Continuous positive airway pressure versus standard care for the treatment of people with mild obstructive sleep apnoea (MERGE): a multicentre, randomised controlled trial

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Summary

Background The evidence base for the treatment of mild obstructive sleep apnoea is limited and definitions of disease severity vary. The MERGE trial investigated the clinical effectiveness of continuous positive airway pressure in patients with mild obstructive sleep apnoea.

Methods MERGE, a multicentre, parallel, randomised controlled trial enrolled patients (≥18 years to ≤80 years) with mild obstructive sleep apnoea (apnoea-hypopnoea index [AHI] ≥5 to ≤15 events per h using either AASM 2007 or AASM 2012 scoring criteria) from 11 UK sleep centres. Participants were assigned (1:1) to either 3 months of continuous positive airway pressure plus standard care (sleep counselling), or standard care alone, by computer-generated randomisation; neither participants nor researchers were blinded. The primary outcome was a change in the score on the Short Form-36 questionnaire vitality scale in the intention-to-treat population of patients with mild obstructive sleep apnoea diagnosed using the American Academy of Sleep Medicine 2012 scoring criteria. The study is registered with ClinicalTrials.gov, NCT02699463.

Findings Between Nov 28, 2016 and Feb 12, 2019, 301 patients were recruited and randomised. 233 had mild obstructive sleep apnoea using AASM 2012 criteria and were included in the intention-to-treat analysis: 115 were allocated to receive continuous positive airway pressure and 118 to receive standard care. 209 (90%) of these participants completed the trial. The vitality score significantly increased with a treatment effect of a mean of 10·0 points (95% CI 7·2–12·8; p<0·0001) after 3 months of continuous positive airway pressure, compared with standard care alone (9·2 points [6·8 to 11·6] *vs* –0·8 points [–3·2 to 1·5]). Using the ANCOVA last-observation-carried-forward analysis, a more conservative estimate, the vitality score also significantly increased with a treatment effect of a mean of 7·5 points (95% CI 5·3 to 9·6; p<0·0001) after 3 months of continuous positive airway pressure, compared with standard care alone (7·5 points [6·0 to 9·0] *vs* 0·0 points [–1·5 to 1·5]). Three serious adverse events occurred (one allocated to the continuous positive airway pressure group) and all were unrelated to the intervention.

Interpretation 3 months of treatment with continuous positive airway pressure improved the quality of life in patients with mild obstructive sleep apnoea. These results highlight the need for health-care professionals and providers to consider treatment for patients with mild obstructive sleep apnoea.

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Introduction

Nearly 1 billion adults aged 30–69 years are estimated to have obstructive sleep apnoea globally, with about 40% of these people having moderate-to-severe disease (apnoea-hypopnoea index [AHI] ≥15 events per h) and 60% mild disease (AHI ≥5 to <15 events per h).[1] Despite this high prevalence, clinical management—including access to treatment—varies widely across the spectrum of obstructive sleep apnoea disease severity and from country to country.

In 2009, the UK Health Technology Assessment Programme, which produces information for the National Institute for Health and Care Excellence, reported that there was clear evidence for the benefit of continuous positive airway pressure (CPAP)—compared with placebo, conservative treatment, or usual care—in patients with moderate-to-severe obstructive sleep apnoea with symptoms of sleepiness.[2] The report also concluded that in patients with mild disease, further investigations of the effectiveness of treatment were needed. Similar reviews undertaken by the American Thoracic Society in 2016 and the American Academy of Sleep Medicine (AASM) in 2019 drew similar conclusions.[3,4] These reviews suggested that future studies should focus on capturing improvements in the diversity of symptoms reported by patients with mild obstructive sleep apnoea, such as reduced energy, feelings of general tiredness, fatigue and poor sleep,

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See Online for appendix

Research in context

Evidence before this study

Mild obstructive sleep apnoea is a highly prevalent condition that is associated with significant morbidity, but few studies have investigated the clinical efficacy of treatment in people with this condition. We searched scientific literature databases, including PubMed, Google Scholar, and Embase from Jan 01, 2006 to July 31, 2019. We did additional internet searches on Clinicaltrials.gov, UptoDate, and the Cochrane Database of Systematic Reviews. We used the search terms ("mild obstructive sleep apnoea" OR "mild obstructive sleep apnea" OR "mild OSA") AND ("positive airway pressure" OR "CPAP" OR "APAP" OR "treatment"). Studies and review articles that contained information on diagnosis and treatment for patients with mild obstructive sleep apnoea were included. Studies that did not list outcomes relevant to the MERGE trial primary and secondary outcomes were excluded. Five systematic review articles examining the evidence base for the treatment of mild obstructive sleep apnoea with continuous positive airway pressure, plus three randomised clinical trials that included populations of patients with mild-to-moderate obstructive sleep apnoea, were identified as key evidence. The reviews undertaken by Cochrane in 2006, the UK Health Technology Assessment Programme in 2009, the American Thoracic Society in 2016, and the American Academy of Sleep Medicine (AASM) in 2006 and 2019, identified an evidence gap for the clinical and cost-effective benefits of treating patients with mild obstructive sleep apnoea. Two of the randomised clinical trials found quality-of-life benefits with continuous positive airway pressure (MOSAIC trial, ISRCTN34164388, and CATNAP trial, NCT00127348), whereas one found no improvements from continuous positive airway pressure treatment in patients with mild obstructive sleep apnoea (APPLES trial, NCT00051363). However, all three trials used the old criteria for the scoring of disease severity, published by AASM in 2007. No studies were found that evaluated the clinical benefits of treatment in patients with mild obstructive sleep apnoea diagnosed using the more recent and more sensitive AASM 2012 scoring criteria.

Added value of this study

The MERGE trial is, to our knowledge, the first study to show improvements in measures of quality of life following continuous positive airway pressure treatment in patients with mild obstructive sleep apnoea, diagnosed using the AASM 2012 scoring criteria. Our findings support the treatment of obstructive sleep apnoea patients at the mildest end of the disease spectrum and are consistent with recommendations made in the 2019 AASM Clinical Practical Guidelines. These guidelines emphasised the need for treatment decisions to be based on symptoms rather than on changes in disease severity defined by counting of respiratory events and associated hypoxia.

Implications of all the available evidence

The implication of the new data is that health-care professionals, and those providing or commissioning services, will be required to review current practice regarding the criteria used for diagnosis and the treatment of mild obstructive sleep apnoea. No global consensus on the scoring criteria that should be used for diagnosis of obstructive sleep apnoea exists, nor is there agreement on whether patients with mild obstructive sleep apnoea should be offered treatment based on the severity of symptoms or counting of respiratory events that occur per hour of sleep, or both. The results of the MERGE trial provide an evidence base for the clinical effectiveness of treatment with continuous positive airway pressure in patients with mild obstructive sleep apnoea, and for the identification of patients with mild obstructive sleep apnoea using a more sensitive, symptom-based clinical assessment. It is anticipated that, where appropriate, these data will support patients with mild obstructive sleep apnoea in accessing optimal health care to maintain quality of life.

impaired cognition, and reduced quality of life (QoL),[3,5,6] thus moving away from the present emphasis on excessive daytime sleepiness as a single outcome measure, and the counting of respiratory events with concomitant hypoxia for the diagnosis of obstructive sleep apnoea severity.[3,4,7]

Uncertainty about the effectiveness of CPAP treatment in patients with mild obstructive sleep apnoea has been compounded by a change in the criteria for scoring of respiratory events, proposed in 2012 by the AASM.[8] The rationale for updating the scoring criteria was to ensure that patients who have frequent arousals from sleep, caused by respiratory events associated with only minimal hypoxia (hypopnoeas), are covered by the diagnostic criteria for obstructive sleep apnoea. Adopting this change in the sensitivity of the scoring criteria increases the number of patients who reach the diagnostic threshold for mild obstructive sleep apnoea.[9,10] To date, no randomised studies have investigated the clinical effectiveness of CPAP treatment in patients with mild disease, diagnosed using the more sensitive AASM 2012 scoring criteria, and whether these patients can benefit from treatment has been unclear.

The MERGE trial was designed to determine whether 3 months of CPAP in patients with mild obstructive sleep apnoea, diagnosed using AASM 2012 scoring criteria, improves QoL measured by the vitality scale of the Short Form (SF)-36 questionnaire, compared with standard care. The secondary focus was a comparison of the effectiveness of CPAP in patients with mild obstructive sleep apnoea diagnosed using the more widely used AASM 2007 scoring criteria.

Methods

Study design and participants

The MERGE trial was a multicentre, parallel-group, randomised controlled trial. Recruitment was via the UK Respiratory Sleep Research Network from 11 geographically diverse National Health Service (NHS) secondary care sleep centres, all with expertise in the management of obstructive sleep apnoea (appendix p 14). The trial was approved by a central ethics committee (REC 16/SC/0387) and all patients gave written informed consent.

Patients were referred to NHS sleep centres for investigation of possible sleep apnoea. Patients were assessed according to standard clinical management at their local sleep service, and those with newly diagnosed mild obstructive sleep apnoea were invited to participate in the trial. Eligibility was assessed by a home sleep test (respiratory polygraphy; ApneaLink Air, ResMed Ltd, Oxfordshire, UK) with measurements of airflow, respiratory effort, pulse oxygen saturation, and pulse rate. Patients (≥18 years to ≤80 years) with an AHI of at least 5 events per h to 15 or fewer events per h (by either AASM 2007 or AASM 2012 scoring criteria) were eligible. The primary analysis population was patients with an AHI of at least 5 events per h to 15 or fewer events per h diagnosed using AASM 2012 scoring criteria.[8] Patients diagnosed by the more widely used AASM 2007 scoring criteria were included in the secondary analysis.

Exclusion criteria were as follows: inability to give fully informed consent, BMI of 40 kg/m² or more, unstable cardiac disease, use of supplemental oxygen, secondary sleep pathology (eg, periodic limb movement syndrome, narcolepsy, circadian disorder, and obesity hypoventilation syndrome), previous CPAP usage, Epworth Sleepiness Scale (ESS) score of 15 or higher, concerns over driving while sleepy, or an inability to tolerate the 1 h CPAP tolerance test. The MERGE trial protocol and statistical analysis plan can be found on the MERGE ClinicalTrials.gov page.

Randomisation and masking

Eligible patients were randomly assigned to CPAP plus standard care (sleep hygiene counselling) or standard care alone, and followed up for 3 months. Patients were randomly assigned (1:1) using a centralised computer-generated schedule, with minimisation by age (<30 years *vs* 30–60 years *vs* >60 years), gender, and BMI (<30 kg/m² *vs* ≥30 kg/m²). Delegated staff at each site accessed the randomisation programme hosted by the Oxford Clinical Trials Research Unit (Registration/Randomisation and Management of Product). Randomisation occurred once baseline data were collected and the 1 h CPAP tolerance test was complete. Neither the participants nor the investigators were blinded to trial interventions. However, baseline QoL questionnaires were self-administered before randomisation and the home sleep tests were scored using automated algorithms. After randomisation, participants were managed by a trial sleep therapist at a central location (Royal Brompton Hospital, London, UK).

Procedures

The home sleep test data were uploaded to a central server (AirView, ResMed Ltd) and analysed by automated scoring algorithms using AASM 2012 and AASM 2007 criteria[11,12] plus a manual review by an independent central scorer (appendix p 3). The scorer was able to change (ie, add or remove) apnoea or hypopnea events when the automated scoring was deemed to be incorrect. Changes were made when the automatically scored events were clearly wrong, usually due to the presence of an artifact; however, in practice, this situation was relatively rare because artifacts were generally removed automatically before the automated analysis (appendix pp 3, 4). Patients were alerted to the fact that there was artifact or insufficient analysable data for the ApnoeaLink Air by a red light on the device the morning after their sleep study. If this occurred, patients were offered the opportunity to repeat the sleep study.

Eligible patients attended two outpatient visits at their local sleep service, one at baseline and one after 3 months. As part of their eligibility assessment, all patients used auto-adjusting CPAP (AirSense 10 AutoSet; or AirSense 10 AutoSet for Her, ResMed Ltd, Oxfordshire, UK) for a 1 h tolerance test. During this test, CPAP was slowly increased from 4 cm H_2O to 10 cm H_2O and the appropriate mask was selected. Patients who found CPAP tolerable then completed the baseline visit, in which demographics and medical history were collected and baseline QoL questionnaires were completed. Patients were also asked which symptoms prompted them to visit their health-care provider. At the end of the baseline visit, patients were randomised.

For the **protocol** see https://clinicaltrials.gov/ct2/show/NCT02699463

At the final trial visit after 3 months of treatment, all participants returned to their local sleep service, where they completed the QoL questionnaires again. Serious adverse events were recorded throughout the trial. Participants in the treatment group were asked if they wished to continue CPAP treatment and participants in the standard care group were offered CPAP treatment.

For standard care, all participants received sleep hygiene counselling, based on UK guidelines and recommendations.[13] Standardised information included healthy sleep behaviours, such as spending adequate amounts of time in bed and organising the bedroom to be conducive to sleep. Participants were provided with written instructions and, after 3 days, received a telephone call or email from a sleep therapist at the central site to review their sleep hygiene behaviours.

In addition to standard care, participants randomly assigned to CPAP were also provided with a domiciliary CPAP device, set in auto-adjusting mode, and given

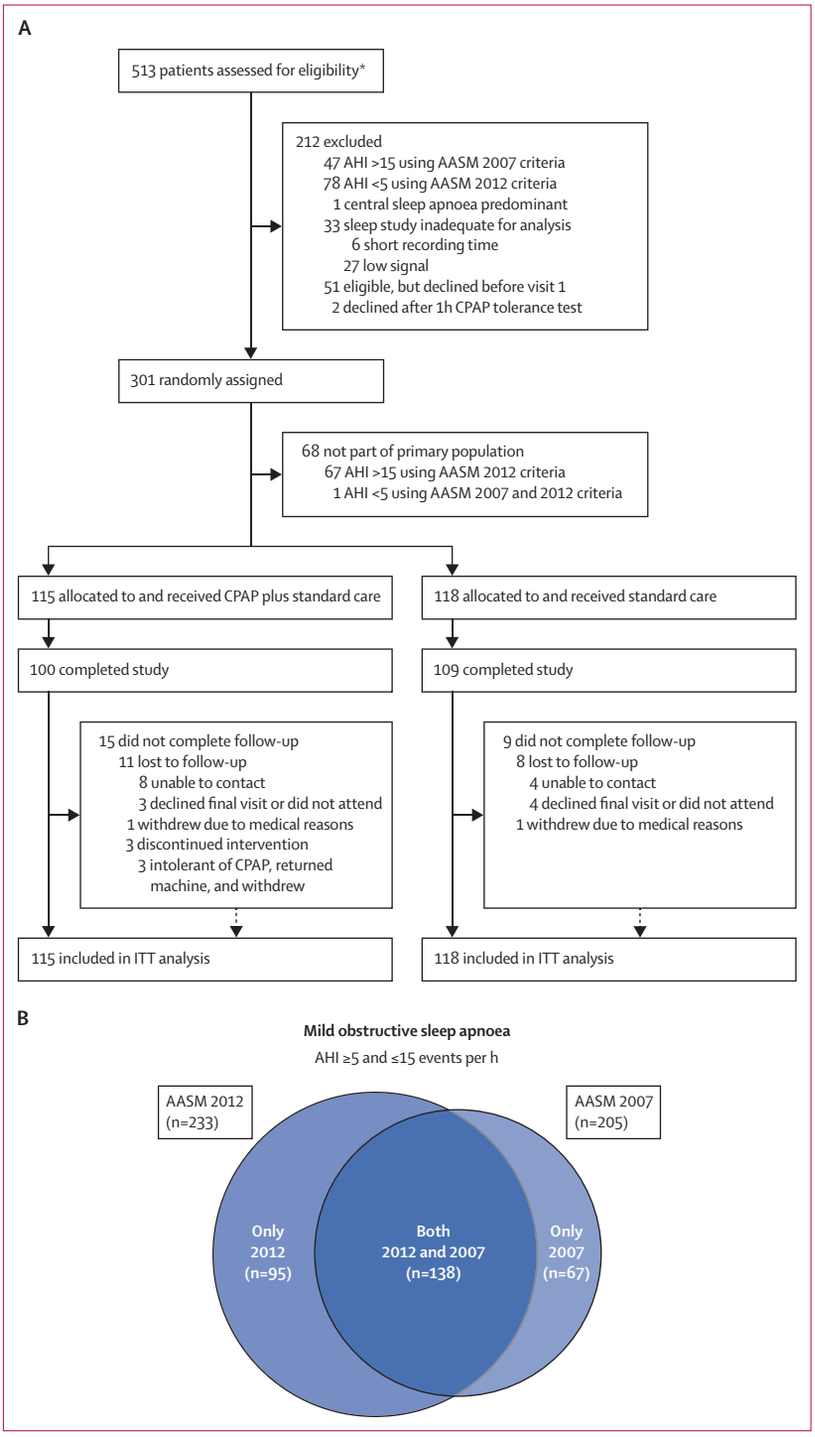

Figure 1: **Study profile for the MERGE trial**
Study profile (A) and breakdown of participants randomly assigned who were diagnosed with the AASM 2012 or 2007 criteria, or both (B). One patient was accidentally included based on the AHI score from the manual review of their sleep study. AHI=apnoea-hypopnoea index. AASM=American Academy of Sleep Medicine. CPAP=continuous positive airway pressure. ITT=intention-to-treat. *Assessed using the ApneaLink Air home sleep study.

education by their local clinical team. After 3 days, participants using CPAP received a phone call or email from a sleep therapist at the central site. The therapist used wireless monitoring to review CPAP efficacy and adherence, and offered participants support and ongoing troubleshooting. Changes to CPAP settings were made on the basis of standard clinical practice in response to suboptimal treatment with high residual AHI (≥5 events per h), high mask leak (>24 L/min) or low adherence (<4 h per night). Details of participants' contacts with the sleep therapist were documented (appendix pp 3, 5).

Outcomes

The primary outcome was change from baseline to 3 months in the vitality scale of the SF-36 questionnaire in patients with mild obstructive sleep apnoea, diagnosed using the AASM 2012 scoring criteria, in the intention-to-treat population. The vitality scale, which aims to capture energy and vitality, is one of the most sensitive measures of improvement following CPAP treatment in patients with moderate-to-severe obstructive sleep apnoea.[14]

Secondary outcomes were change from baseline to 3 months in patients with mild obstructive sleep apnoea, diagnosed using both the AASM 2012 and AASM 2007 scoring criteria, in the following QoL measures: SF-36 (eight scales yielding two summary measures: physical component score and the mental component score); ESS; Fatigue Severity Scale (FSS); Functional Outcomes of Sleep Questionnaire (FOSQ); Hospital Anxiety and Depression Scale (HADS); Insomnia Severity Index; and European QoL five dimensions Questionnaire (EQ-5D-3L). Another secondary outcome was the comparison of automated scoring and manual review of scoring, using the AASM 2012 criteria (details in appendix pp 3, 4).

Statistical analysis

The sample size calculation was based on data from patients with mild obstructive sleep apnoea in the Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular (MOSAIC) study.[15] With 80% power at a two-sided significance level of 5%, a total of 224 patients (112 per group) would be required to detect a difference of 6·6 in mean score change between the two treatment groups (CPAP mean 10·8 [SD 17·0]; standard care mean 4·2 [SD 18·1]). Assuming a 10% dropout rate and to ensure that enough patients were enrolled on the basis of AASM 2012 scoring criteria for mild obstructive sleep apnoea, target recruitment was set at 300 participants, considering that patients were accepted into the trial using a diagnosis based on either AASM 2007 or AASM 2012 scoring criteria.

All data were documented on case report forms at the trial sites and entered into an electronic data capture system (OpenClinica) developed by the Oxford Clinical Trials Research Unit. Statistical analysis was done by independent statisticians (appendix p 2) in accordance with a predefined analysis plan. All data were imported

into SAS Version 9.4 software (SAS Institute Inc, Cary, NC, USA) for statistical analysis.

Statistical analyses were done on an intention-to-treat basis, using a type 1 error rate of 0·05, unless otherwise specified. This population was divided into two overlapping subgroups: all randomised participants with mild obstructive sleep apnoea based on the AASM 2012 scoring criteria, and those with mild obstructive sleep apnoea based on the AASM 2007 criteria. An additional subgroup of participants diagnosed with no obstructive sleep apnoea using 2007 scoring criteria but mild obstructive sleep apnoea using 2012 criteria was also defined. Summaries and analyses were done for all three subgroups, with primary emphasis on the group of participants with mild obstructive sleep apnoea diagnosed according to AASM 2012 scoring criteria.

Descriptive statistics were generated for all baseline characteristics, sleep study data, adherence to CPAP, and study outcomes, including sample size, mean (SD) or median (IQR) for continuous parameters, and frequencies and percentages for categorical parameters.

The prespecified primary analysis outcome was done using a mixed-effects repeated measures model to account for missing values. Results were presented as the mean between-group difference in the change in vitality score, adjusted for baseline score, with the associated 95% CI, effect size, and p value. Because all missing values resulted from missed 3 month visits, it is possible the primary analysis overestimated the treatment effect. Therefore, additionally, mean change in vitality score was also compared between groups using analysis of covariance adjusting for baseline vitality (ANCOVA), where missing 3-month scores were replaced with baseline scores using a last-observation-carried-forward approach. The ANCOVA model was considered a conservative approach in that patients would have seen no improvement had they remained in the trial. Although results from both analysis models are presented, the ANCOVA model was given primary emphasis within this report. Homogeneity of the primary outcome across study sites was assessed using the mixed-effects regression model for participants who completed the study. The effect of a treatment-by-site interaction was tested at a significance level of 0·10.

Secondary outcomes of change in QoL scores from baseline to 3 months were compared between groups using ANCOVA; missing 3-month scores were replaced with baseline scores using a last-observation-carried-forward approach. Secondary outcomes were evaluated in all three subgroups: participants with a diagnosis of mild obstructive sleep apnoea based on AASM 2012 criteria; those with a diagnosis based on AASM 2007 criteria; and participants with no obstructive sleep apnoea according to 2007 criteria, but mild obstructive sleep apnoea based on 2012 criteria. These secondary analyses were considered to be exploratory and no formal adjustments for multiple significance testing were made.

	Continuous positive airway pressure (n=115)	Standard care (n=118)
Age (years)	50·6 (11·3)	50·2 (12·1)
Female	34 (30%)	37 (31%)
Male	81 (70%)	81 (69%)
BMI (kg/m²)	30·3 (4·0)	30·2 (4·6)
Ethnicity		
White	105 (91%)	103 (87%)
Non-white	10 (9%)	15 (13%)
Neck circumference (cm)	40·70 (3·66)	39·85 (4·61)
Self-reported medical history		
Hypertension	38 (33%)	28 (24%)
Depression	27 (24%)	38 (32%)
Anxiety	18 (16%)	33 (28%)
Insomnia	14 (12%)	18 (15%)
Heart disease and cardiovascular disorders	11 (10%)	8 (7%)
Diabetes	7 (6%)	14 (12%)
Other*	76 (66%)	84 (71%)
QoL measures: mean higher score indicates better status		
SF-36: vitality	44·2 (10.8)	42·0 (10·2)
SF-36: physical component	48·0 (9·7)	47·2 (10·8)
SF-36: mental component	46·9 (11·1)	44·3 (12·3)
FOSQ	16·4 (2·9)	15·9 (2·7)
EQ-5D: index (n=187)	0·76 (0·19)	0·74 (0·19)
EQ-5D: VAS score (n=187)	70·9 (18·8)	65·8 (18·5)
QoL measures: mean lower score indicates better status		
ESS (points)	9·9 (4·5)	10·0 (4·2)
FSS	35·4 (14·0)	38·0 (13·5)
HADS: anxiety	6·6 (4·4)	7·5 (4·0)
HADS: depression	5·0 (3·9)	6·1 (4·1)
ISI	12·4 (5·6)	13·3 (5·7)
Sleep study results		
AHI (events per h)	10·60 (7·1–12·6)	9·85 (6·8–13·2)
Obstructive apnoea index (events per h)	0·62 (0·2–1·9)	0·90 (0·3–2·3)
Central apnoea index (events per h)	0·00 (0·0–0·3)	0·21 (0·0–0·5)
Hypopnoea index (events per h)	7·64 (6·0–10·8)	8·06 (5·6–10·4)
>4% ODI (events per h)	6·50 (5·0–9·0)	6·70 (4·4–9·4)
>3% ODI (events per h)	13·50 (10·1–15·5)	12·90 (9·9–16·1)
Percentage of sleep time with saturation ≤90%	3·0% (1–9)	3·0% (1–10)

Data presented as mean (SD), n (%), or median (IQR). AASM=American Academy of Sleep Medicine. QoL=quality of life. SF-36=Short Form-36. FOSQ=Functional Outcomes of Sleep Questionnaire. EQ-5D=European QoL five dimensions Questionnaire. VAS=visual analogue scale. ESS=Epworth Sleepiness Scale. FSS=Fatigue Severity Scale. HADS=Hospital Anxiety and Depression Scale. ISI=Insomnia Severity Index. AHI=apnoea-hypopnoea index. ODI=oxygen desaturation index. *See appendix for list of other medical comorbidities.

Table 1: **Baseline demographic and clinical characteristics of patients with mild obstructive sleep apnoea diagnosed using AASM 2012 scoring criteria**

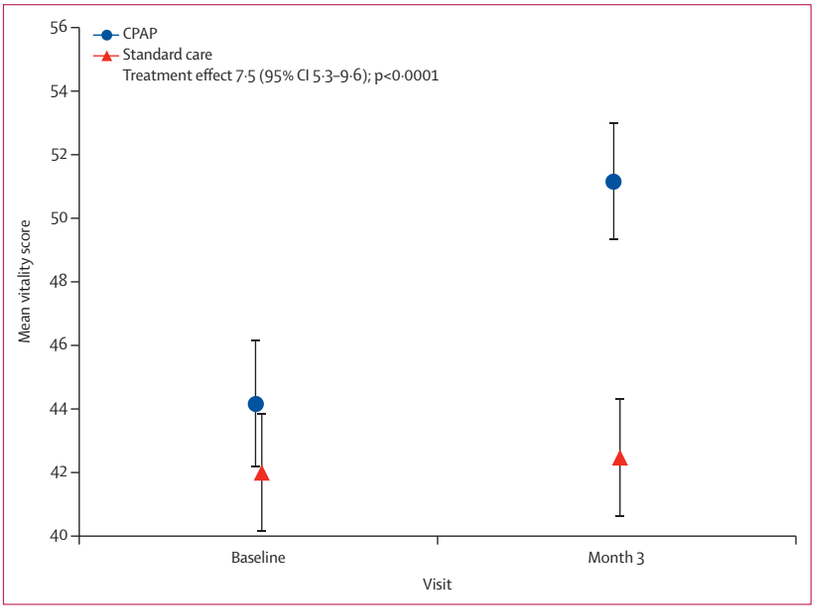

Figure 2: **Changes from baseline in the primary outcome, vitality scale of the Short Form-36**
The intention-to-treat population of patients with mild obstructive sleep apnoea, diagnosed using the American Academy of Sleep Medicine 2012 scoring criteria. An increase in score represents an improvement in self-assessed health status. Error bars denote 95% CI. CPAP=continuous positive airway pressure.

The MERGE trial was managed by the Trial Steering Committee (appendix p 2); we did not use a data monitoring committee. This trial was registered with ClinicalTrials.gov, NCT02699463.

Role of the funding source

ResMed Ltd sponsored the trial and provided the CPAP equipment. The development of the trial protocol and trial oversight were carried out by the Trial Steering Committee. The funders were involved in the study design and were able to critique during the writing of the report, which included the interpretation of data. The collection of data was independently carried out at 11 NHS secondary care sleep centres. The data analysis was completed by independent statisticians. The trial data management and electronic data capture were managed by the Oxford Respiratory Trials Unit. AJW, JLK, ELH, MDD, LAW, and MJM had access to the raw data. The Chief Investigator (MJM) had full access to all the trial data and had final responsibility for the data analysis and publication.

Results

Between Nov 28, 2016 and Feb 12, 2019, 301 patients with mild obstructive sleep apnoea (AHI ≥5 to ≤15 events per h) were recruited and randomised. 233 were

	Continuous positive airway pressure (n=115)	Standard care (n=118)	Treatment difference	Effect Size	p value
Short Form-36: an increase in score indicates improvement					
Vitality	7·5 (6·0 to 9·0)	0·0 (–1·5 to 1·5)	7·5 (5·3 to 9·6)	0·91	<0·0001
Physical component	1·0 (–0·1– to 2·2)	–0·6 (–1·8 to 0·5)	1·6 (–0·0 to 3·3)	0·26	0·05
Mental component	4·2 (2·8 to 5·6)	–0·7 (–2·1 to 0·7)	4·9 (2·9 to 6·9)	0·64	<0·0001
Physical functioning	1·0 (–0·1 to 2·1)	–0·7 (–1·8 to 0·4)	1·7 (0·1 to 3·3)	0·28	0·03
Role-physical	3·1 (1·6 to 4·5)	–0·6 (–2·0 to 0·8)	3·7 (1·6 to 5·7)	0·47	0·0005
Bodily pain	0·3 (–1·2 to 1·9)	–0·2 (–1·8 to 1·3)	0·6 (–1·6 to 2·8)	0·07	0·61
General health	1·5 (0·5 to 2·5)	–1·1 (–2·0 to –0·1)	2·5 (1·1 to 3·9)	0·47	0·0004
Social functioning	2·5 (1·2 to 3·7)	–1·2 (–2·5 to 0·0)	3·7 (1·9 to 5·5)	0·53	<0·0001
Role-emotional	2·8 (1·0 to 4·5)	–0·9 (–2·6 to 0·8)	3·7 (1·2 to 6·2)	0·38	0·004
Mental health	2·9 (1·6 to 4·2)	–0·6 (–1·8 to 0·7)	3·5 (1·7 to 5·3)	0·51	0·0001
Other QoL measures: an increase in score indicates improvement					
FOSQ	1·4 (1·1 to 1·7)	0·1 (–0·2 to 0·4)	1·3 (0·9 to 1·8)	0·78	<0·0001
EQ-5D					
Index (n=189)	0·03 (0·00 to 0·06)	–0·00 (–0·03 to 0·02)	0·03 (–0·00 to 0·07)	0·26	0·08
Visual analogue scale score (n=189)	3·1 (0·3 to 5·9)	–0·9 (–3·7 to 1·8)	4·0 (0·1 to 7·9)	0·30	0·05
QoL measures: a decrease in score indicates improvement					
ESS	–3·0 (–3·6 to –2·3)	0·0 (–0·6 to 0·6)	–3·0 (–3·8 to –2·1)	–0·88	<0·0001
FSS	–7·2 (–8·9 to –5·4)	1·4 (–0·3 to 3·1)	–8·6 (–11·0 to –6·1)	–0·92	<0·0001
HADS					
Anxiety	–0·5 (–1·0 to –0·1)	0·3 (–0·2 to 0·7)	–0·8 (–1·5 to –0·2)	–0·32	0·02
Depression	–1·2 (–1·7 to –0·7)	0·4 (–0·1 to 0·9)	–1·6 (–2·3 to –0·9)	–0·63	<0·0001
ISI	–4·0 (–4·8 to –3·2)	0·1 (–0·6 to 0·9)	–4·1 (–5·2 to –3·0)	–0·99	<0·0001

Adjusted means, 95% CIs, and p values are from an ANCOVA model of change from baseline, adjusting for baseline score. Missing scores at month 3 were replaced with baseline scores using a last-observation-carried-forward approach. AASM=American Academy of Sleep Medicine. FOSQ=Functional Outcomes of Sleep Questionnaire. EQ-5D=European QoL five dimensions Questionnaire (EQ-5D-3L). ESS=Epworth Sleepiness Scale. FSS=Fatigue Severity Scale. HADS=Hospital Anxiety and Depression Scale. ISI=Insomnia Severity Index.

Table 2: **Quality-of-life change from baseline in patients with mild obstructive sleep apnoea diagnosed using AASM 2012 scoring criteria**

diagnosed with mild obstructive sleep apnoea using AASM 2012 scoring criteria, and 205 using AASM 2007 criteria; 95 (32%) participants had mild obstructive sleep apnoea (AHI ≥5 events per h) using 2012 criteria, but no diagnosis (AHI <5 events per h) as per 2007 criteria. Of the participants with mild obstructive sleep apnoea according to AASM 2012 criteria, 115 were allocated to and received CPAP plus standard care, and 118 were allocated to and received standard care alone. 209 (90%) participants completed the trial (figure 1, appendix p 4).

Baseline demographic and clinical characteristics were similar between the group that received CPAP and the group that received standard care (table 1). The cohort had a mean age of 50·4 years (SD 11·7), was 30·5% female, and had a mean BMI of 30·2 kg/m² (SD 4·3); baseline median AHI was 10·1 events per h (IQR 7·1–12·9). The participants were symptomatic (SF-36 vitality 43·1 points [SD 10·6]; ESS 10·0 points [SD 4·4]). The self-reported reason for referral and self-reported medical history are summarised in the appendix (pp 4, 5).

The vitality score of the SF-36 was significantly increased after 3 months of CPAP treatment (figure 2). From the primary outcome analysis, the adjusted mean change was 9·2 points (95% CI 6·8 to 11·6) for CPAP; –0·8 points (–3·2 to 1·5) for standard care, with a treatment effect of 10·0 points (7·2 to 12·8), p<0·0001. Results from the ANCOVA last-observation-carried-forward analysis, a more conservative approach to handling missing data, were also significant; the adjusted mean change was 7·5 points (95% CI 6·0 to 9·0) for CPAP; 0·0 points (–1·5 to 1·5) for standard care, with a treatment effect of 7·5 points (5·3 to 9·6), p<0·0001 (table 2, appendix p 5). Site and treatment-by-site effects were jointly tested and were not significant (p=0·41), indicating that the mean change in the vitality score of the SF-36 was homogeneous across study sites. Regarding missing data, for the 233 participants in the analysis population, there were 94·6% non-missing primary outcome data available for the primary analysis.

Most secondary outcomes improved significantly with CPAP treatment, compared with standard care, including subjective sleepiness (ESS), fatigue (FSS), anxiety and depression (HADS), insomnia (Insomnia Severity Index), and functionality (FOSQ; table 2). The mental component score of the SF-36 was significantly improved, as were its key scales (vitality, social functioning, role-emotional, and mental health); however, the physical component score of the SF-36, including bodily pain, was not significantly improved with CPAP treatment (figure 3).

Patients with mild obstructive sleep apnoea diagnosed using AASM 2007 scoring criteria showed similar significant improvements in QoL measures to patients diagnosed using AASM 2012 criteria (appendix p 5). Subgroup analysis of the 95 participants on the mildest end of the disease spectrum (ie, patients diagnosed with mild obstructive sleep apnoea using the 2012 criteria, but classed as normal with the 2007 criteria) also showed a significant improvement in vitality score and other QoL measures when comparing CPAP treatment with standard care (appendix p 5).

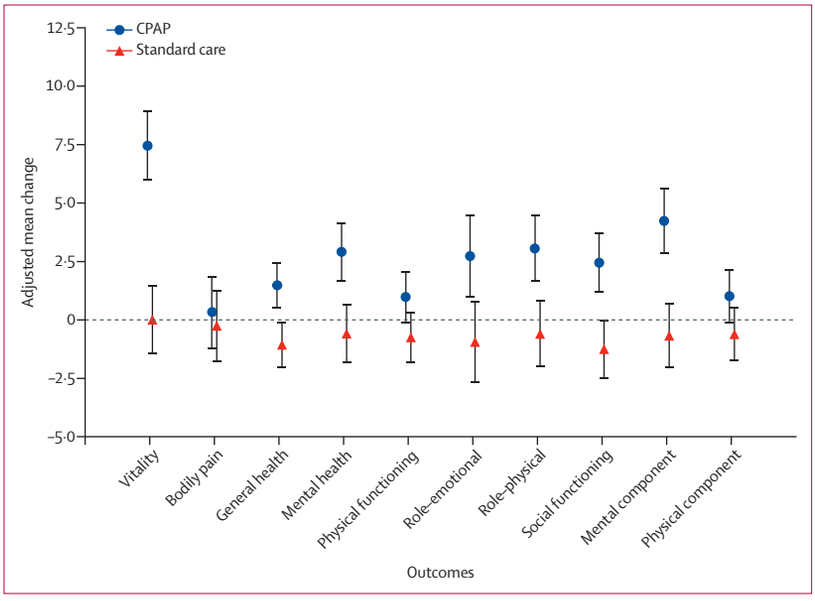

Figure 3: **Changes from baseline in Short Form-36 physical and mental components and their composites**
The intention-to-treat population of patients with mild obstructive sleep apnoea, diagnosed using the American Academy of Sleep Medicine 2012 scoring criteria. Error bars denote 95% CI. CPAP=continuous positive airway pressure. An increase in score represents an improvement.

The median CPAP usage over 3 months was 4 h 0 min (IQR 1 h 36 min to 5 h 44 min). The group median of each individual's median pressure was 7·3 cm H_2O (IQR 6·2–8·8), (95th percentile 10·1 cm H_2O [IQR 8·6–11·8]) with a residual AHI of 1·5 (IQR 0·8–2·5) events per h; the median mask leak was 1·6 L/min (IQR 0·4–4·1). Of the participants randomised to CPAP, 81 (81%) of 100 wished to continue using CPAP after completion of trial. A summary of participant contact with the sleep therapist at the central site is described in the appendix (p 5). Three serious adverse events were recorded during the trial, one in the CPAP group; all were classified as being unrelated to the interventions (appendix p 6).

Discussion

The MERGE trial found a significant improvement in the vitality score on the SF-36 QoL questionnaire in patients with mild obstructive sleep apnoea after 3 months of CPAP treatment plus standard care, when compared with standard care alone. This improvement in QoL was accompanied by a reduction in sleepiness, and improvements in fatigue and depression. Diagnoses of mild obstructive sleep apnoea using the less sensitive, but more extensively used, AASM 2007 scoring criteria produced similar results. Additionally, patients at the mildest end of the disease spectrum (ie, those patients diagnosed with mild obstructive sleep apnoea using the 2012 criteria, but classed as normal with the 2007 criteria), also had a significant improvement in QoL.

Importantly, these patients would have been excluded from having a diagnosis of mild obstructive sleep apnoea using the older AASM 2007 scoring criteria, despite being symptomatic, on average, and improving with CPAP treatment.

To date, six randomised controlled trials have been carried out in patients with mild obstructive sleep apnoea; however, none has investigated the clinical effectiveness of CPAP in the patients scored with the AASM 2012 criteria used in the MERGE trial. Three were single-centre trials, completed before the standardisation of scoring criteria in 2007.[16–18] Nonetheless, these early trials reported some benefits of treatment in patients with mild obstructive sleep apnoea. One of the three subsequent, multicentre trials recruited patients on the basis of symptoms and found that CPAP treatment improved sleepiness in minimally symptomatic patients with mild-to-moderate obstructive sleep apnoea.[15] The second included patients with mild and moderate obstructive sleep apnoea, diagnosed using the AASM 2007 criteria, and reported an improvement in functional outcomes.[19] The third trial was carried out in patients with a spectrum of obstructive sleep apnoea severity, recruited using local adverts, in addition to a clinical population, and did not show any improvement in sleepiness in the patients with mild obstructive sleep apnoea after 6 months of CPAP treatment.[20] Taken together, these data suggested that patients with mild obstructive sleep apnoea who seek clinical support, gain benefit from treatment.

In the MERGE trial, the greatest therapeutic benefit in QoL occurred in the primary outcome, the vitality scale measured by the SF-36. Additional secondary improvements were noted in the mental component scales, including social functioning, role-emotional, and mental health. These findings are consistent with previous trials[15,21] and the Cochrane conclusion that have all previously reported large improvements in health status, following CPAP treatment that closely reflect the benefits reported by patients in clinical practice.[22] The results also emphasise the various neural, psychological, and cognitive effects of obstructive sleep apnoea.[23] Investigation of mood, captured by the HADS scale, showed greater improvements in depression scores than in anxiety. This pattern is consistent with previous studies,[16,17] indicating a role for CPAP treatment in mood enhancement.

Investigation of the therapeutic benefits using effect sizes showed that the largest effect size occurred in the Insomnia Severity Index.[24] This finding was unexpected; however, the questions in this scale probably captured generalised poor sleep, linked to the feeling of fatigue reported by our patients, rather than insomnia itself. The large effect size observed for measures of fatigue (change in FSS) would appear to support this suggestion.

In the MERGE trial, the most frequently self-reported reasons for seeking treatment were snoring, witnessed apnoeas, daytime sleepiness, and fatigue. These reasons were consistent with our clinical experience that patients with mild obstructive sleep apnoea have multiple symptoms. Furthermore, the design of the MERGE trial reflected previous observations of the sensitivity of energy and vitality to detect change in treated patients with moderate-to-severe obstructive sleep apnoea;[14,15,21] therefore, the vitality scale of the SF-36 was used as a primary outcome measure. However, if the focus of the trial had been a decrease in sleepiness, the secondary outcome of a change in ESS also improved and exceeded the minimum clinically important difference.[25]

On completion of the 3-month trial, 81% of patients who were randomly assigned to CPAP treatment wished to continue using CPAP; in the MOSAIC trial, 71% of patients wished to continue using CPAP.[15] These data show that even those patients with mild obstructive sleep apnoea feel that the benefits of treatment outweigh the burden of regular CPAP use. Future studies are needed to determine the cost-effectiveness of CPAP treatment in the mild obstructive sleep apnoea population and whether alternative treatment options, such as positional or mandibular advancement device therapies, are as effective in this patient population.[18]

In general, with a low percentage of missing data, the effects of missing data should be small. However, all missing data were due to missed 3-month visits, so the primary model might have overestimated the treatment effect. To address this possibility, a supporting analysis of covariance was done, using a conservative last-observation-carried-forward approach, in which missing 3-month scores were replaced with baseline scores (ie, indicating that patients would have seen no improvement had they remained in the trial). This model also yielded a significant treatment effect and therefore was given primary emphasis within this report.

Several limitations need to be considered when interpreting the findings of the MERGE trial. We had no sham control or blinding in the study design. Sham CPAP was not used as a comparator because we reasoned that in patients with mild obstructive sleep apnoea, CPAP might conceivably worsen symptoms—for example, by disrupting sleep. Alternatively, the minimal pressure might have provided partial therapy. Additionally, evidence shows that the use of standard care as a comparator produces similar results to sham CPAP.[2,26,27] Our finding of greater improvements in the mental components of the SF-36, compared with physical components, suggests that the treatment response was unlikely to be attributable entirely to a placebo effect, which would have been expected to produce similar changes across all scales, both mental and physical.[28] Additionally, the absence of sham control or blinding could have resulted in some of those participants randomly assinged to standard care feeling disappointed. We do not think that this occurred in the MERGE trial,

because participants who were randomly assigned to standard care knew that they would be offered CPAP treatment at the end of their participation in the trial.

The MERGE trial used respiratory polygraphy, rather than polysomnography, for diagnosis of obstructive sleep apnoea. This approach was taken to facilitate the pragmatic trial design, enabling recruitment within NHS clinical pathways, where polysomnography is not commonly used. Although this approach makes the results of the MERGE trial widely applicable, questions are raised when applying the AASM 2012 scoring criteria to the identification of arousals from sleep. The automated algorithm used in the MERGE analysis scored an arousal from sleep at the termination of a hypopnoea using machine-learning techniques to interpret surrogate measures of arousal, such as airflow. The algorithm has been shown to have good sensitivity and specificity compared with manually scored polysomnograpy.[12] Nevertheless, we cannot rule out the possibility of an underestimation of the AHI, due to the use of respiratory polygraphy, and therefore the inclusion of participants with moderate obstructive sleep apnoea, who might be expected to have a greater improvement in symptoms. However, this limitation does not account for the improvement in QoL observed in the patients at the mildest end of the disease spectrum.

Consistent with clinical practice, the MERGE trial was designed using the AHI from a single night of respiratory polygraphy for the diagnosis of mild obstructive sleep apnoea. This single-night recording does not account for night-to-night variability in AHI.[29] Moreover, adopting the usual NHS clinical care pathways means that potential bias could have occurred during recruitment, due to variances in local diagnostic pathways at each recruitment site and the shortage of funding to screen all patients with mild obstructive sleep apnoea. Furthermore, because we recorded data only from patients who were assessed for eligibility, we do not know the proportion of patients with mild obstructive sleep apnoea at each of the centres during the study period.

A strength of the trial was the good adherence to CPAP treatment, which was maintained for 3 months across different sleep clinics. This contrasts with previous trials in the UK, in which adherence was relatively low.[15,21] In the MERGE trial, central sleep therapists used wireless monitoring to regularly review CPAP efficacy and adherence and offered ongoing patient support through emails and phone calls. This centralised support might have contributed to the improved CPAP adherence.[30] Conversely, the support might also have introduced bias into the study because most participants receiving CPAP had more frequent clinical contact compared with patients treated with standard care. Longer-term (eg >1 year) clinical follow up is needed to determine whether the improved adherence is sustainable, and whether the benefits gained from CPAP are maintained. Data from the PREDICT trial[21] support the notion that those patients who adhere to CPAP treatment at 3 months, do so over 12 months with similar treatment benefit.

In conclusion, the MERGE trial has shown the clinical effectiveness of CPAP treatment in patients with mild obstructive sleep apnoea. The primary outcome was prespecified and the improvement in the vitality scale of the SF-36 QoL measure occurred alongside a reduction in sleepiness, with improvements in fatigue and depression. The implication of the trial is that the 60% of patients with obstructive sleep apnoea who have mild disease should be considered for CPAP treatment because they are likely to gain symptomatic benefit.

Contributors

AJW, JLK, CDT, AM, SEC, JFO, AHN, AVB, JRS, and MJM were involved in the trial design and ongoing development of the study. All authors were involved in the data analysis and all aspects of writing the report. AW and JK had specific responsibility for oversight of the trial, data collection, and are first authors of the report. EH was trial manager for MERGE, with specific responsibility for data recording and governance of the trial. LW and MD were statisticians for MERGE and responsible for the data analysis. PC was an independent member of the Trial Steering Committee. JS was a senior investigator for MERGE, chair of the Trial Steering Committee, and had specific responsibility for clinical oversight of the trial. MM was chief investigator for MERGE.

Declaration of interests

AJW reports personal fees from ResMed, during the conduct of the study. JLK reports grants, equpment, and ongoing trial support from ResMed, during the conduct of the study. CDT reports personal fees from Bayer, outside the submitted work. AHN reports equipment, funding, and ongoing trial support from ResMed, during the conduct of the study. MDD reports personal fees from ResMed, during the conduct of the study. LAW reports personal fees from ResMed Corporation, during the conduct of the study. PMAC has advised Phillips Respironics about ventilator design and spoken at meetings sponsored by them. AVB reports personal fees from ResMed, during the conduct of the study. JRS reports personal fees from ResMed UK and Bayer Germany, outside the submitted work. MJM reports grants from ResMed, during the conduct of the study. AM, SEC, JFO, and ELH declare no competing interests.

Data sharing

Requests for access to deidentified data can be made to the corresponding author of the paper and will be assessed for approval by an oversight committee from the MERGE trial.

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