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The Impact of Obstructive Sleep Apnoea Treatment on Microvascular Complications in Patients with Type 2 Diabetes: A Feasibility Randomised Controlled Trial

Subtitle: CPAP Impact on Microvascular Complications in T2D Patients

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Disclosure

All authors declared no conflict of interest except:

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- Srikanth Bellary reports: I have received speaker fees and honoraria from Novo Nordisk, Eli Lilly, Boehringer Ingelheim and Astra Zeneca.
- Mayank Patel reports: I have received speaker fees from Eli Lilly and Company, Insulet and Astra Zeneca.

- This is a multicentre study that was mainly conducted at the University of Birmingham. However, participants were recruited from 13 different NHS Trusts throughout England **Appendix S1 in the online supplement.**
- I, the corresponding author, declare that this manuscript is original and can confirm that the manuscript has been read and approved by all named authors.
- The study reports a clinical trial that was registered on the ISRCTN registry (https://www.isrctn.com/ISRCTN12361838, Registered 04 April 2018, Protocol version: v5.0 02.12.19).
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Abstract

Background: Obstructive Sleep Apnoea (OSA) is associated with an increased risk of diabetes-related complications. Hence, it is plausible that Continuous Positive Airway Pressure (CPAP) could have a favourable impact on these complications.

Objective: To assess the feasibility of conducting a randomised control trial (RCT) in patients with type 2 diabetes (T2D) and OSA over 2 years.

Methods: An open-label multicentre feasibility RCT of CPAP vs no CPAP in patients with T2D and OSA. Patients with resting oxygen saturation <90%, central apnoea index >15/hour or Epworth Sleepiness Scale (ESS) ≥11 were excluded. OSA was diagnosed using a multichannel portable device (ApneaLink Air™, ResMed). The primary outcome measures were related to feasibility, and the secondary outcomes were changes in various clinical and biochemical parameters related to diabetes outcomes.

Results: Eighty-three (40 CPAP vs 43 no CPAP) patients were randomised, with a median (IQR) follow-up of 645 [545, 861] days. CPAP compliance was inadequate, with a median usage of approximately 3.5 hours/night. Early CPAP use predicted longer-term compliance. The adjusted analysis showed a possible favourable association between being randomised to CPAP and several diabetes-related endpoints (chronic kidney disease (CKD), neuropathy, and quality of life (QoL)).

Conclusions: It was feasible to recruit, randomise, and achieve a high follow-up rate over 2 years in patients with OSA and T2D**.** CPAP compliance might improve by a run-in period before randomisation. A full RCT is necessary to assess the observed favourable association between CPAP and CKD, neuropathy, and QoL in patients with T2D.

Keywords: adherence, continuous positive airway pressure, feasibility, obstructive sleep apnoea, nephropathy, neuropathy, quality of life, retinopathy, type 2 diabetes.

Summary

OSA and T2D have a bidirectional relationship; patients with OSA are at high risk of developing T2D and vice versa. OSA is linked to an increased risk of advanced retinopathy and renal function decline. Several RCTs of CPAP (the gold standard treatment of OSA) in patients with T2D did not assess the CPAP's impact on diabetes-related hard endpoints due to their focus on glycaemic control and were relatively short.

It is feasible to recruit and randomise over a period of 2 years. CPAP compliance may improve by the run-in period before randomisation. Conducting a complete RCT is necessary to assess the observed favourable relation between CPAP and complications of T2D. CPAP has potential benefits in reducing diabetes-related complications.

Introduction

Obstructive Sleep Apnoea (OSA) is characterised by frequent partial or complete obstructions of the upper airway during sleep, resulting in cyclical episodes of hypoxemia, sleep fragmentation, changes in heart rate and blood pressure, and increased intrathoracic pressure [1]. These episodes lead to various pathophysiological consequences, such as intermittent hypoxia, sympathetic activation, systemic inflammation, oxidative stress, and changes in the endocrine system [2]. OSA has consequently been linked to hypertension, cardiovascular disease (CVD), hyperlipidaemia, Type 2 diabetes (T2D), road traffic accidents, and impaired quality of life [3]. OSA is very common, affecting 12.5% - 83.8% of men and 3.7% -70.8% of women, depending on the country and study population, with approximately 936 million individuals aged between 30 to 90 who have OSA with Apnoea Hypopnea Index (AHI $\geq$ 5) worldwide [4].

T2D is very common with an increasing global prevalence [5]. The World Health Organisation (WHO) estimated that the total number of individuals living with diabetes had increased to 537 million adults in 2021 [6]. The burden of T2D on patients, the health care system, and wider society is high, with an increased risk of CVD and microvascular complications such as neuropathy, nephropathy, retinopathy, and foot ulcer [7,8]. Despite improvements in the management of T2D and the attainment of treatment targets, the burden of diabetes complications remains significant [9,10]. Therefore, there is a need to identify new innovative treatment strategies to reduce the impact of T2D further.

The close link between OSA and T2D is unsurprising, considering that obesity and advanced age are common risk factors [5,11]. We have previously demonstrated that patients with OSA are at increased risk of developing T2D and *vice versa* [12]. We have also shown that patients with T2D and OSA are at increased risk of developing cardiovascular disease (CVD) and microvascular complications compared to patients with T2D without OSA, [13] and that in patients with T2D, OSA is associated with an increased risk of developing advanced retinopathy and renal function decline [14,15]. This is likely because both OSA and T2D display a similar impact on vascular disease risk factors, including inflammation, oxidative stress, and endothelial dysfunction, driving the development of these complications [16]. Hence, it is plausible that treating OSA in patients with T2D could potentially reduce the burden of diabetes-related complications.

Continuous Positive Airway Pressure (CPAP) is the gold standard for OSA treatment; however, compliance is challenging [17]. Several randomized control trials of CPAP in patients with T2D have been conducted. These trials primarily focused on glycaemic control and were relatively short. Therefore, they could not evaluate the impact of CPAP on other important diabetes-related hard endpoints [18,19]. Our overall aim is to conduct an RCT assessing the impact of CPAP on microvascular complications in patients with T2D. Hence, we first conducted an RCT of CPAP vs no CPAP in people with T2D with OSA to determine the feasibility of this approach and assist in designing a future definitive trial.

Methods:

The protocol of this feasibility RCT has been published previously in [20]. Here, we provide an overall summary.

Objectives:

The primary objectives are consistent with the feasibility design and related to the feasibility aspects of the RCT. These include:

1. Assess the willingness of participants to be randomised.
2. Assess the willingness of clinicians to recruit participants.
3. Assess follow-up rates and adherence/compliance rates.
4. Provide data to inform the sample size for a substantive trial.
5. Optimise the choice of outcome measures for a substantive trial.

The secondary objectives focused on exploring CPAP's impact on microvascular complications and clinical and biochemical parameters in patients with T2D (please refer to the online supplement).

Study design:

We conducted a multicentre feasibility RCT in England**.** The RCT was embedded in an observational study examining the associations between sleep disorders and T2D-related outcomes over two years. The observational study recruited patients with T2D regardless of their OSA status but included testing for OSA. In this manuscript, we report on the RCT.

The RCT was an open-label, randomised, controlled, parallel-arm clinical trial of patients with T2D and OSA. Participants were randomised in a 1:1 ratio to CPAP or no CPAP in addition to receiving routine care for two years, with assessments performed at baseline and study end

[20]. All patients were contacted via phone every six months till the study concluded. Patients randomised to CPAP received extra contact at 2- and 4- weeks and further ad-hoc contact. The follow-up duration and assessments were impacted by the COVID-19 pandemic (COVID-19 in online supplement).

This RCT was carried out in accordance with the Research Governance Framework for Health and Social Care, the relevant UK Statutory Instruments (including the Data Protection Act 2018 and the Human Tissue Act 2008), and Good Clinical Practice principles. [20] The study was registered on the ISRCTN registry (https://www.isrctn.com/ISRCTN12361838, Registered 04 April 2018, Protocol version: v5.0 02.12.19). The study was approved by National Research Ethics Committee West Midlands – The Black Country, reference 18/WM/0070. All study participants consented through a two-stage process, one for the observational study and the other for the feasibility of RCT.

Settings and participants

Participants were recruited from diabetes clinics in 13 different NHS Trusts throughout England **Appendix S1 in the online supplement.** Recruitment occurred between July 2018 and February 2020 and stopped at this date due to the COVID-19 pandemic. Participants for the feasibility RCT were recruited from the observational study. A full list of the inclusion/exclusion criteria has been published previously and can be found in **Table 1.** They were selected to ensure patient safety while allowing ease of recruitment and kept relatively liberal to aid recruitment. Patients with evidence of excessive daytime sleepiness were excluded from randomisation because they would have received CPAP treatment in real life. Not receiving a CPAP will impact their driving license.

OSA diagnosis:

OSA was assessed based on a single overnight home-based polygraphy using a portable device (ApneaLink Air, ResMed). The ApneaLink Air device comes with the AirView diagnostics cloud-based system (AV). Sleep studies were scored based on the American Academy of Sleep Medicine (AASM) guidelines. Hypopnea was defined as ≥4% oxygen desaturation with ≥30% reduction in nasal airflow signal [21]. Apnoea was defined as a ≥90 % reduction in airflow for a period of ≥10 seconds [21]. An apnoea-hypopnea index (AHI) ≥ of 5 events per hour was consistent with the diagnosis of OSA[22]. The severity of OSA was assessed based on the AHI and oxygen desaturation index (ODI) based on 4% oxygen desaturation. OSA was classified as

mild, moderate, and severe based on AHI ≥ 5 but < 15, ≥ 15 but < 30, and ≥ 30 events per hour, respectively[23].

Randomisation

A minimisation algorithm within the computerised randomisation system was used to ensure balance in the treatment allocation over the following variables: ethnicity (White Europeans, others), gender (female and male), and severity of OSA (AHI< 15, ≥15).

CPAP initiation and compliance:

In the CPAP arm, each participant was provided with a CPAP machine (ResMed Airsense 10 Autoset™). Compliance was monitored remotely via a secured website, AirView (AutoRamp™, ResMed, UK); AV is compliant with the national and international security policies and practices, including NHS IG Toolkit: Ref: 8J317 *(2015-2016 – Score 90%),* ISO 27001 Certificate (IDS Host), and the Data Protection Act 2018 and the EU General Data Protection Regulation 2018. All patients were given an appropriate mask, connecting hose, a heated humidifier, and all the necessary accessories to operate the CPAP equipment for the trial.

The CPAP device was delivered and initiated by the sleep physiologist (MN) at the patient's convenient place. The sleep physiologist discussed the OSA diagnosis and CPAP benefits, explained technical aspects and general usage of the device, provided information and potential solutions to the expected side effects of CPAP, and contacted the patients by telephone 2-3 times during the first week of CPAP for any troubleshooting. Patients were encouraged to contact the sleep physiologist for troubleshooting at any time and were contacted when compliance dropped.

Sleep data were monitored once to twice weekly. Adequate compliance in this trial was defined as an average use of CPAP > 4 h/night on 70% of nights[20].

Outcomes measures:

The primary outcomes aimed to assess the feasibility of running a substantive RCT using the following criteria:

1. Recruiting the proposed sample size within the planned time frames.

2. Meeting the proposed time frames regarding interpreting the sleep assessments and initiating patients on treatment (within 8 weeks from registration or 2 weeks from randomisation).
3. Achieving a follow-up rate ≥ 80% for randomised patients.
4. Achieving a CPAP usage ≥ 4 h/night on ≥ 70% of nights in ≥ 80% of patients randomised to CPAP treatment.
5. Generating a mean and standard deviation regarding the predicted response to the intervention to allow future sample size calculations.

Secondary outcomes aimed to explore the impact of CPAP on diabetes-related endpoints. (Please refer to the online supplement). All secondary outcomes were measured at baseline and the 2-year follow-up visit.

Statistical analysis:

As this was a feasibility study, no formal sample size calculations were undertaken. However, around 500 patients who fulfil the main inclusion criteria were expected to be enrolled and screened for OSA, with approximately 140 of them randomized for the RCT based on OSA prevalence and severity that we reported in the previous study [24]. An a priori Statistical Analysis Plan (SAP) was agreed upon to provide point estimates and 95% Confidence Intervals (CI) for two-sided tests for all outcome measures. All outcomes were analysed using the intention-to-treat method, where participants were analysed in the groups to which they were randomised, regardless of protocol noncompliance. Outcomes were measured at the 2-year follow-up time point and were adjusted for minimisation variables and baseline value as fixed effects. If participants were missing follow-up values, they were not included in the analysis, but their baseline values were still included in the summary statistics. A log-binomial model with a log link was used for binary outcomes to generate adjusted relative risks (RR) and 95% CI at the follow-up time point. Continuous outcomes were analysed using a linear regression model to generate mean differences and 95% CI. Appropriate summary statistics are reported for each outcome (e.g., proportions [%], mean [SD], median [IQR]). Sensitivity analyses were limited to eGFR and consisted of a per-protocol analysis where those who were non-adherent to their allocated intervention were excluded. No subgroup analyses were planned for this feasibility study.

The impact of the Covid-19 pandemic:

Please refer to the online supplement.

Results:

Of 229 patients recruited to the observational cohort study, 83 participants fulfilled the eligibility criteria for the RCT. They were randomised to CPAP (n=40) and no CPAP (n=43) in addition to the continuation of routine care over a period of 2 years. The median (IQR) follow-up period was 645 [545, 861] days. A total of 12 patients withdrew from the CPAP arm and no withdrawal from the no CPAP arm. Out of the 12, 9 withdrew from treatment but agreed to continue with follow-up data collection, 2 withdrew from treatment and follow-up, and 1 provided no withdrawal information. Only the participants who withdrew from treatment and follow-up were included as withdrawals in **Figure 1**, as follow-up was still expected from other withdrawals. There was 1 protocol deviation reported in the no CPAP arm where a patient with an ESS score ≥ 11 was randomised in error.

Baseline Characteristics (Table 2):

The study population was mostly middle-aged men of White European ethnicity. Most of the study population had obesity (77.7%). The use of BP-lowering and lipid-lowering medications and insulin was high (43%, 74.4 % and 48.2 %, respectively). A history of stroke was present in 3% of the study population (0% CPAP vs 5.6% (N=2) no CPAP), while 16.2% had Myocardial infarction (9.7% (N=3) in CPAP vs 21.6% (N=8) in No CPAP). The baseline medications in **Table 2** show a high prevalence of antihypertensive medications in both CPAP and no CPAP arm (76.3% vs. 88.1%). The prevalence of AHI >=15 was 79.1% (N=34) in the no CPAP arm and 67.5% (N=27) in the CPAP arm, while 10 ≤AHI<15 prevalence was 32.5% (N=13) in the CPAP arm vs 20.9% (N=9) in the no CPAP arm.

Feasibility Outcomes (Table 3):

Three out of the 5 feasibility criteria were not met. Only about 60% of the study population was recruited within the planned time frames. The planned recruitment period was from April 2018 to October 2019, with a target of opening 10 sites by September 2018. The first site was opened in July 2018, and it took until January 2019 to reach 10 sites, with the first patient recruited in August 2018. The delay in obtaining R&D approvals from various local sites significantly contributed to the overall delay in recruitment. Further delays were caused by medical engineering taking longer than expected sign-off equipment at various sites. It took 213 days, on average, from the first formal approach to a site to the first recruitment. In addition, the goal was to recruit 40 registered patients a month from all the research centres. The actual recruitment did not exceed 25 per month in specific centres, resulting in an

increase in participating centres from 10 to 13. Our target of initiating CPAP within 8 weeks of registration or 2 weeks of randomisation was achieved in 37.5% of participants due to multiple factors, including delays in the supplies of the CPAP equipment and a lack of patients' availability within the planned time.

Only 8 out of 40 patients achieved our criteria for CPAP compliance. As detailed above, out of the 40 patients, 12 patients withdrew from CPAP treatment, and a further 2 patients did not use the CPAP. When examined, the remaining patients' median CPAP usage per night was more than 3.5 hours in **Table 4.** This suggests significant CPAP usage in a proportion of the study population despite failing the strict compliance criteria of 4 hours on 70% of the nights. There are likely several factors contributing to the high number of withdrawals and CPAP nonusers (please see the discussion). Our data shows that the withdrawals happened in the first 10 months. Having a run-in period before randomisation might have identified those individuals unlikely to be able to adhere to CPAP. In our trial, we found that CPAP compliance at 2 weeks predicted CPAP compliance at 1 year using adherence threshold of 70% and 50% [X^2 (1, N=25) = 4.1, p= .043) and X^2 (1, N=25) = 17.6, p <0.01 respectively] in **Table S1 in the online supplement.** The high follow-up rate was achieved likely due to the flexibility in collecting data remotely, including the CPAP usage.

Secondary outcomes:

CPAP and clinical and biochemical variables related to T2D

The impact of CPAP on various clinical and biochemical variables related to diabetes and obesity is summarised in **Table S2 in the online supplement**. Analysis was adjusted for age, gender, ethnicity, OSA severity and baseline value of the outcome of interest. All data available at both time points is reported, but only participants who had both baseline and follow-up values were included in each analysis. BP and adiposity variables were more favourable in patients randomly assigned to CPAP. Overall, the analysis showed no significant association between being randomised to CPAP and these clinical and metabolic parameters.

CPAP and renal outcomes

Patients who were randomised to CPAP had higher eGFR and lowered ACR at baseline. By the study's end, eGFR, and ACR, numerically improved in the CPAP arm but not in the no CPAP arm **Table 5.**

CPAP and Quality of Life

The CPAP group had a higher physical component score at baseline than no CPAP. By the study's end, this score was maintained in the CPAP arm and worsened in the no CPAP arm. The mental component scores at baseline and study end were similar in patients randomised to CPAP or no CPAP and improved in both arms **Table S4 in the online supplement.**

CPAP and retinopathy

It was impossible to analyse this outcome due to the small number of patients for whom we managed to obtain retinal screening results, especially for the follow-up time point. Data are summarised in **Table S5 in the online supplement.**

CPAP and Peripheral Neuropathy

The Michigan Neuropathy Screening Instrument (MNSI)

An MNSI score on the examination component (MNSIe) > 2 or the questionnaire component (MNSIq) ≥ 7 was considered consistent with the diabetic peripheral neuropathy (PN) [25,26]. Being randomised to CPAP was associated with a possible numerically favourable impact on peripheral neuropathy compared to no CPAP, whether defined based on MNSIe, MNSIq or total score **Table 6.** The individual components of the MNSIe are reported in **Table S6 in the online supplement.**

There was no evidence of a difference between CPAP and no CPAP except in regard to the vibration perception at the great toe.

Neuropad and biothesiometry

The Neuropad is based on a cobalt II compound that turns pink after being exposed to dermal foot perspiration for 10 minutes in the plantar foot areas. The change in the colour is recorded as none, partial, or complete[27]. The Neuropad assessment improved in both trial arms during follow-up, but being randomised to CPAP was associated with numerically a lower proportion of abnormal neuropad testing.

A biothesiometer was used to test the vibration perception on the great toe of each foot; an average of three measurements were considered [28]. Vibration perception was numerically better in association with being randomised to CPAP vs no CPAP. The CPAP arm had a lower

proportion of patients with abnormal Neuropad testing or abnormal vibration perception at baseline compared to no CPAP in **Table 7.**

Monofilament

Foot insensitivity to a 10-g monofilament (applied to 10 positions)was defined as a score of 8 to 10 being normal, and a response of 0 to 7 is abnormal[26]. Abnormal monofilament test was less common in the CPAP arm at baseline vs no CPAP. During follow-up, there was an improvement in the monofilament testing in the CPAP arm and a worsening in the no CPAP arm in **Table 7.**

Discussion:

This manuscript reports the longest CPAP trial in patients with T2D and is the first to focus on diabetes complications. This feasibility RCT highlights the challenges that can be faced when conducting CPAP trials in patients with T2D and the possible underlying causes.

We found that clinicians are willing to recruit patients, and patients are willing to be randomised. Neither the study teams nor the patients reported concerns with the portable sleep studies, despite the recruiting teams having no prior experience conducting OSA research. Study teams were trained to educate the patients about using portable sleep devices and how to download the data to the cloud-based system. This study also achieved high follow-up rates despite the challenging circumstances, likely due to the reliance on remote monitoring. However, 3 out of 5 feasibility criteria were not met.

Two unmet criteria are related to timelines (recruitment and CPAP initiation). The recruitment timelines targets were missed mostly due to the lengthy delays in obtaining local approvals from the study sites despite no difficulties obtaining overall ethical approval for the study. We have no definite reason for this delay. We postulate that it is due to the high workload on the R&D departments that resulted in some studies being prioritized over others.

We met the target for scoring the sleep studies quickly after the studies were uploaded to the online portal. However, initiating CPAP with a specific timescale was not achieved due to constraints imposed by patients' diaries. Evidently, these targets were unrealistic, and future studies should allocate more time for opening study sites in the UK and provide longer intervals between randomisation and CPAP initiation, which should not affect future trials' integrity.

In addition, we failed to achieve our target of CPAP compliance. It is well recognised that achieving adequate CPAP compliance is challenging in real-life or clinical trials. After the first night of CPAP, 8 –15% of patients refuse further treatment [29], and at least 50% discontinue usage within 1 year [29]. Nonadherence rates of 29% to 83% were reported in different clinical trials [30]. Several factors have been linked to a lack of adherence, including higher disease severity, sleepiness, mood disorders, ethnicity, socioeconomic status, claustrophobia, unrealistic expectations, and poor disease and treatment knowledge [31,32]. Some factors are associated with better adherence, such as using CPAP auto titration, heated humidification, self-efficacy and the presence of a bed partner [32]. In our study, we aimed to improve adherence through various strategies, including auto-titration CPAP with humidifiers, remote monitoring, intensive follow-up, and extensive education on CPAP initiation troubleshooting. However, factors such as excessive daytime sleepiness and a modest AHI (below 15) in some patients have contributed to low adherence. Withdrawals from CPAP occurred in the first 10 months of the trial, with reasons to stop using CPAP, such as other health problems (e.g., osteoarthritis), lack of support at home, and change in personal circumstances (e.g., frequent travels). Our exploratory analysis showed that CPAP compliance from as early as 2 weeks could predict CPAP compliance at 1 year, which is consistent with other studies [31]. A run-in period of as short as 2 weeks might have reduced the number of patients not using CPAP after randomisation and improved adherence.

We have measured the impact of CPAP treatment on many clinical variables over the 2 years, with a specific focus on diabetes-related microvascular complications. Previous RCTs of CPAP in patients with T2D were relatively short (3-6 months) and mainly focused on glycaemic outcomes or cardiovascular disease risk factors [33]. Hence, this trial adds many novel insights into the links between OSA and diabetes-related outcomes. However, due to the feasibility nature of the trial and to increase the burden on patients, we elected to use no treatment at the control [34].

Also, the study was not powered to detect statistically significant differences between treatment arms. These analyses should be treated as hypothesis-generating to inform the choice of future definitive RCTs. Despite not meeting the compliance criteria, we found a possible favourable association between being randomised to the CPAP arm vs no CPAP in relation to several outcomes related to CKD, PN and QoL. If these findings are proven in future RCTs, this will provide another treatment option to reduce the burden of T2D on individuals

and the healthcare system. Despite recent improvements in the treatment options for diabetes complications, there is still a big unmet need [35,36].

The observed favourable associations between CPAP use and improved nephropathy/nephropathy markers are plausible biologically. OSA has been linked to the development and progression of CKD, nephropathy, and retinopathy in patients with T2D, as well as the worsening of intermediary mechanisms such as oxidative stress, inflammation, and endothelial function [14,15,37,38]. CPAP has been shown to have favourable effects on many of the above mechanisms and pathways that lead to microvascular complications[39].

We have not specified the routine care in the protocol or directly collected data about the routine care received. Hence, we cannot be sure there were no differences in routine care that might have impacted the study outcomes. However, there is no meaningful impact of CPAP on glycaemic control, lipids, blood pressure or adiposity **Table S2**. We have also found that there were some differences in the prescription of glucose- and lipid-lowering treatments, insulin and antihypertensives in favour of the no CPAP arm by the study end **Table S3**. Hence, if there were any differences in routine care, they are likely to be in favour of the no CPAP arm and not biasing the observed findings in favour of CPAP.

This feasibility RCT has limitations, including low CPAP Compliance and a high proportion of missing data regarding clinical variables attributed partly to the COVID-19 pandemic. The study is not adequately powered to determine the clinical benefits of CPAP treatment. Also, by excluding patients with excessive daytime sleepiness from the RCT, we might have excluded patients with more severe diseases that might have better CPAP compliance. However, we needed to ensure patients' safety by excluding patients where randomisation to no CPAP would have been unsafe. Based on the study protocol, patients initiated on CPAP had extra contact to initiate CPAP and support CPAP compliance. This extra contact was mainly in the early stages of the study. Differences in contact between study arms might impact the study outcomes. However, this is unlikely to be the case in this study due to the long time between the extra contact and the endpoints' assessment time.

In our trial, we did not have study-end AHI measurement, so we cannot confirm that the findings are related to improvement in AHI. However, we have used an intention-to-treat analysis in order to reduce biases that might overestimate the effect of the intervention, and we found no meaningful impact of CPAP on important risk factors related to the outcome,

such as blood pressure, glycaemic control, lipids, and adiposity measures. Also, we have adjusted the comparison of the secondary study outcomes between study arms to some important biologically important variables. However, the list of variables was not exhaustive, and other variables could be relevant, such as BMI. BMI improved in both arms, and the adjusted difference is clinically not meaningful. Due to the feasibility nature and small sample size, we elected not to adjust for further variables, including BMI, especially since the findings of this trial need to be tested in full RCTs.

Furthermore, Clinical measures were used to assess PN instead of more sensitive tools, such as nerve conduction studies, for practical reasons and based on previous trials [40]. Patients continued to receive routine care regardless of being randomised to CPAP or no CPAP. On the other hand, this trial has notable strengths. It is the longest CPAP RCT trial in patients with T2D, assessing outcomes beyond glycaemic control and related to hard endpoints. The trial also achieved high follow-up rates through the remote data collection method.

Conclusion

In conclusion, conducting long-term RCT with the current design is probably not feasible. However, having a run-in period and selecting those more compliant with CPAP could be feasible in a full RCT. It is important to assess the OSA treatment on diabetes-related microvascular complications considering the high burden of these diseases. It might significantly impact reducing those burdens on patients and the healthcare system. However, such potential benefits need to be examined in future RCTs.

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Abbreviation index:

- ACR: urinary albumin/creatinine ratio
- AHI: apnoea hypopnea index
- BMI: body mass index
- BP: blood pressure
- CKD: chronic kidney disease
- CPAP: continuous positive airway pressure
- CV: cardiovascular
- DN: diabetic nephropathy
- DPN: diabetic peripheral neuropathy
- DR: diabetic retinopathy
- E/I ratio: expiration/inspiration ratio
- eGFR: estimated glomerular filtration rate
- ESS: Epworth sleepiness scale
- HC: hip circumference
- MNSI: Michigan Neuropathy Screening Instrument
- OS: oxidative stress
- OSA: obstructive sleep apnoea
- QoL: quality of life
- T2DM: type 2diabetes
- WC: waist circumference
- WHR: waist−hip ratio

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Table 1: Summary of inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Observational cohort study	
• Are ≥ 18 years old, • Diagnosis of T2D, • eGFR ≥ 15 mL/min/1.73 m2 in the last 12 months.	• History of T1D. • Known OSA • Active malignancy • CKD from reasons other than diabetes. • Receivingchemotherapy, immunosuppressant drugs, or home oxygen treatment. • History of recurrent hospital admissions due to infective exacerbation of a respiratory condition. • Received contrast imaging within the last 2 months • Pregnancy. • Intending to undergo bariatric surgery during the study duration. • Unable to comply with the study protocol. • Unable to give informed consent. • Professional drivers, operators of heavy machinery, and/or working at high altitude. • History of falling asleep whilst driving within last two years.
Feasibility RCT	
• Adults who were willing to be randomised to CPAP vs no CPAP • Has ESS (Epworth Sleepiness Scale) <11 • has an Apnoea-Hypopnea Index (AHI) ≥ 10	• Participants who have resting oxygen saturation < 90% or • Participants who have episodes of central sleep apnoea at > 15/hours

Estimated glomerular filtration rate (eGFR)

Table 2: Patient characteristics at baseline as total and categorised based on randomisation to CPAP. Data presented as % (n), median [IQR], n or mean (SD), n

Baseline Characteristics	CPAP (N=40)	No CPAP (N=43)	Total (N=83)
Age (years)	60.5 (11.9), 40	64.5 (9.5), 42	62.5 (10.9),82
Gender (Male%)	25 (62.5%)	34 (79.1%)	59 (71.1%)
Ethnicity (White %)	35 (87.5%)	39 (90.8%)	74 (89.1%)
Diabetes duration (Years)	10.6 (7.2), 39	13.7 (8.4), 43	12.2 (7.9), 82
Never smoked: N (%)	18 (45.0%)	16 (37.2%)	34 (41.0%)
BMI (kg/m2)	34.4 (6.5), 37	36.5 (7.7), 39	35.4 (7.2), 76
BMI classes (N (%)):			
< 25 kg/m2	2 (5.4%)	2 (5.1%)	4 (5.3%)
25 to <30 kg/m2	9 (24.3%)	4 (10.3%)	13 (17.1%)
30 to <35 kg/m2	10 (27.0%)	13 (33.3%)	23 (30.3%)

≥ 35 kg/m2	16 (43.2%)	20 (51.3%)	36 (47.4%)
Blood pressure			
Systolic BP (mmHg)	130.9 (13.5), 39	137.9 (14.4), 42	134.5 (14.3), 81
Diastolic BP (mmHg)	77.1 (8.5), 38	77.7 (10.7), 42	77.4 (9.7), 80
Diabetes treatments			
Oral Glucose Lowering Agents	36 (92.3%)	37 (90.2%)	73 (91.3%)
Insulin use	15 (37.5%)	25 (58.1%)	40 (48.2%)
GLP-1 use	7 (18.4%)	5 (12.8%)	12 (15.6%)
Lipid lowering agents N (%)	30 (75.0%)	31 (73.8%)	61 (74.4%)
Anti-hypertensives N (%)	13 (33.3%)	21 (52.5%)	34 (43.0%)
Comorbidities			
Stroke	0 (-)	2 (5.6%)	2 (3.0%)
Myocardial Infraction	3 (9.7%)	8 (21.6%)	11 (16.2%)
AHI Median (IQR)	17.7 (13.7, 32.4), 40	24.4 (19.2, 41.1), 38	21.4 (14.9, 36.6)
Epworth sleepiness Scale score	6.0 [3.0, 7.5], 40	6.0 [4.0, 8.0], 42	6.0 [3.0, 8.0], 82

***CPAP arm,** there were 3 missing BMI, 1 missing systolic BP, 2 missing diastolic BP, and 1 missing diabetes duration
***No CPAP arm; there** were 4 missing BMI, 1 missing systolic BP, 1 missing diastolic BP, and 1 missing Age

Table 3: Summary of achievement of Feasibility outcomes

	CPAP (N=40)	No CPAP (N=43)	Total (N=83)
Recruit the proposed sample size within the planned time frames			
Proportion recruited of target	57.1%	61.4%	59.2%
Meet the proposed time frames regarding interpreting the sleep assessments and initiating patients on treatment			
CPAP initiations completed within 8 weeks of registration or 2 weeks of randomisation	12/32[1] (37.5%)		
Achieve a follow-up rate ≥80% for randomised patients[2]			
Follow-up rate	33/38[3] (86.8%)	33/43 (76.7%)	66/81[3] (81.5%)
Achieve a CPAP usage ≥4 hours/night on ≥70% of nights in ≥80% patients randomised to CPAP treatment			
CPAP usage ≥4 hours/night on ≥70% of nights	8/40 (20.0%)		
Generate a mean and standard deviation regarding predicted response to the intervention:			
Baseline eGFR: Mean (SD, n)	86.1 (26.4, 40)	74.9 (21.9, 41)	79.9 (24.8, 81)
Follow-up eGFR: Mean (SD, n)	93.4 (30.9, 21)	75.5 (31.4, 28)	83.2 (32.1, 49)

[1] 8/40 participants did not start the CPAP after randomisation: 5 withdrew before being issued a device, and 3 had no CPAP initiation date.
[2] Participants are considered to have follow-up data if they have attended their 24-month follow-up visit or have follow-up CPAP data recorded.
[3] 2 participants withdrew from the follow-up data being collected.

Table 4: Summary of CPAP usage at multiple time points during the study in patients who used CPAP. Data presented as Median [IQR]

Time point	2 weeks (N=25)[1]	4 weeks (N=26)	1 year (N=26)	2 years (N=5)
Number of days used	11.0 [5.0, 13.0]	20.0 [7.0, 27.0]	260.0 [11.0, 346.0]	592.0 [360.0, 653.0]
Days ≥4h per night	7.0 [3.0, 10.0]	14.0 [1.0, 22.0]	169.5 [3.0, 267.0]	505 [257.0, 559.0]
Average time used per night (Hours: minutes)	3:49 [1:29, 4:30]	3:32 [0:49, 4:45]	3:40 [0.06, 4:45]	4:58 [4:48, 10:13]

[1] Of the 40 participants allocated to CPAP: 12 participants withdrew from using CPAP and two did not use CPAP. One participant is missing 2-week data only. Five participants had 2-year CPAP data available.

Table 5: Summary of the relationship between CPAP and renal outcomes. Data presented as mean (SD, n) or N (%). Analysis was performed using mean difference and RR as appropriate. A RR <1 favours CPAP. The mean difference was calculated as CPAP - no CPAP.

	Baseline		Study-end		Adjusted mean difference (95% CI) or relative risk (95% CI)
	CPAP (N)	No CPAP (N)	CPAP (N)	No CPAP (N)	
eGFR (mL/min/1.73m^2)	86.1 (26.4, 40)	73.9 (21.9, 41)	93.4 (30.9, 21)	75.5 (31.4, 28)	4.3[1] (-12.0, 20.6)
eGFR <60 (mL/min/1.73m$^{2)}$	7 (17.5%)	12 (29.3%)	4 (19.1%)	9 (31.0%)	1.4[1] (0.2, 12.3)
Urinary ACR (mg/mmol)	11.4 (26.2, 33)	41.6 (83.3, 38)	2.0 (2.8, 18)	38.3 (96.5, 22)	-21.1[2] (-56.4, 14.2)
Albuminuria status					
Abnormal N (%)	8 (24.2%)	15 (39.5%)	2(11.1%)	9 (38.1%)	0.33[2] (0.03, 3.9)
Microalbuminuria	6	5	2	4	
Macroalbuminuria	2	10	0	5	

CPAP arm: eGFR 2 missing at the end-study visit, albuminuria 7 missing at baseline, and 5 missing at study-end
No CPAP arm: eGFR 2 missing at baseline, and 4 missing at the study-end visit. Albuminuria 5 was missing at baseline, and 11 was missing at the study end.
[1]Adjusted for ethnicity, gender, OSA severity, age, systolic blood pressure, diastolic blood pressure, HbA1c (mmol/mol) and baseline value. Only participants with both baseline and follow-up values are included in this analysis.
[2]Adjusted for ethnicity, gender, OSA severity, age, systolic blood pressure and baseline value. Only participants with both baseline and follow-up values are included in the analysis. A relative risk <1 or a mean difference < 0 favours CPAP.

Table 6: MNSI score

	Baseline		Follow-up		Adjusted relative risk[1] (95% CI)
	CPAP N (%)	No CPAP N (%)	CPAP N (%)	No CPAP N (%)	
MNSI questionnaire					
Abnormal	5 (12.5%)	12 (27.9%)	0 (-)	7 (26.9%)	0.78 (0.4, 1.6)
Normal	35 (87.5%)	31 (72.1%)	18 (100.0%)	19 (73.1%)	
Missing	0	0	6	9	
MNSI examination					
Abnormal	18 (47.4%)	20 (50.0%)	7 (36.8%)	7 (50.0%)	0.83 (0.3, 2.7)
Normal	20 (52.6%)	20 (50.0%)	12 (63.2%)	7 (50.0%)	
Missing	2	3	5	21	

MNSI overall score					
Abnormal	19 (50.0%)	22 (55.0%)	7 (41.2%)	12 (80.0%)	0.51 (0.1, 2.3)
Normal	19 (50.0%)	18 (45.0%)	10 (58.8%)	3 (20.0%)	
Missing	2	3	7	20	

Note: MNSI questionnaire has a range from 0 to 13, where 0 is the best, and 13 is the worst.
Note: MNSI examination has a range from 0 to 8, where 0 is best, and 8 is worst.
Note: For the MNSI questionnaire score, 'normal' is categorised as a score <7 and 'abnormal' is categorised as a score ≥7. For the MNSI examination score, 'normal' is categorised as a score ≤2 and 'abnormal' is categorised as a score >2. MNSI's overall score is 'abnormal' if the participant has an 'abnormal' score in the questionnaire and/or the examination and 'normal' otherwise.
[1]Adjusted for ethnicity, gender, OSA severity, age, and baseline value. A relative risk <1 favours CPAP. Only participants with both baseline and follow-up values are included in this analysis.

Table S7: Neuropod, vibration, and 10-gram monofilament

	Baseline		Follow-up		Adjusted relative risk[1] (95% CI)
	CPAP N (%)	No CPAP N (%)	CPAP N (%)	No CPAP N (%)	
Neuropod/ Both feet[2]					
Incomplete/ abnormal	24 (63.2%)	31 (73.8%)	12 (57.1%)	11 (68.8%)	0.87 (0.3, 2.3)
Partial	17	24	10	10	
None	7	7	2	1	
Complete	14 (36.8%)	11 (26.2%)	9 (42.9%)	5 (31.3%)	
Missing	2	1	2	17	
Vibration perception/ Average both feet[3]					
Abnormal (>25V)	8 (33.3%)	17 (60.7%)	4 (36.4%)	3 (60.0%)	0.64 (0.04, 9.2)
Normal (≤25V)	16 (66.7%)	11 (39.3%)	7 (63.6%)	2 (40.0%)	
Missing	16	15	12	28	
10-gram Monofilament/ Both feet[4]					
Abnormal	15 (38.5%)	22 (52.4%)	6 (28.6%)	15 (88.2%)	0.49 (0.1, 1.5)
Reduced	*12*	*13*	*4*	*10*	
Absent	*3*	*9*	*2*	*5*	
Normal	24 (61.5%)	20 (47.6%)	15 (71.4%)	2 (11.8%)	
Missing	1	1	2	16	

[1]Adjusted for ethnicity, gender, OSA severity, age, and baseline value. A relative risk <1 favours CPAP. Analysis is 'Incomplete ['Partial '+'None'] vs 'Complete'. Only participants with both baseline and follow-up values are included in this analysis
[2] If either foot is scored as 'None', then 'Both feet' is categorised as 'None'; if either foot is categorised as 'Partial', but neither as 'None', then 'Both feet' is categorised as 'Partial'; if both feet are scored as 'Complete', then 'Both feet' is categorised as 'Complete.'
[3] If either foot is high, then 'both feet' are high.
[4] If either foot is scored as 'Absent', then 'Both feet' is categorised as 'Absent'; if either foot is categorised as 'Reduced', but neither as 'Absent', then 'Both feet' is categorised as 'Reduced'; if both feet are scored as 'Normal, then 'Both feet' is categorised as 'Normal.'

Figure.1: Flow diagram of the study. The 24-month follow-up visit represents the study-end visit and may have occurred before 24 months in some participants**.**