29)
Peripheral vascular disease	32 (23)	26 (19)
Atrial fibrillation	41 (30)	28 (20)
Heart failure	11 (8)	7 (5)
Cerebral vascular disease	19 (14)	16 (11)

Data are mean (SD), median (25th–75th percentiles), or number of patients (%). BSC=best supportive care. CPAP=continuous positive airway pressure. Data were unavailable for body-mass index for two patients (one in BSC group, one in group CPAP), oxygen desaturation index for two patients (one in BSC group, one in CPAP group), time SpO₂ for 48 patients (23 in BSC group, 25 in CPAP group), Oxford Sleep Resistance test for two patients in CPAP group, European Quality of Life-5 dimensions for one patient in BSC group, Mini Mental state Examination for one patient in BSC group, and heart failure for one patient in BSC group. The oxygen desaturation index and Epworth sleepiness score are those recorded at the baseline visit; which in some cases differed from the values recorded at diagnosis (note the values recorded during the baseline visit were used in the analysis).

Table: Baseline characteristics

At 3 months, ESS was significantly reduced in patients receiving CPAP treatment (–3·8, SD 0·4) compared with those given BSC (–1·6, 0·3) with a treatment effect of –2·1 (figure 2). Adjustment for age, sex, body-mass index, and baseline ODI made no difference to the result, neither did the sensitivity analysis, which excluded two patients who swapped from BSC to CPAP before the 3-month visit. Imputation analyses showed the primary result was robust to missing data (appendix p 6). The treatment effect was significantly greater in patients with higher baseline ESS (appendix p 7) or higher CPAP use (appendix p 14).

The average QALYs obtained with the EQ-5D were 0·68 (95% CI 0·64 to 0·72) for CPAP (n=113) and 0·67 (0·63 to 0·71) for BSC (n=118) with the adjusted increase in QALYs for CPAP being non-significant at 0·01 (–0·03 to 0·04; p=0·787). The EQ-5D scores did not differ significantly between groups at each month
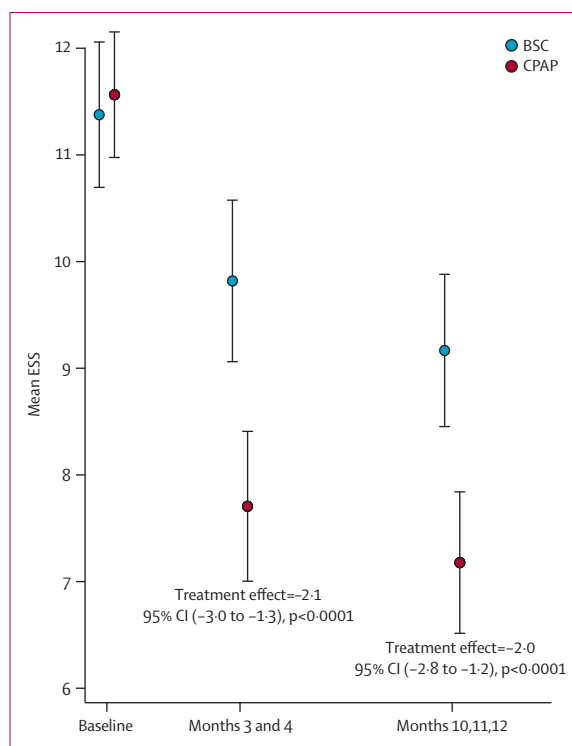
Figure 2: **Treatment effect of CPAP compared with BSC on subjective sleepiness measured by mean ESS**
Adjusted treatment effects and 95% CI at months 3 and 4 (coprimary endpoint) and mean of months 10, 11, and 12 (secondary endpoint). Lower scores indicate an improvement; each score is out of a total of 24 points. BSC=best supportive care. CPAP=continuous positive airway pressure. EES=Epworth sleepiness score.

(appendix p 8) and resource use per costs were similar across groups (appendix p 15).

The annual cost of CPAP treatment per patient was estimated at £201. This amount included the annual equivalent costs of the CPAP device at £70 and the humidifier at £27 (the humidifier was only given to 82 [59%] of the 140 patients), totalling £86 on average per patient, plus the cost of masks at £114 (£104, assuming that 10% of patients received two masks each) and the cost of two filters per patient per year at £1·13 (average cost of filters was £0·58). Overall the average cost per patient allocated to CPAP was £1363 (95% CI 1121–1606) and for BSC was £1389 (1116–1662). After adjustment for costs incurred to the month previous to enrolment, the CPAP group accrued on average −£35 (95% CI −390 to 321) health-care costs. The results were not sensitive to different assumptions regarding missing data. However, when alternative assumptions were made for the frequency of replacing equipment, the cost per QALY increased (appendix p 16). Additionally, the cost-effectiveness of CPAP was more robust in patients with higher baseline ESS (appendix p 17). The probability that the CPAP was cost effective at the thresholds conventionally used in the NHS (£20 000 per QALY gained) was 0·61.

The improvement in the ESS on CPAP compared with BSC was maintained at 12 months, with a treatment effect of −2·0 (figure 2; appendix p 14).

When cost-effectiveness was assessed with SF-6D, CPAP improved QALYs by 0·018 (95% CI 0·003 to 0·034) and the probability of CPAP being cost-effective was 0·96 (appendix p 16).

Objective sleepiness was significantly reduced at 3 months (p=0·024), but less so at 12 months (p=0·058; appendix pp 9, 18). This was also the case with mobility (p=0·029 at 3 months, p=0·80 at 12 months; appendix p 19). Change in ESS and change in OSLER time were significantly correlated at 3 months (−0·22; p=0·0008) and 12 months (−0·17; p=0·010).

The energy/vitality domain of the SF-36 improved at 3 months (p=0·001) and 12 months (p=0·004; figure 3); this was also the case for the disease-specific quality of life (appendix p 20). Measures of mood, functionality, nocturia, accidents, and cognitive function were unchanged (appendix pp 19, 21).

At 3 months, CPAP reduced total cholesterol (treatment effect −0·2 mmol/L, 95% CI −0·3 to 0·0; p=0·048) and LDL cholesterol (−0·15 mmol/L, −0·29 to −0·01; p=0·042), but the effect was not sustained at 12 months (appendix p 22). Systolic blood pressure was improved (treatment effect 3·7 mm Hg, 95% CI 0·2 to 7·3; p=0·040) at 12 months, because of a decrease in systolic blood pressure in the BSC group (appendix p 22). The incidence of new cardiovascular events did not differ between groups at 3 months (p=0·48) or 12 months (p=0·72). Atrial fibrillation was the predominant new pathology (appendix p 23).

Of 140 patients randomly assigned to CPAP, 120 (86%) at 3 months and 99 (71%) at 12 months self-reported they were still using CPAP. Usage data for CPAP were obtained for 117 patients at 3 months with a median usage of 1 h 52 min (IQR 19 min to 5 h 12 min) per night and for 102 patients at 12 months with a median usage of 2 h 22 min (10 min to 5 h 9 min) per night. Assuming zero usage in those patients who stopped treatment during follow-up or had missing data gave a more conservative estimate of median usage of CPAP of 1 h 33 min (IQR 13 min to 5 h) per night at 3 months and 1 h 26 min (4 min to 4 h 45 min) per night at 12 months. Additional data for CPAP usage are shown in appendix p 24.

37 serious adverse events were recorded during the trial; 15 (in 12 patients, including one death) in the CPAP group and 22 (in 13 patients, including one death) in the BSC group; all adverse events were independently classified as being unrelated to the trial. CPAP was associated with common self-reported side-effects (appendix p 25). No clinically important harm from use of CPAP was noted.

Discussion

This 12-month randomised, controlled trial has unequivocally shown that CPAP reduced subjective sleepiness in older people with OSA syndrome at

3 months, despite low overall CPAP usage. The beneficial effects were maintained at 12 months, and the magnitude of the improvement is similar to that seen in middle-aged patients with similar levels of disease severity treated with CPAP.[5] The reduction in subjective sleepiness was corroborated by a significant improvement in objective sleepiness, measured by the OSLER test at 3 months. CPAP also produced significantly better quality-of-life outcomes, as measured with the SAQLI and SF-36. The relative increase in QALYs was not significant in the primary cost-effectiveness analysis; this could have been because the EQ-5D is a less sensitive measure of health status attributable to sleepiness because it contains no relevant dimension for this symptom. Overall, the marginal economic benefit of CPAP was linked to a reduction in health-care use, offsetting the cost of the CPAP equipment; this was more robust if using SF-6D to measure health benefits and in patients with higher ESS.

Secondary outcomes related to cognitive function did not show any difference between the two groups, despite improvements in sleepiness in the CPAP group. Additionally, mood, which might also affect cognitive function, was not significantly different between the two groups. Although, patients in this trial had a low prevalence of depression compared with those in a recent study,[24] and the baseline cognitive scores were often within the age-adjusted normative range, which could have resulted in a ceiling effect. The low overall use of CPAP in our trial might also have been a factor, or older people prepared to participate in a year-long trial might be constitutionally different to those whose cognitive function leads to clinically significant compromise. Cognitive deficits have been reported in middle-aged patients with moderate to severe OSA syndrome;[25] however, the effect of OSA syndrome on cognitive deficits in mildly symptomatic patients is questionable.[26]

In terms of the cardiovascular outcomes, significant improvement was noted for total cholesterol at 3 months in the CPAP group, but this was not sustained at 12 months. The fall in cholesterol was similar to findings in a group of patients with more severe OSA syndrome after a 1-month CPAP trial.[27] CPAP produced no improvement in blood pressure. At first sight, this might be surprising because CPAP has been shown in other randomised controlled trials to reduce blood pressure by roughly 2–10 mm Hg in patients with OSA syndrome.[28,29] However, our findings are consistent with a recent meta-analysis in patients with minimally symptomatic OSA, which showed that CPAP does not have a beneficial effect on blood pressure.[29] In the BSC group, systolic blood pressure fell, a finding also reported in another recent study of minimally symptomatic patients with OSA.[30] We speculate that this could be because the control group followed the BSC advice more closely than did the CPAP group. This suggestion cannot be verified, although the lack of weight loss in both groups could imply similar adherence with the BSC information (appendix p 26).
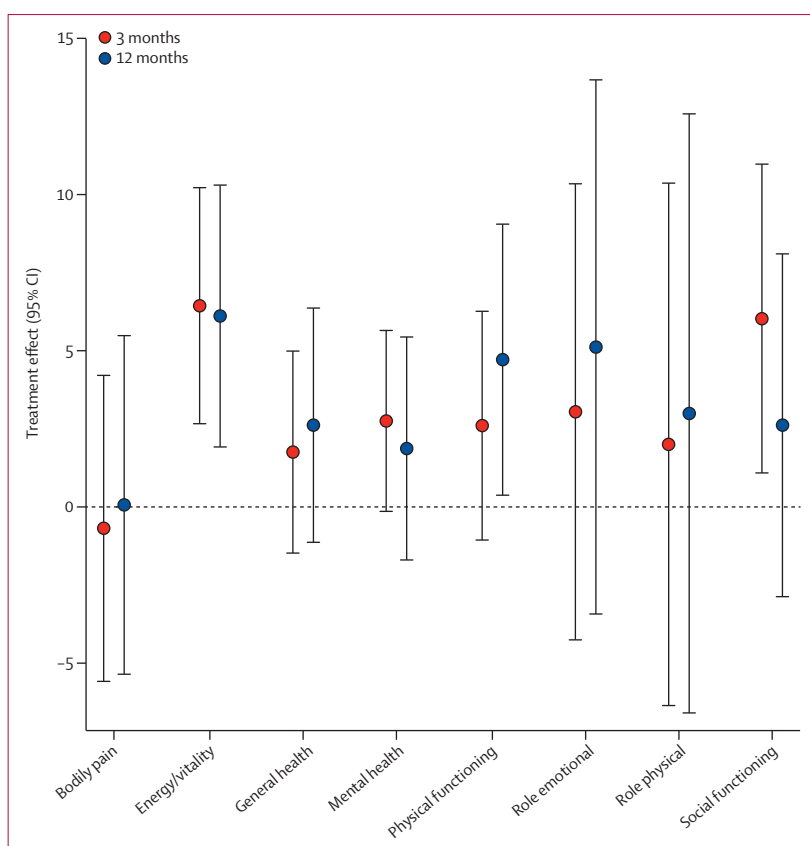

Figure 3: 36-item Short-Form Health Survey (SF-36) treatment effects at 3 months and 12 months
Adjusted treatment effects and 95% CI of continuous positive airway pressure versus best supportive care and the eight summary components of the SF-36 at 3 months and 12 months.

Further research is needed to clarify the cardiovascular effect of CPAP treatment in older people with OSA syndrome. Other secondary outcomes, including nocturia and home and driving accidents (appendix p 19), also did not improve with CPAP, which could be because of their multifactorial causes.

The mean usage of CPAP was low at 3 months and 12 months and this might have diluted the significant treatment effect we noted between the groups. We adopted a standard NHS clinical (real-world) approach to initiate and manage CPAP treatment across the 14 sleep centres in the UK that participated in the trial. The centres varied in size and experience; however, any effect of the differences between centres was accounted for by adjustment for centre in a random effects model in every analysis.

The real-world clinical management adopted in PREDICT could have resulted in the lower CPAP usage compared with that in a more intensive trial approach[26] or shorter duration studies.[27] However, such adoption ensured that the outcomes of PREDICT reflect clinical practice, which in turn strengthens the validity and applicability of our results. Furthermore, the mean usage of CPAP was similar to a 6-month, randomised, controlled trial of CPAP in minimally symptomatic patients with OSA,[30] and we noted a dose–response relation between the

The ESS was selected as the primary outcome measure for sleepiness in PREDICT because it is the most widely used subjective scale of sleepiness severity in clinical and research practice; it is also the measure from which the UK National Institute for Health and Care Excellence guidelines are drawn.[5] The effect of CPAP on ESS in middle-aged patients with mild OSA has been reported as –1·07 (SD 2·4).[5] We therefore powered PREDICT for a one point change in ESS; however, we did not know if this would translate to functionality changes in older patients. The improvements in ESS and quality of life at 3 months and 12 months might go some way to support the notion that changes of this magnitude in ESS are clinically meaningful in this age group. However, some of the secondary endpoints might have lacked power to detect a clinically meaningful effect, and we also noted that many of the measures started at normal levels (eg, depression), thus there was minimum room for improvement.

A possible limitation of the PREDICT trial was that sham CPAP was not used as a comparator, although any placebo effect there might have been in the CPAP group could reasonably be expected to have disappeared by 12 months. Additionally, the objective OSLER test and the dose–response relation between the treatment effect and CPAP usage support a real effect. Sham devices have been validated as a placebo for CPAP, but there is no consensus on the ideal comparator, and trials with BSC produce results essentially identical to those from trials with subtherapeutic or sham CPAP.[5] BSC was chosen as the trial comparator for PREDICT because it was more appropriate for a pragmatic multicentre design with a 12-month follow-up.

The strength of the PREDICT trial was that patients presenting to our sleep clinics, requiring investigation and treatment for OSA syndrome were drawn from geographically diverse areas (appendix p 27) and were treated in a real-world clinical setting. Additionally, to our knowledge, PREDICT is one of the first trials specifically aimed at older people (≥65 years). The mean age of 70 years, with no participants younger than 65 years, differs significantly from the mean age of 58 years (SD 7) in another recent UK trial,[30] the MOSAIC study (appendix p 10). The PREDICT trial has also been one of the longest, randomised, trials of CPAP treatment for OSA syndrome, directly measuring both therapeutic and economic benefits.

The PREDICT trial was designed to be done in sleep clinics in the UK where polysomnography is not routinely done for the diagnosis of OSA syndrome. Use of polysomnography would have been financially and practically prohibitive. Respiratory polygraphy could have reduced the ODI if the older patients slept poorly, because the ODI is calculated as apnoeas and hypopnoeas divided by time asleep, and using the polyrgraphy meant that the time asleep could only be estimated from total time in bed (which might be an overestimation of the

treatment effect and CPAP usage, consistent with previous trials in middle-aged populations.[5] Adherence to auto-titrating and fixed CPAP has not been shown to differ, although other factors, such as reduced social support, could have contributed to lower CPAP adherence, because 50% of the patients in our trial reported sleeping alone.

total time asleep). However, the randomised, controlled trial design meant that any underestimation of the change in ODI would be evenly distributed across groups. Likewise, the distribution of comorbidities likely to produce central events, such as heart failure, was similar across groups; notably, no central or mixed events were scored, and patients with other sleep disorders were excluded. For these reasons we do not think the use of polygraphy restricted the findings of PREDICT.

To our knowledge, PREDICT is the first trial to measure both SF-36 and EQ-5D over a 12-month period, enabling a full health economic evaluation of the treatment of OSA syndrome in older people (panel). As already noted, the SF-6D has a dimension on vitality, which could render it more sensitive to changes in sleepiness and sleep quality than EQ-5D. Other studies have compared SF-36 with EQ-5D and also noted that SF-36 is more sensitive to the effect of CPAP on health-related quality of life.[34,35] Differences in data collection processes could also have affected the health-related quality of life reported by our patients. The EQ-5D was collected every month through the sleep diary, which was filled in by the patient at home. The SF-36, from which SF-6D was derived, was collected in a clinic visit at baseline, 3 months, and 12 months.

With respect to generalisability, the PREDICT trial did not focus on asymptomatic older people with OSA and although it could be argued that the patients studied had a fairly low mean ESS at baseline, they were sufficiently symptomatic to seek treatment. At the other end of the disease spectrum, exclusion of highly symptomatic patients with OSA syndrome (216 [20%] of 1073 patients; appendix pp 3, 4) in whom CPAP was considered mandatory, is likely to have diminished the treatment effect. The exploratory analyses showed that the treatment effect was larger in patients with a higher baseline ESS or greater use of CPAP. The marginal improvement in cost-effectiveness was also greater in the more symptomatic patients.

In summary, the PREDICT trial addresses the inequality of research in older people with OSA syndrome, and incorporates data for comorbidity that is often lacking in clinical guidelines.[36] The trial shows that in older patients with OSA syndrome, CPAP treatment reduces symptoms of excessive daytime sleepiness, as it does in middle-aged populations. On the basis of these findings, we recommend that CPAP treatment should be offered routinely to older patients with OSA syndrome, especially those with higher ESS. Future research should focus on how best to optimise CPAP delivery in this age group.

Contributors
All authors (except RJD) were members of the Trial Management Committee and Trial Steering Committee with responsibility for the progress and conduct of the trial. All authors were involved in the study design and development of case report forms, analysis of data, and all aspects of writing the report. AM was Clinical Research Fellow for PREDICT with specific responsibility for all data collection and oversight of the trial, and first author of the report. DJB was a statistician for PREDICT, a member of the Trial Management Committee, Trial Steering Committee, and Data Monitoring Committee. RF was a health economist for PREDICT with specific responsibility for the health economic analysis and write-up of the report. ML-S was trial manager for PREDICT with specific responsibility for all aspects of data collection and recording, plus governance of the trial. SG was health economist for PREDICT with specific responsibility for the health economic analysis and write-up of the report. RJD was a senior investigator for PREDICT, and a member of the Trial Steering Committee who was involved in all aspects of the study design and development of case report forms; however, he died during the early part of the study. AJN was a statistician for PREDICT, a member of the Trial Management Committee, Trial Steering Committee, and Data Monitoring Committee with specific responsibility for the statistical analysis of the trial. JRS was a senior investigator for PREDICT with specific responsibility for clinical oversight of the trial. RLR and MJM were coprincipal investigators for PREDICT; MJM and RLR share last authorship. MJM was corresponding author with the final responsibility to submit for publication.

References
1 Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; **328:** 1230–35.
2 Jennum P, Riha RL. Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. *Eur Respir J* 2009; **33:** 907–14.
3 Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; **177:** 1006–14.
4 Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014; **383:** 736–47.
5 McDaid C, Griffin S, Weatherly H, et al. Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. *Health Technol Assess* 2009; **13:** 1–119, 143–274.
6 Ancoli-Israel S. Sleep apnea in older adults—is it real and should age be the determining factor in the treatment decision matrix? *Sleep Med Rev* 2007; **11:** 83–85.
7 Willcox SM, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. *JAMA* 1994; **272:** 292–96.
8 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14:** 540–45.
9 Brooks R. EuroQol: the current state of play. *Health Policy* 1996; **37:** 53–72.
10 Bennett LS, Stradling JR, Davies RJ. A behavioural test to assess daytime sleepiness in obstructive sleep apnoea. *J Sleep Res* 1997; **6:** 142–45.
11 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002; **21:** 271–92.
12 Flemons WW, Reimer MA. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *Am J Respir Crit Care Med* 1998; **158:** 494–503.

13 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67:** 361–70.

14 McGee MA, Johnson AL, Kay DW. The description of activities of daily living in five centres in England and Wales. Medical Research Council Cognitive Function and Ageing Study. *Age Ageing* 1998; **27:** 605–13.

15 Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39:** 142–48.

16 Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. *Arch Gen Psychiatry* 1983; **40:** 812.

17 Reitan R. Trail Making Test. Tucson, AZ: Reitan Neuropsychology Laboratory, 1979.

18 Wechsler D. Wechsler Adult Intelligence Scale, 3rd edn (WAIS-III). San Antonio, TX: Psychological Corporation, 1997.

19 Deary IJ, Liewald D, Nissan J. A free, easy-to-use, computer-based simple and four-choice reaction time programme: the Deary-Liewald reaction time task. *Behav Res Methods* 2011; **43:** 258–68.

20 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011; **30:** 377–99.

21 Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med* 2004; **23:** 2509–25.

22 Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005; **14:** 487–96.

23 Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001; **10:** 779–87.

24 Douglas N, Young A, Roebuck T, et al. Prevalence of depression in patients referred with snoring and obstructive sleep apnoea. *Intern Med J* 2013; **43:** 630–34.

25 Twigg GL, Papaioannou I, Jackson M, et al. Obstructive sleep apnea syndrome is associated with deficits in verbal but not visual memory. *Am J Respir Crit Care Med* 2010; **182:** 98–103.

26 Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* 2012; **35:** 1593–602.

27 Robinson GV, Pepperell JC, Segal HC, Davies RJ, Stradling JR. Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials. *Thorax* 2004; **59:** 777–82.

28 Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002; **359:** 204–10.

29 Bratton DJ, Stradling JR, Barbé F, Kohler M. Effect of CPAP on blood pressure in patients with minimally symptomatic obstructive sleep apnoea: a meta-analysis using individual patient data from four randomised controlled trials. *Thorax* 2014; published online June 19. DOI:10.1136/thoraxjnl-2013-204993.

30 Craig SE, Kohler M, Nicoll D, 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:** 1090–96.

31 Egea CJ, Aizpuru F, Pinto JA, et al. Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: a multicenter study. *Sleep Med* 2008; **9:** 660–66.

32 Ruttanaumpawan P, Gilman MP, Usui K, Floras JS, Bradley TD. Sustained effect of continuous positive airway pressure on baroreflex sensitivity in congestive heart failure patients with obstructive sleep apnea. *J Hypertens* 2008; **26:** 1163–68.

33 Parra O, Sanchez-Armengol A, Bonnin M, et al. Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. *Eur Respir J* 2011; **37:** 1128–36.

34 Jenkinson C, Stradling J, Petersen S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. *J Sleep Res* 1997; **6:** 199–204.

35 Jenkinson C, Stradling J, Petersen S. How should we evaluate health status? A comparison of three methods in patients presenting with obstructive sleep apnoea. *Qual Life Res* 1998; **7:** 95–100.

36 Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age Ageing* 2013; **42:** 62–69.