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Early View

Original article

Continuous Positive Airway Pressure effect on visual acuity in patients with type 2 diabetes and Obstructive Sleep Apnoea: a multicentre randomised controlled trial

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Continuous Positive Airway Pressure effect on visual acuity in patients with type 2 diabetes and Obstructive Sleep Apnoea: a multicentre randomised controlled trial

Authors:

Sophie D West[1,2], Benjamin Prudon[3], Joan Hughes[1], Rajen Gupta[4], Seid B Mohammed[5], Stephen Gerry[5], John R Stradling[6] for the ROSA Trial investigators

[1]Newcastle Regional Sleep Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne NE7 7DN, United Kingdom, [2]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom
[3]Department of Respiratory Medicine, University Hospital of North Tees, Stockton-on-Tees, United Kingdom, [4] Newcastle Eye Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne NE1, United Kingdom, [5] Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [6]Oxford Respiratory Trials Unit, Churchill Hospital, Oxford, UK and NIHR Oxford Biomedical Research Centre

Corresponding Author:
Dr Sophie West, Newcastle Regional Sleep Service, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, UK

Sophie.west@nuth.nhs.uk telephone 0044 191 2336161, fax 0044 191 2137397

Authors contributions

Conception and design: SW, JRS. Recruitment and data collection: BP, JH, RG. Analysis: SM and SG. Data interpretation: SW, JRS, RG. Drafting the manuscript for important intellectual content: SW. All authors have approved the final manuscript.

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For Twitter :

UK RCT shows 1 year of CPAP for OSA in people with type 2 diabetes and macular oedema does not improve visual acuity

ABSTRACT:

Objective:

We sought to establish whether CPAP for OSA in people with type 2 diabetes and diabetic macular oedema (DME) improved visual acuity.

Methods:

We randomly assigned 131 eligible patients aged 30 to 85 years from 23 UK centres with significant DME causing visual impairment (LogMAR letters identified, ≥ 39 to ≤ 78, score 0.92 to 0.14) plus severe OSA on screening to either: usual ophthalmology care (n=67) or usual ophthalmology care plus CPAP (n=64) for 12 months.

Results:

Mean age of participants was 64 years, 73% male, mean BMI 35.0 kg/m^2. Mean 4% oxygen desaturation index was 36/hour. There was no significant difference in the visual acuity at twelve months between the CPAP group and the control group, mean LogMAR (95%CI) 0.33 (0.29, 0.37) vs. 0.31 (0.27, 0.35), p=0.39, and no significant correlation between change in LogMAR and average CPAP use. The median daily CPAP use (SD, range) was 3.33 (2.25, 0-7.93) hours at three months, 3.19 (2.54, 0-8.07) hours at six months and 3.21 (2.7, 0-7.98) hours at twelve months.

Conclusion: CPAP therapy for OSA did not improve visual acuity in people with type 2 diabetes and diabetic macular oedema compared to usual care alone over 12 months.

Key Words:

Obstructive Sleep Apnoea, type 2 diabetes, diabetic macular oedema, CPAP, randomised controlled trial

INTRODUCTION

By 2030 diabetes mellitus is expected to affect 8% of the world's adult population.[1] The risk of developing diabetic retinopathy (DR) and maculopathy correlates with diabetes duration.[2] Targeted treatment of glycaemia, hypertension and dyslipidaemia is recommended to reduce the risk of DR.[3-5] When DR and maculopathy are present, ophthalmic treatment options include retinal laser photocoagulation to prevent visual loss[6], and intravitreal anti-Vascular Endothelial Growth Factor (VEGF) [7] or intraocular corticosteroid to improve visual acuity.[8]

Obstructive Sleep Apnoea (OSA) occurs during sleep with recurrent upper airway obstruction, causing apnoea, hypoxia and subsequent arousal with pulse and blood pressure rises.[9] This sleep fragmentation can cause excessive sleepiness, but may be asymptomatic. OSA is commonly associated with obesity and is increasing in worldwide prevalence alongside T2DM.[10]

OSA is particularly prevalent in adults with T2DM; rates vary from 23% to 87%. [11,12] People with DR and maculopathy have a high OSA prevalence, with 34-54% of people with diabetic macular oedema (DME) having OSA on screening sleep studies.[13,14] Guidelines recommend screening for OSA in people with T2DM; many remain undiagnosed.[15]

Treatment of significant OSA includes weight loss and Continuous Positive Airway Pressure (CPAP); a positive air pressure applied via a mask covering the nose and/or mouth to splint the pharynx, prevent obstruction and consequent intermittent hypoxia.[16] CPAP improves daytime sleepiness and quality of life in those with moderate to severe OSA and is widely used. There are well documented improvements in blood pressure with CPAP.[17] Randomised controlled trials of CPAP have not shown overall effects on diabetes control or insulin resistance [18-20], nor a benefit in cardiovascular risk.[21,22].

Hypoxia, oxidative stress and inflammation are proposed mechanisms in the development of DR.[23] Serum rhodopsin mRNA changes occur in people with OSA,[24] and the retinal nerve fibre layer thickness is significantly reduced, correlating with OSA severity.[25] Changes can be seen in retinal vasculature, with OSA patients having increased retinal venular dilation than controls [26]. People with OSA and T2DM have significantly higher grades of retinopathy and prevalence of maculopathy than those without OSA. [27] A meta-analysis showed OSA to be significantly associated with increased risk of diabetic retinopathy[28]; recently OSA was identified as an independent predictor for retinopathy progression.[29] One uncontrolled study using CPAP in people with OSA and DME showed benefits in visual acuity in high CPAP compliers.[30]

We hypothesised that treatment of OSA with CPAP would improve diabetic macular oedema and thus visual acuity. We performed a randomised controlled trial of CPAP in people with DR and impaired vision due to DME and concurrent OSA.

METHODS

Study Design and Oversight

The multicentre Retinopathy and Obstructive Sleep Apnoea (ROSA) Trial was a 12 month randomised controlled trial conducted between 2012 and 2017 (ISRCTN number 95411896). The study had ethical approval (Reference 12/NE/0234); all participants gave written informed consent. There were 23 UK recruiting Ophthalmology centres; the Newcastle Regional Sleep Service was the Coordinating Centre.

Patients and Procedures

An initial patient identification phase was previously published.[14] Patients with severe OSA (4% ODI ≥ 20/hour or AHI ≥ 30/hour) were contacted by the Coordinating Centre. Eligible patients were those with: best corrected visual acuity (BCVA) ≥ 39 and ≤ 78 letters in at least one eye (using Early Treatment Diabetic Retinopathy Study protocol (ETDRS) at a testing distance of 4 meters), central macular oedema in the visually impaired eye(s), and willing to have CPAP. Exclusion criteria were: previous CPAP for OSA, significant cataract affecting vision, disability precluding informed consent or protocol adherence, excessive sleepiness in any driver (based on raised ESS), respiratory failure. The latter two were referred for urgent OSA management.

Randomisation and interventions

Patients were randomised (1:1) to CPAP or control by a central telephone service using computer derived treatment allocation (SealedEnvelope^{TM}) with minimisation for: office blood pressure, OSA severity, HbA1c and visual acuity severity. All

patients had usual best-practice clinical care for DME during the trial, with ocular interventions as clinically indicated, determined by their ophthalmologist. They were all provided with written information on optimising sleep hygiene and benefits of weight loss to OSA by the research team. In addition to usual care, patients randomised to CPAP (Autoset S9, ResMed) were instructed by staff who routinely initiate CPAP. Humidification and interface choices were made individually. Patients were given written and audio-visual information on CPAP plus telephone support: the Coordinating Centre contacted all patients after two, seven and 30 days to help manage any CPAP difficulties. Patients could telephone for help, and additional visits at the local recruiting centre were arranged as required.

Study measurements

The primary endpoint of the trial was best corrected visual acuity (BCVA) of the study eye (LogMAR with refraction, 4 metre ETDRS) at 12 months. Assessments were performed at baseline, three, six and twelve months. Ophthalmological measurements were completed by trained individuals blind to the patient's study group. BCVA was performed with ETDRS charts after an assessment for lens status and refraction.[31] Visual acuity was recorded as number of letters identified and equivalent LogMAR value. Central 1mm macular thickness was measured through OCT (Spectralis®, Topcon 2000 or Cirrus, according to centre). Digital retinal photography took one fovea and one disc centred image. The same equipment was used by each site for all patients. Retinal photographs were graded by two independent graders using UK diabetic eye screening grading definitions (v1.3). If grades conflicted, an arbitration review was completed. During the baseline and 12 month assessment, grading of any cataract was completed using the LOCS 2

protocol.[32] The total number of all ocular interventions in 12 months was recorded (antiVEGF therapy, intravitreal corticosteroids, focal and grid photocoagulation).

Office blood pressure, weight, height, neck and waist circumference were measured plus oxygen saturation via finger probe. Non-fasting cholesterol, HDL, triglycerides, and HbA1c were checked at each visit, plus thyroid function at baseline only. Self-assessed health status measurements were taken at each visit: Short Form 12 (SF-12)[33], Visual Function Questionnaire 25 (VFQ-25)[34], short Calgary Sleep Apnea Quality of Life Index (Short SAQLI)[35] plus the Epworth Sleepiness Scale (ESS).[36]

Statistical Analysis

We calculated 90 patients randomised 1:1 would provide 80% power to detect 0.1 difference in LogMAR with 5% significance, based on pilot data showing mean difference in LogMAR score at 6 months between compliers with CPAP and non-compliers was 0.1 (SD 0.17).[30] We allowed extra recruitment for an estimated 5% dropout and 15% non-adherence rate based on previous CPAP studies. To enable exploratory subset analysis, an increase in numbers of 30% was planned. Recruitment took longer than anticipated; 131 completed follow up by trial completion. All analyses were intention-to-treat (ITT). All participants with at least one post-randomisation assessment of the primary outcome were included in the primary analysis. The primary outcome of LogMAR at 12 months was analysed using a mixed-effects model, accounting for repeated measures over time. The model includes LogMAR score as a response variable. Two sided p-value <0.05 was considered significant. Retinopathy, maculopathy and photocoagulation at 12

months was analysed by comparing group proportions using Pearson's Chi-Squared test. We further investigated whether adherence to CPAP therapy influenced the primary outcome in different ways. We defined 'high' and 'low' compliers based around the mean total hours of CPAP used per night at 6 and 12 months, to give similar sized numbers in each group (thus high compliers >=2 hours/night, low <2 hours/night). In addition the patients were divided into quartiles based on median daily usage of CPAP and with a comparison of the change in LogMAR at 12 months adjusting for the baseline LogMAR between Q2, Q3 and Q4 versus the reference group Q1. Analyses were undertaken using Stata version 14.2 (StataCorp, College Station, TX) and validated in SAS 9.4, by independent clinical trial statisticians.

RESULTS

Study participants

There were 222 patients who met the initial eligibility criteria with severe OSA (Figure 1). At baseline visit, 131 participants were eligible to be randomised. Two patients randomised to control requested CPAP during the study, due to worsening sleepiness. Some patients randomised to CPAP had zero adherence. The baseline characteristics of the participants are shown in Table 1. They were: 92% white Europeans, 5% Asian, 3% Black, 1% Egyptian. The distribution of minimisation factors for randomisation were well balanced between the two groups.

LogMAR

There were no significant differences in LogMAR at three, six or twelve months between the patients in the CPAP group and the control group, after adjusting for the

minimisation factors (table 2, figure 2). The mean (SD) change in LogMAR at 12 months was CPAP -0.02 (0.15) and control -0.04 (0.17). After adjustment for baseline CMT, this result remained not statistically significant. There was no significant correlation between the change in LogMAR and average CPAP use at three, six or twelve months (r=-0.15, p=0.31). The change in LogMAR from baseline to six months or from six months to twelve months was not statistically significant in either the low and high CPAP compliers group, with paired t-test (figure 3). Further division of the CPAP group into quartiles based on median daily usage showed no significant change in LogMAR at 12 months in any group, or any suggestion of a dose-response relationship (Q1 mean (95% CI) LogMAR 0.34 (0.26,0.42), Q2 0.31 (0.23, 0.39) p=0.63, Q3 0.37 (0.28,0.45) p=0.64, Q4 0.29 (0.21,0.37) p=0.41).

Central Macular Thickness (CMT)

There was a significant difference in CMT at 3 months, with the CPAP group having increased CMT implying worsening oedema compared to the control group: CPAP group mean (95%CI) 339.4 (319.5, 359.3) µm vs. control group 312.6 (296.1, 329.2) µm, p= 0.045. At 6 months and 12 months there was no significant difference between the two groups: CPAP group 12-month mean (95% CI) 320.4 (298.2, 342.6) µm vs. control group 309.2 (286.5, 331.9) µm, p=0.53.

Ocular interventions

There was no statistically significant difference between the mean (SD) number of ocular interventions over 12 months in the CPAP group 5.2 (3.6 to 6.8) and the control group, 3.6 (2.5 to 4.8), p=0.125.

Progression of DR

The change of proportion of retinopathy, maculopathy and photocoagulation from the baseline to at 12 months was not statistically significant in either group (Table 3).

Self-assessed health status

There was no significant difference between the groups in the VFQ-25 or the SF-12 at 3, 6 or 12 months. The Short SAQLI showed a statistically significant difference at 3 months between the groups implying symptomatic benefit from CPAP (mean (95%CI) CPAP 2.3 (2.1,2.5) vs. control 2.8 (2.6,2.9), p=0.003), but no significant difference between groups at 6 or 12 months.

ESS

There was no significant difference in the ESS between groups at 3, 6 or 12 months (table 4). High CPAP compliers showed a statistically significant fall of ESS at 3 months (p=0.02) but no significant fall at 6 and 12 months.

CPAP

The CPAP download data from the last study period is shown in table 5. The proportion of nights with 4 or more hours using CPAP data shows 19% of people used CPAP for 60-100% of nights at 3 months, 27% at 6 months and 22% at 12 months.

Blood tests

There was no statistically significant change in HbA1c, cholesterol, HDL and triglycerides between the treatment groups at any of the time points.

DISCUSSION

This multi-centre UK randomised controlled trial of CPAP in patients with OSA and impaired vision due to DME and type 2 diabetes has shown no benefit to visual acuity from CPAP compared to standard ophthalmological care over a 12-month period. There was no statistically or clinically significant improvement with CPAP in the variables of vision, DME or retinal photography at any time point, nor change in other measures. There have been no other randomised controlled trials conducted in this area. This is therefore novel data, useful for clinical practice.

OSA was found in 75% of people studied in the total cohort. Those people with symptomatic OSA with daytime sleepiness should be referred for CPAP to improve these symptoms.[16] There has been increasing interest in whether CPAP can be used to treat conditions causally associated with OSA, such as hypertension, insulin resistance, type 2 diabetes, and cardiovascular disease.[18,21,22,37] This is particularly relevant to those people with asymptomatic OSA, who do not require CPAP for daytime sleepiness, but in whom it might mitigate risk from another condition. The numbers of people with these comorbid conditions are enormous, so robust evidence to guide therapeutic decisions is essential.

There was no additional benefit of CPAP for severe OSA for any ocular measure. The CPAP group had deterioration in CMT at three months which just reached statistical significance; it did not persist at six and 12 months. This was not associated with any significant difference in visual acuity between the two groups. This difference is not clinically significant; typically this would require an increase in

CMT of ≥10% from baseline and a decrease in visual acuity of ≥5 letters.[38] The CPAP group had a non-significant higher average number of ocular interventions than the control group at 12 months; perhaps these interventions occurred because of the CMT increase, and they were effective at correcting ongoing CMT differences between groups. It is not clear why the CPAP group would have increased CMT at 3 months compared to the control group; changes in ocular perfusion with CPAP are potentially plausible, causing an effect on ocular vascular permeability, but unlikely. No changes in CMT were found in the only other study of CPAP on DME.[30] That smaller, uncontrolled study gave 32 people with DME and OSA CPAP for six months. Post-randomisation division into high and low compliers showed those who used CPAP well (n=13, mean >2.5 hours/night) had significant improvements in visual acuity compared to those who were less compliant (n=15), with an adjusted treatment effect on VA of high adherence versus low adherence of 0.11 (95% confidence interval 0.21 to -0.002; p = 0.047), equivalent to a one-line improvement on LogMAR chart. There was no significant improvement in DME or retinal photographs, but interest in the potential benefit of CPAP to visual acuity led to this randomised controlled trial.

In this trial, patients randomised to CPAP received additional support from sleep teams to optimise their adherence with this therapy. Despite this, the adherence to CPAP was lower than that seen in other trials of CPAP in individuals with OSA also found by screening specific non-sleep clinic populations: mean adherence in the SAVE study of people with coronary or cerebrovascular disease was 3.3 hours /night over several years, and it was 3.5 hours/night in a study of CPAP versus oxygen in

OSA found in patients with cardiovascular disease, or known cardiovascular risk factors.[22,39] The SAVE trial gave pre-randomisation subtherapeutic CPAP to ensure participants were adherent for an average of three hours per night; this excluded 324 people, or 10%, which no doubt improved trial CPAP adherence rates by excluding those who could not tolerate it at the outset. We felt a “real world” trial including all patients would be more applicable to clinical practice. All these studies prove that high adherence to CPAP in patients who have not presented to the sleep clinic with symptoms is difficult to achieve. It is known that CPAP use varies in patients in clinical practice. Possibly the patients in this study with type 2 diabetes, DME and other medical problems, but without sleepiness, found the additional burden of CPAP too much. The level of CPAP adherence may have been insufficient to affect visual outcomes, but there was no suggestion of any correlation of changes in visual acuity with CPAP use, nor any improvement seen in high compared to low CPAP users. A per protocol analysis was conducted for the primary outcome of LogMAR BCVA at 12 months, excluding the patients in the control arm who received CPAP (n=2) and those in the CPAP group who never used CPAP (n=5): it showed no difference to the results found in the intention to treat analysis (p=0.38). It therefore seems that although CPAP effectively treated OSA, confirmed by CPAP download data, it did not improve visual outcomes. CPAP may be unable to reverse established ocular damage in people who have diabetic macular oedema. Alternatively, best ophthalmic care (photocoagulation, antiVEGF, intravesical corticosteroids) may stabilise and improve vision, leaving no additional role for CPAP to reduce DME. Whether CPAP could be used as a potential tool for to prevent diabetic retinopathy, rather than reversing it, or delaying its progression, remains an area of interest and future

studies are needed to ascertain whether CPAP has a valid role in this arena, particularly given the poor adherence in this group of patients.

In this study, daytime sleepiness and quality of life, measured by the ESS and the SAQLI respectively, significantly improved in those with high CPAP compliance at three months. It is surprising this was not sustained throughout the trial and that there was no significant improvement in the SF-12 between groups. Both have been shown to improve in previous randomised controlled trials of CPAP.[40] The lower median CPAP adherence than other studies of people with symptomatic OSA may be the reason; or the lack of therapeutic benefit may have tempered their use of CPAP. The participants in this study were screened for OSA, but had never sought previous help for OSA symptoms. Although the mean baseline ESS was within the normal range, other studies have shown that improvements in sleepiness occur regardless of the baseline ESS.[21, 41] Whilst the prevalence of OSA was high in this cohort, these were not people who had presented with sleep symptoms, and therefore may have different treatment responses to those people with symptomatic OSA. At the end of the trial, 63% of patients randomised to CPAP opted to continue, suggesting they had some form of symptomatic benefit from this.

An observational prospective longitudinal study assessed 230 patients from diabetes clinics at two UK centres with assessments of DR via photography and OSA via home sleep studies [29]. Sight threatening DR (STDR) prevalence was higher in patients with OSA than those without OSA (42.9% vs. 24.1%, p=0.004). After a median follow-up of 43 months, patients with OSA were more likely to develop

preproliferative/proliferative DR (18.4% vs. 6.1%; P=0.02). OSA remained an independent predictor of progression after adjustment for confounders (OR 5.2; 95% CI 1.2–23.0; P=0.03). All patients with moderate or severe OSA at baseline were referred for CPAP. High CPAP adherence significantly lowered progression to advanced DR and maculopathy (n=15). Whilst this study showed potential benefits from CPAP, it was in a small sub group of non-randomised patients. The authors emphasised the need for a randomised control trial of CPAP.

In conclusion, this is the only randomised controlled study to evaluate the effect of CPAP for OSA on visual acuity in people with macular oedema and type 2 diabetes. CPAP should continue to be given to patients with symptomatic OSA, but there is no evidence from this study to support its use as an alternative therapy for diabetic macular oedema when standard ophthalmic therapy is already being given.

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REFERENCES

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice 2010;87:4-14.

2. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BE, Klein R, Krishnaiah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Xu L, Yasuda M, Zhang X, Mitchell P, Wong TY; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes care 2012;35:556-64.

3. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837-53.

4. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008;115:1859-68.

5. Ucgun NI, Yildirim Z, Kilic N, Gursel E. The importance of serum lipids in exudative diabetic macular edema in type 2 diabetic patients. Annals of the New York Academy of Sciences 2007;1100:213-7.

6. Preliminary report on effects of photocoagulation therapy. The Diabetic Retinopathy Study Research Group. American journal of ophthalmology 1976;81:383-96.

7. Heier JS, Korobelnik JF, Brown DM, Schmidt-Erfurth U, Do DV, Midena E, Boyer DS, Terasaki H, Kaiser PK, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Vitti R, Berliner AJ, Zeitz O, Metzig C, Holz FG. Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies. Ophthalmology 2016;123:2376-85.

8. Boyer DS, Yoon YH, Belfort R, Jr. Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y, Whitcup SM; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014;121:1904-14.

9. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiological reviews 2010;90:47-112.

10. Heinzer R, Vat S, Marques-Vidal P, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P, Tafti M, Haba-Rubio J. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. The Lancet Respiratory medicine 2015;3:310-8.

11. West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax 2006;61:945-50.

12. Foster GD, Sanders MH, Millman R, Zammit G, Borradaile KE, Newman AB, Wadden TA, Kelley D, Wing RR, Sunyer FX, Darcey V, Kuna ST; Sleep AHEAD Research Group. Obstructive sleep apnea among obese patients with type 2 diabetes. Diabetes care 2009;32:1017-9.

13. Mason RH, West SD, Kiire CA, Groves DC, Lipinski HJ, Jaycock A, Chong VN, Stradling JR. High prevalence of sleep disordered breathing in patients with diabetic macular edema. Retina 2012;32:1791-8.

14. Prudon B, Hughes J, West S. A novel postal-based approach to diagnosing obstructive sleep apnoea in a high-risk population. Sleep medicine 2017;33:1-5.

15. Shaw JE, Punjabi NM, Wilding JP, Alberti KG, Zimmet PZ. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. Diabetes research and clinical practice 2008;81:2-12.

16. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. The Cochrane database of systematic reviews 2006:CD001106.

17. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. JAMA. 2015 Dec 1;314(21):2280-93.

18. West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax 2007;62:969-74.

19. Lam JC, Lam B, Yao TJ, Lai AY, Ooi CG, Tam S, Lam KS, Ip MS. A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnoea. The European respiratory journal 2010;35:138-45.

20. Shaw JE, Punjabi NM, Naughton MT, Willes L, Bergenstal RM, Cistulli PA, Fulcher GR, Richards GN, Zimmet PZ. The Effect of Treatment of Obstructive Sleep Apnea on Glycemic Control in Type 2 Diabetes. American journal of respiratory and critical care medicine 2016;194:486-92.

21. Craig SE, Kohler M, Nicoll D, Bratton DJ, Nunn A, Davies R, Stradling J. 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;67:1090-6.

22. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS; SAVE Investigators and Coordinators. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. The New England journal of medicine 2016;375:919-31.

23. Arden GB, Sivaprasad S. Hypoxia and oxidative stress in the causation of diabetic retinopathy. Current diabetes reviews 2011;7:291-304.

24. Wong A, Merritt S, Butt AN, Williams A, Swaminathan R. Effect of hypoxia on circulating levels of retina-specific messenger RNA in type 2 diabetes mellitus. Annals of the New York Academy of Sciences 2008;1137:243-52.

25. Kargi SH, Altin R, Koksal M, Kart L, Cinar F, Ugurbas SH, Ayoglu F . Retinal nerve fibre layer measurements are reduced in patients with obstructive sleep apnoea syndrome. Eye (Lond) 2005;19:575-9.

26. Shankar A, Peppard PE, Young T, Klein BE, Klein R, Nieto FJ. Sleep-disordered breathing and retinal microvascular diameter. Atherosclerosis 2013;226:124-8.

27. West SD, Groves DC, Lipinski HJ, Nicoll DJ, Mason RH, Scanlon PH, Stradling JR. The prevalence of retinopathy in men with Type 2 diabetes and obstructive sleep apnoea. Diabetic medicine:2010;27:423-30.

28. Zhu Z, Zhang F, Liu Y, Yang S, Li C, Niu Q, Niu J. Relationship of Obstructive Sleep Apnoea with Diabetic Retinopathy: A Meta-Analysis. BioMed research international 2017;2017:4737064.

29. Altaf QA, Dodson P, Ali A, Raymond NT, Wharton H, Fellows H, Hampshire-Bancroft R, Shah M, Shepherd E, Miah J, Barnett AH, Tahrani AA. Obstructive Sleep Apnea and Retinopathy in Patients with Type 2 Diabetes. A Longitudinal Study. American Journal of Respiratory and Critical Care Medicine 2017;196:892-900.

30. Mason RH, Kiire CA, Groves DC, Lipinski HJ, Jaycock A, Winter BC, Smith L, Bolton A, Rahman NM, Swaminathan R, Chong VN, Stradling JR. Visual improvement following continuous positive airway pressure therapy in diabetic subjects with clinically significant macular oedema and obstructive sleep apnoea: proof of principle study. Respiration; international review of thoracic diseases 2012;84:275-82.

31. Service NTI. Early treatment of diabetic retinopathy study (ETDRS) manual of operations. In; 1985:PB85-223006.

32. Chylack LT, Jr., Leske MC, McCarthy D, Khu P, Kashiwagi T, Sperduto R. Lens opacities classification system II (LOCS II). Arch Ophthalmol 1989;107:991-7.

33. Jenkinson C, Layte R. Development and testing of the UK SF-12 (short form health survey). Journal of health services research & policy 1997;2:14-8.

34. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001;119:1050-8.

35. Flemons WW, Reimer MA. Measurement properties of the calgary sleep apnea quality of life index. American journal of respiratory and critical care medicine 2002;165:159-64.

36. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.

37. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. 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.

38. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. The New England journal of medicine 2015;372:1193-203.

39. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, Tracy RP, Rueschman M, Blumenthal RS, Lewis EF, Bhatt DL, Redline S. CPAP versus oxygen in obstructive sleep apnea. The New England journal of medicine 2014;370:2276-85.

40. Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet 1999;353:2100-5.

41. Bratton DJ, Gaisl T, Schlatzer C, Kohler M. Comparison of the effects of continuous positive airway pressure and mandibular advancement devices on sleepiness in patients with obstructive sleep apnoea: a network meta-analysis. Lancet Respir Med. 2015;3(11):869-78.

Figure legends

Figure 1. Screening, randomisation and follow up analyses

Figure 2: Mean difference with 95% CIs of LogMAR at 3, 6 and 12 months

Figure 3. LogMAR after CPAP therapy in high versus low compliers

Table 1: Baseline characteristics of the study participants

Characteristics		**CPAP** *N (%) or Mean (SD) [Range]*	**Control** *N (%) or Mean (SD) [Range]*
Gender	***Male***	43 (67.2)	52 (80.0)
	Female	21 (32.8)	13 (20.0)
Age (years)		64.88 (10.44) [41.66 83.42]	64.19 (9.13) [39.03 81.10]
BMI (kg/m^2)		34.78 (8.74) [20.3 82.7]	35.23 (6.32) [22.0 50.5]
Neck circumference (cm)		43.16 (4.09) [34.5 60.0]	44.81 (4.07) [36.0 54.0]
Waist circumference (cm)		115.15 (11.99) [93 149.5]	118.59 (17.21) [67 151]
Duration of diabetes (years)		15.91 (8.73) [1 37]	15.63 (9.47) [1 51]
Epworth Sleepiness Score total		9.1 (5.9) [0 22]	9.0 (5.8) [0 24]
Apnoea hypopnea index/hour		32.9 (16.9) [0 82]	33.7 (18.67) [0 107]
Daytime oxygen saturations on air at rest (%)		96.4 (1.9) [89 100]	96.5 (1.6) [91 99]
Oxygen desaturation index		36.5 (17.9) [20 99]	36.3 (15.6) [20 84]
SAQLI score total		3.0 (1.4) [1.1 5.7]	3.1 (1.4) [1.0 6.3]
SF12 score total			
Physical Health Composite score		38.6 (6.5) [24.2 53.2]	38.7 (6.4) [25.3 49.7]
Mental Health Composite score		50.2 (8.2) [29.9 67.8]	50.4 (7.6) [29.4 62.1]
VFQ 25 score total		70.0 (19.9) [28.0 98.2]	75.3 (19.4) [18.9 98.5]
Total cholesterol (mmol/L)		4.27 (1.09) [2.4 7.1]	4.09 (1.08) [2.2 7.4]
HDL (mmol/L)		1.18 (0.36) [0.6 2.3]	1.20 (0.36) [0.6 2.03]
Triglycerides (mmol/L)		2.08 (1.08) [0.7 5.5]	2.08 (1.41) [0.6 7.3]
TSH (mU/L)		2.5 (1.5) [0.7 7.5]	2.0 (1.2) [0.4 6.6]
T4 (Pmol/L)		14.8 (2.3) [10 19]	14.7 (2.2) [9.3 19.2]
HbA1C (mmol/mol)		66.9 (17.6) [40 127]	66.0 (23.3) [13.4 163]
LogMAR BCVA		0.36 (0.21) [-0.08 1.08]	0.35 (0.22) [-0.18 0.9]
Central Macular Thickness (CMT)		364.3 (107.9) [173 742]	346.3 (102.6) [119 671]
Retinopathy	**1**	36 (59)	33 (54)
	2	18 (30)	21 (34)
	3	7 (11)	7 (12)
Maculopathy	**0**	17 (28)	28 (46)
	1	44 (72)	33 (54)
Photocoagulation	**0**	31 (51)	27 (44)
	1	30 (49)	34 (56)

BMI = body mass index, ODI =4% oxygen desturation index per hour, SAQLI = sleep apnoea quality of life index, SF12= short form 12, VFQ-25 = visual function questionnaire, TSH = thyroid stimulating hormone, HDL = high density lipoprotein

Table 2. Results of LogMAR at 3, 6, and 12 months

Month	N	CPAP Mean* (95% CI)	N	Control Mean* (95% CI)	Mean Difference (95% CI)	P-value*
3 Months	59	0.34 (0.31 to 0.38)	60	0.30 (0.27 to 0.34)	0.04 (-0.01 to 0.09)	0.113
6 Months	60	0.33 (0.30 to 0.37)	60	0.30 (0.26 to 0.33)	0.03 (-0.02 to 0.09)	0.217
12 Months	57	0.33 (0.29 to 0.37)	60	0.31 (0.27 to 0.35)	0.03 (-0.03 to 0.08)	0.390

**Calculated from linear mixed model adjusting for baseline LogMAR and minimisation factors*

Table 3: Progression of Diabetic Retinopathy at 12 Months

		Progression of Diabetic Retinopathy at 12 Months*		P-value*
	Grade	**CPAP** n/N (%)	**Control** n/N (%)	
Retinopathy	1	32/53 (60)	31/54 (57)	0.825
	2	13/53 (25)	16/54 (30)	
	3	8/53 (15)	7/54 (13)	
Maculopathy	0	22/53 (42)	25/54 (46)	0.618
	1	31/53 (58)	29/54 (54)	
Photocoagulation	0	22/53 (42)	20/54 (37)	0.636
	1	31/53 (58)	34/54 (63)	

** From Pearson's Chi-Squared test*

Table 4: Epworth Sleepiness Score

Month	N	CPAP Mean* (95% CI)	N	Control Mean* (95% CI)	Mean Difference (95% CI)	P-value*
3 Months	59	7.7 (6.8, 8.7)	60	8.0 (7.2, 8.9)	-0.3 (-1.6, 1.0)	0.633
6 Months	59	6.7 (5.7, 7.7)	60	7.6 (6.7, 8.5)	-0.9 (-2.2, 0.5)	0.210
12 Months	57	7.2 (6.1, 8.3)	60	7.6 (6.7, 8.5)	-0.4 (-1.9, 1.1)	0.587

**calculated from linear mixed model adjusting for the baseline ESS score and minimisation factors.*

Table 5: CPAP usage at 3, 6 and 12 months

	3 months		6 months		12 months	
	N	*Mean (SD) [Range]*	*N*	*Mean (SD) [Range]*	*N*	*Mean (SD) [Range]*
Pressure 95th centile (cm/H2O)	*57*	*10.9 (3.6) [4, 19.3]*	*48*	*11.6 (3.6) [4.6, 19.2]*	*42*	*11.5 (3.6) [4.0, 18.2]*
Apnoea-hypopnoea index/hour	*57*	*1.9 (2.7) [0, 10]*	*48*	*1.9 (2.5) [0, 11.8]*	*42*	*1.7 (2.3) [0, 8.4]*
Obstructive events/hour	*57*	*0.78 (1.44) [0, 8.3]*	*48*	*0.65 (1.11) [0, 6.2]*	*42*	*0.54 (0.79) [0, 3.1]*
Central events /hour	*57*	*0.84 (1.66) [0, 8.5]*	*48*	*0.75 91.34) [0, 6.2]*	*42*	*0.70 (1.37) [0, 6.5]*
Median daily usage (hours)	*57*	*3.33 (2.25) [0, 7.93]*	*57*	*3.19 (2.54) [0, 8.07]*	*57*	*3.21 (2.70) [0, 7.98]*
Average daily usage (hours)	*57*	*2.35 (2.09) [0, 7.48]*	*57*	*2.16 (2.30) [0, 6.9]*	*57*	*1.78 (2.18) [0, 6.53]*

FIGURE 1. SCREENING, RANDOMISATION AND FOLLOW UP ANALYSES

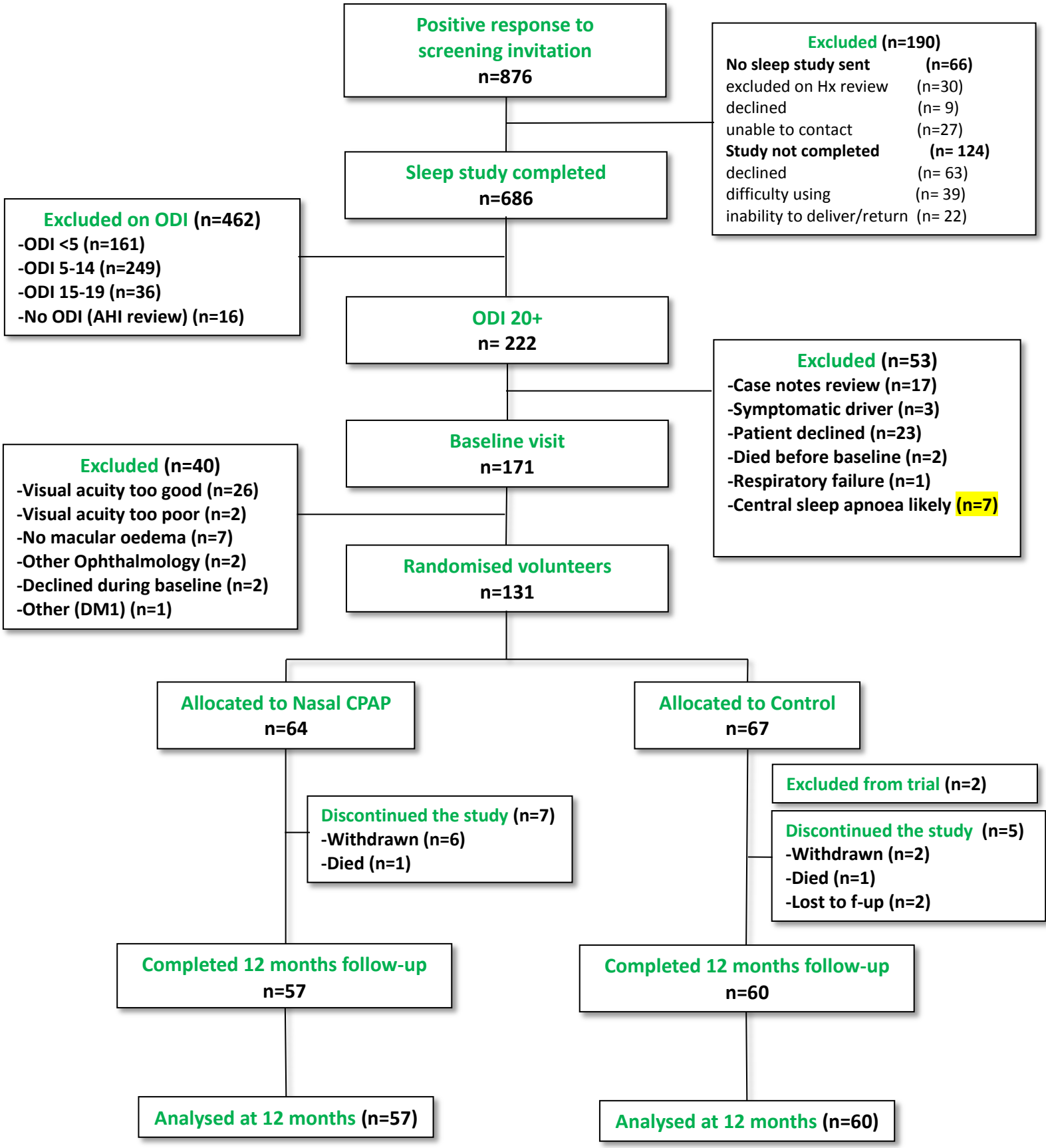


Figure 2.

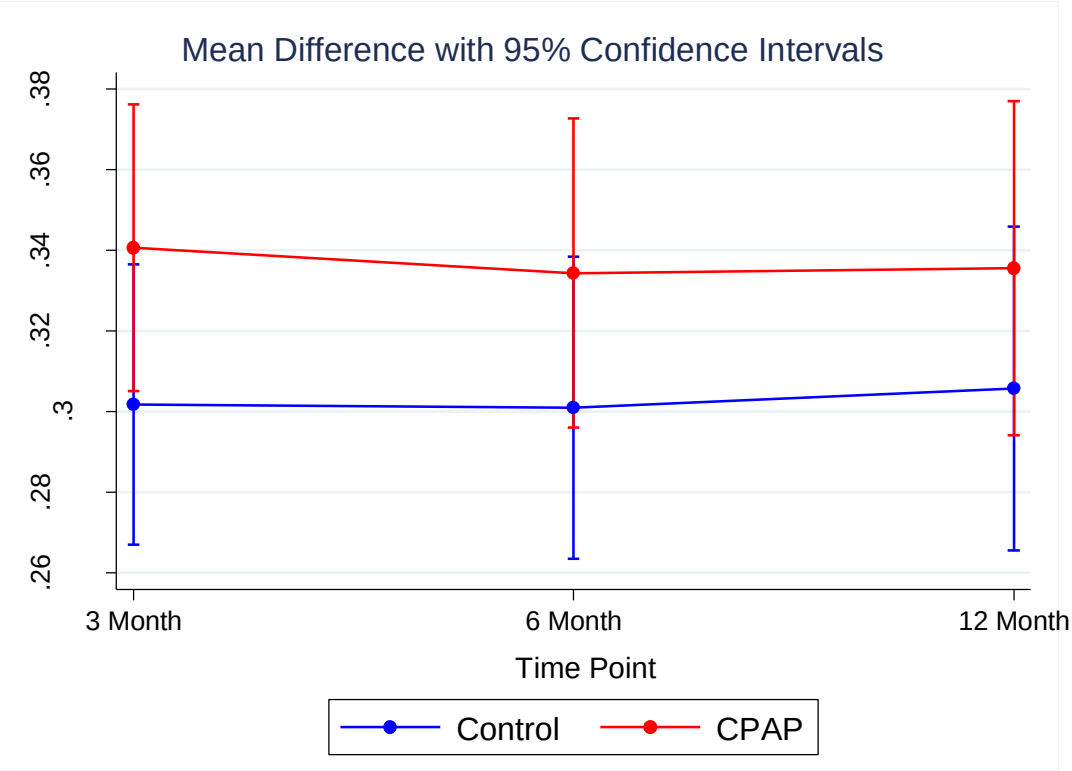
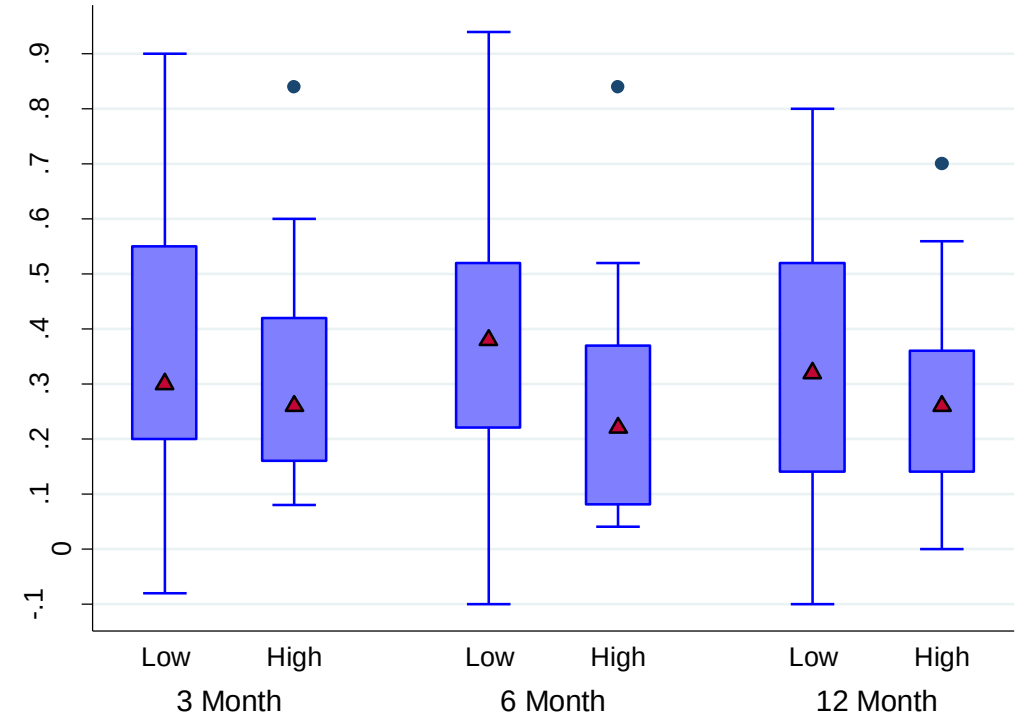


Figure 3.



Online supplement

ROSA Principal Investigators:

Mr Rajen Gupta, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

Mr Maged Habib, Sunderland Eye Infirmary SR2 9HP

Mr Martin McKibbin, St James's University Hospital, Leeds LS9 7TF

Mr Faruque Ghanchi, Bradford Royal Infirmary BD9 6RJ

Miss Abosede Cole, Bristol Eye Hospital BS1 2LX

Mr Patrick Richardson, Royal Derby Hospital DE22 3DT

Miss Sahar Al-Husainy, Heartlands Hospital, Birmingham B9 5SS

Mr Andy Morris, The Royal Bournemouth Hospital BH7 7DW

Mr Imran Rahman, Blackpool Victoria Hospital FY3 8NR

Mr Sajjad Haider and Mr Saju Thomas, University Hospital of North Durham & Darlington Memorial Hospital DL3 6HX

Mr Sridhar Manvikar, The James Cook University Hospital, Middlesbrough TS4 3BW

Ms Yvonne D'Souza, Manchester Royal Eye Hospital M13 9WL

Mr Nonavinakere P Manjunatha, Hospital of St Cross Rugby & University Hospital Coventry CV22 5PX

Ms Christina Rennie, University Hospital Southampton SO16 6YD

Ms Anju Kadyan, Royal Shrewsbury Hospital SY3 8XQ

Mr Naren Dhingra, Pinderfields Hospital, Wakefield WF1 4DG

Dr Justin Pepperell, Musgrove Park Hospital, Taunton TA1 5DA

Dr Andrew Brown, University Hospital of North Staffordshire, Stoke-on-Trent ST4 6QG

Dr Neil Ward, Derriford Hospital, Plymouth PL6 8D

Dr Giuliana Silvestri, Royal Victoria Hospital, Belfast BT12 6BA

Mrs Rehna Khan, Huddersfield Royal Infirmary HD3 3EA

Mr Tim Jackson, King's College Hospital, London SE5 9RS

Mr Chris Brand, Royal Hallamshire Hospital, Sheffield S10 2JF

Methods

Eligible subjects aged 30 to 85 years with an existing diagnosis of T2DM and DME with visual impairment were offered a screening sleep study via their Ophthalmology Centre. Domiciliary cardiopulmonary sleep study equipment (ApneaLink, ResMed) was posted to their homes. Automatic analysis of the studies was performed, with manual review.

Randomisation was performed with minimisation for: office blood pressure (above/below 140/90), OSA severity (above/below ODI 40 per hour), HbA1c

(above/below 58 mmol/mol) and visual acuity severity (above/below ETDRS of 69 letters). If both eyes were eligible, one eye was randomly selected by computer.

Results

Of the 131 people randomised, 32 patients had two eligible eyes for the study; 20 had right eye randomised. All data from participants from one site were excluded (n=2, both control) as it became clear at the end of the trial that the site had not completed the trial protocol specifications. Another site failed to provide photographs for grading. Some photographs from other sites had not been completed to the protocol specifications and were ungradable.

Safety

There was no significant difference between the proportion of patients experiencing an adverse event or serious adverse event between treatment groups.