

# A systematic review on adherence to continuous positive airway pressure (CPAP) treatment for obstructive sleep apnoea (OSA) in individuals with mild cognitive impairment and Alzheimer's disease dementia

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## ARTICLE INFO

Handling editor: M Vitello

### Keywords:

Alzheimer's  
Sleep apnoea  
Dementia  
Continuous positive airway pressure  
Cognitive impairment

## ABSTRACT

Obstructive sleep apnoea (OSA) is highly prevalent in mild cognitive impairment (MCI) and Alzheimer's disease (AD). The gold standard treatment for OSA is continuous positive airway pressure (CPAP). Long-term, well-powered efficacy trials are required to understand whether CPAP could slow cognitive decline in individuals with MCI/AD, but its tolerability in this group remains uncertain. The present review investigates CPAP adherence among individuals with OSA and MCI/AD. Electronic searches were performed on 8 databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Six independent studies and four secondary analyses included 278 unique participants (mean age = 72.1 years). In five of the retained studies, around half of participants (45% N = 85 MCI, 56% N = 22 AD) were adherent to CPAP, where  $\geq 4$  h use per night was considered adherent. Three of the retained studies also reported average CPAP use to range between 3.2 and 6.3 h/night. CPAP adherence in individuals with MCI and AD is low, albeit similar to the general elderly population. Reporting adherence in future studies as both average duration as well as using a binary cut-off would improve our understanding of the optimum CPAP use in dementia clinical trials and care.

## 1. Introduction

Obstructive sleep apnoea (OSA) is complete or partial collapse of the upper airway, impeding breathing despite respiratory effort during sleep. High prevalence rates are common across the general population, with a large proportion of patients remain undiagnosed and therefore untreated [1,2]. This prevalence pattern also extends to the dementia cohort, with estimates of OSA rates within Alzheimer's disease (AD) ranging from 43 to 91% [3,4] and between 11 and 71% in mild cognitive impairment (MCI) [5].

Factors associated with OSA including intermittent hypoxia, sleep fragmentation, reduced slow wave sleep and intrathoracic pressure

swings are proposed to drive AD pathology including amyloid and tau accumulation, reduced neural plasticity, and increased neuronal loss [6]. Individuals with OSA or OSA comorbid with MCI experience a faster increase in brain amyloid- $\beta$ 42 (A $\beta$ 42) and reduced cerebrospinal fluid (CSF) A $\beta$ 42, as well as increased CSF total-tau (t-tau) and phosphorylated tau (p-tau) compared with those without OSA [7]. Similarly, untreated OSA patients have lower CSF A $\beta$  concentrations, higher CSF lactate levels and higher t-tau/A $\beta$  ratio compared to OSA patients using CPAP [8]. OSA is also associated with brain vascular changes, specifically white matter hyperintensities (WMH) – a common marker of cerebral small vessel disease which can increase stroke and dementia risk [9]. Overall, the presence of sleep-disordered breathing (SDB) is associated with an increased risk of developing cognitive impairment by

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**Glossary of terms**

|       |   |
|-------|---|
| CAI   | CPAP adherence intervention               |
| HCPCS | Healthcare Common Procedure Coding System |
| PBS   | peer buddy system                         |

**Abbreviations**

|           |  |
|-----------|--|
| A $\beta$ | amyloid beta   |
| AHI       | apnoea-hypopnoea index                                     |
| AD        | Alzheimer's disease  |
| BMI       | body mass index  |
| CDR       | cognitive dementia rating                                  |
| CERAD     | Consortium to Establish a Registry for Alzheimer's Disease |
| CAI       | CPAP adherence intervention                                |
| CPAP      | continuous positive airway pressure                        |
| CSF       | cerebral spinal fluid                                      |
| DSM       | diagnostic and statistical manual of mental disorders      |

|              |  |
|--------------|--|
| HCPCS        | Healthcare Common Procedure Coding System  |
| ICD          | International Classification of Diseases   |
| MCI          | mild cognitive impairment  |
| MMSE         | mini-mental state examination  |
| NIA-AA       | National Institute on Aging and Alzheimer's Association  |
| NINCDS-ADRDA | National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association |
| OSA          | obstructive sleep apnoea   |
| PBS          | peer buddy system  |
| PRISMA       | Preferred Reporting Items for Systematic Reviews and Meta-Analyses   |
| PSG          | polysomnography  |
| SDB          | sleep disordered breathing   |
| P-tau        | phosphorylated tau   |
| T-tau        | total tau  |

26–35%, and slight worsening in executive function [10].

The gold standard treatment for OSA is continuous positive airway pressure (CPAP), a machine used to deliver a set pressure to the airways throughout the respiratory cycle during sleep [11,12]. Emerging evidence suggests that CPAP may exert a positive impact on cognition [13–16], however, the evidence is not entirely consistent [17] and there remains uncertainty surrounding which specific cognitive domains improve with CPAP [18]. It is important to also note that, although some studies did not find a significant improvement in cognitive performance, CPAP use did benefit other important clinical parameters including daytime sleepiness, anxiety and depressive symptoms, as well as helping to reduce health-care costs [19,20]. Nevertheless, larger and more longitudinal trials are needed to confirm whether CPAP can ameliorate or reverse the impact of OSA on cognition and/or AD pathology accumulation.

Recent advances in AD treatment include anti-amyloid monoclonal antibodies – lecanemab and donanemab, which are gradually entering clinical practice [21,22]. While this provides evidence that Alzheimer's progression is modifiable, these drugs are far from curative. The drugs slow decline over 18 months by 27–35% and carry significant side effects including amyloid related imaging abnormalities leading to, in worst cases, disability and death. Hence, safe treatments that could potentially improve cognition or delay Alzheimer's pathology, such as CPAP for OSA in AD, are still imperative.

A considerable limiting factor for CPAP use is low adherence. A retrospective observational study found that only 33% of presurgical patients diagnosed with OSA were adherent to CPAP (defined as CPAP use  $\geq 4$  h/night) and the overall median use was only 2.5 h/night [23]. Previous reviews conducted on CPAP adherence demonstrated non-adherence rates, based on 7 h/night sleep time across 82 papers, to be 34.1% [24]. However, these reviews did not collate information on CPAP adherence in individuals with MCI and AD specifically. Given the behavioural symptoms of individuals with MCI and AD, such as memory problems, apathy, depression and agitation, it is likely that adherence could be lower in this population [25]. This paper systematically reviews the literature exploring CPAP use in MCI and AD cohorts with OSA. Establishing levels of adherence to CPAP in these cohorts will underpin the development of clinical trials of CPAP in MCI and AD populations, with the aim of slowing decline or even improving their cognition.

**2. Methods**

This review followed the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA). The protocol was

registered in PROSPERO (CRD42021292782).

**2.1. Inclusion criteria****2.1.1. Participants must meet all of the following characteristics**

- 1) Adults aged 18 and over
- 2) Male or female
- 3) a. Diagnosis of OSA as defined by satisfying established diagnostic criteria e.g., apnoea-hypopnoea index (AHI) of 5 or more, or equivalent.
- b. Diagnosis of MCI or AD dementia as defined by satisfying established diagnostic criteria e.g., diagnostic and statistical manual of mental disorders-IV (DSM-IV), DSM-V, Albert criteria, Peterson criteria, or equivalent.

**2.2. Intervention**

CPAP treatment.

**2.3. Comparison**

A comparison arm was not necessary for the designed question, hence adherence data retrieved from RCTs focussed solely on the treatment group.

**2.4. Outcome**

Information related to CPAP use including metrics or adherence data.

**2.5. Search strategy**

The search strategy was developed by the specialist medical librarian (SR) in collaboration with subject matter experts within the review team. The final searches comprised of text words and subject headings relating to dementia, sleep apnoea and CPAP (see Supplementary data). The following electronic databases were searched by the specialist medical librarian: Embase (Ovid), MEDLINE (Ovid), Scopus, British Nursing Index (ProQuest), PsycInfo (ProQuest), CINAHL (Ebsco), EMCARE (Ovid) and AMED (Ovid) (from inception to December 10, 2021 and updated on November 25, 2022). Some relevant reviews were manually searched to identify any additional eligible studies which were not identified by the database search.

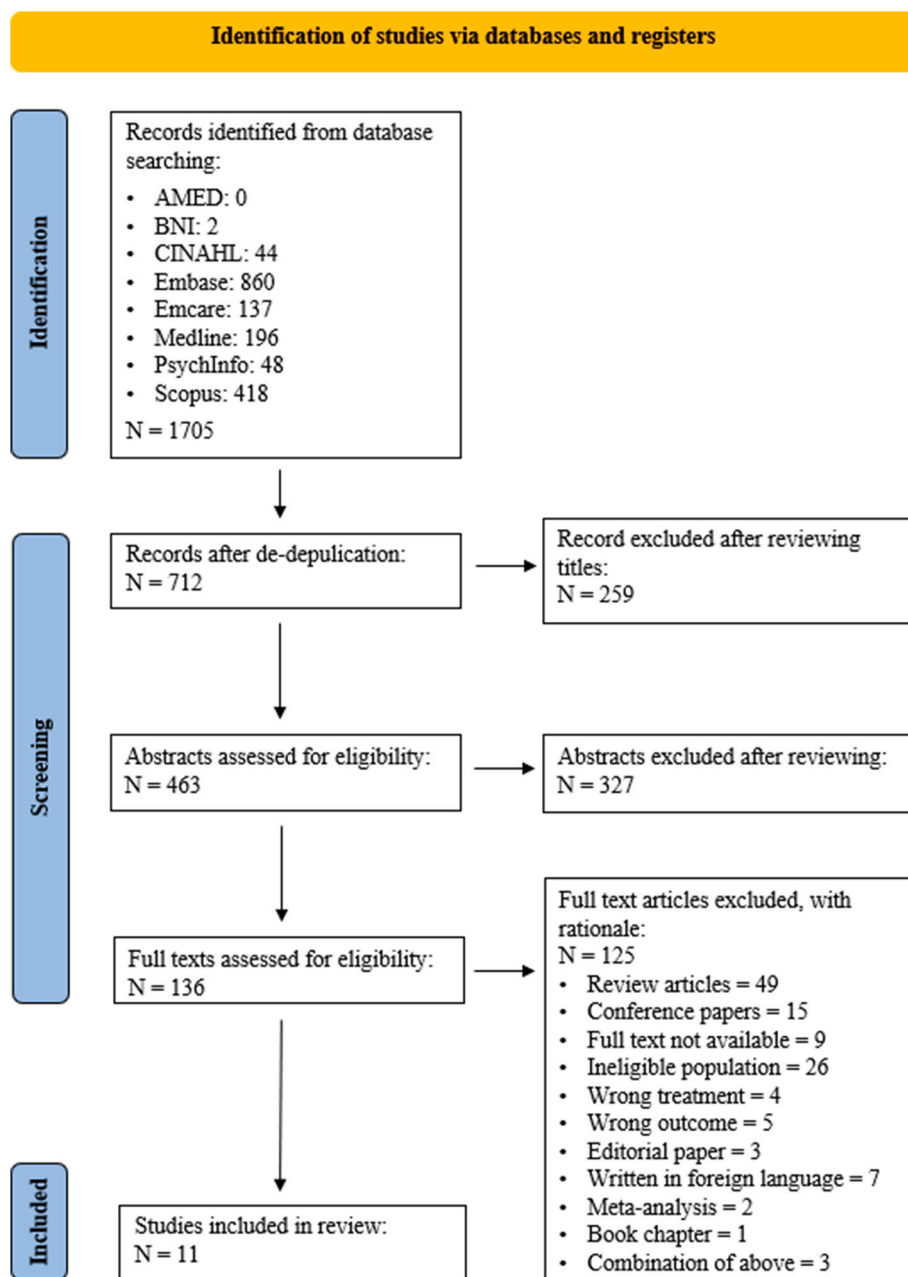


Fig. 1. PRISMA flow chart of the study selection process. Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

## 2.6. Study selection and reviewing procedure

De-duplication was carried out by SR and CO. A sample of 10% of the article titles and abstracts were reviewed by a group of reviewers (CO, AB and VG), to ensure consensus in decision making. The remaining titles and abstracts were reviewed by CO. The remaining articles' full texts were reviewed by CO, BB and VG. 10% of the full texts were reviewed as a team and the remaining full texts were split between the 3 reviewing members and reviewed independently. An updated search was conducted on November 25, 2022 to ensure all relevant literature were included. The updated search was de-duplicated by SR and SH. All article titles and abstracts, as well as full texts, were screened independently by HL and DW. Full-texts were checked against the inclusion criteria and reasons for excluding titles at the full-text screening stage were recorded.

## 2.7. Data extraction

Data from retained articles were manually extracted into a data extraction table using Microsoft Excel. Data extracted from the retained articles included: author, year of publication, study type, patient characteristics, condition/diagnosis, intervention and intervention duration, outcome measure, clinical characteristics and cognitive characteristics. Authors of a few of the studies were contacted for full texts and for clarity on some of the study data.

## 2.8. Quality assessment

The quality of the retained studies was evaluated using Joanna Briggs Institute checklist for battery of tools [26]; specifically, those for quasi-experimental, cohort and randomised controlled trials. Independent evaluation of quality was undertaken by four reviewers (CO, VG, HL and DW) and consensus was reached. For the quality appraisal,

**Table 1**  
Study characteristics for the 7 retained studies and 4 secondary analyses.

| Author/Year                             | Study type  | Condition                    | OSA diagnostic criteria  | Country   | No. of total participants (female) | Mean age (years)                                   | Study duration | Outcome measure  |
|---|---|------------------------------|--|-----------|------------------------------------|--|----------------|--|
| Ancoli-Israel et al. (2008) [32]        | Randomised double-blind placebo-controlled trial  | Mild to moderate AD with OSA | AHI $\geq 10$ diagnosed by PSG   | USA       | 52 (13)                            | 78.6 (CPAP group)<br>77.7 (placebo group)<br>78.4  | 6 weeks        | Hidden clocks in CPAP machine  |
| Ayalon et al. (2006) [28] <sup>a</sup>  | Secondary analysis of Ancoli-Israel et al. (2008) | Mild to moderate AD with OSA | AHI $\geq 10$ diagnosed by PSG   | USA       | 30 (7)                             | 78   | 6 weeks        | Hidden clocks in CPAP machine  |
| Chong et al. (2006) [30] <sup>a</sup>   | Secondary analysis of Ancoli-Israel et al. (2008) | Mild to moderate AD with OSA | AHI $\geq 10$ diagnosed by PSG   | USA       | 39 (10)                            | 78   | 6 weeks        | Hidden clocks in CPAP machine  |
| Cooke et al. (2009) [29] <sup>a</sup>   | Secondary analysis of Ancoli-Israel et al. (2008) | Mild to moderate AD with OSA | AHI $\geq 10$ diagnosed by PSG   | USA       | 10 (3)                             | 75.7   | 13.3 months    | Not applicable   |
| Dunietz et al. (2021) [34] <sup>b</sup> | Retrospective cohort study                        | MCI with OSA and AD with OSA | ICD-9 diagnosis code   | USA       | 1520 (666)                         | 65-85+   | 3 years        | $\geq 2$ HCPCS equipment claims  |
| Hoyos et al. (2022) [37]                | Randomised-controlled crossover trial             | MCI with OSA                 | AHI $\geq 15$ diagnosed by PSG   | Australia | 29 (13)                            | 68.1   | 12 weeks       | Data downloaded from CPAP machine using Secure Digital cards   |
| Liguori et al. (2021) [36]              | Retrospective cohort study                        | MCI with OSA and AD with OSA | AHI $\geq 10$ diagnosed by cardiorespiratory polygraphy  | Italy     | 24 (8)                             | 74.8   | 3.8 years      | Not recorded   |
| Richards et al. (2019) [33]             | Quasi-experimental study                          | Amnesic MCI with OSA         | AHI $\geq 10$ diagnosed by PSG (split- or whole-night)   | USA       | 54 (24)                            | 70.1   | 1 year         | Not recorded   |
| Skiba et al. (2020) [17]                | Retrospective cohort study                        | MCI with OSA                 | AHI 5–14.9 = mild OSA, AHI 15–29.9 = moderate OSA and AHI $>30$ = severe OSA diagnosed by PSG or home sleep apnoea testing | USA       | 96 (33)                            | 70.4   | 2.8 years      | Data downloaded from CPAP machine or medical equipment company or review of electronic health record |
| Troussiere et al. (2014) [35]           | Observational study                               | Mild to moderate AD with OSA | AHI $\geq 30$ diagnosed by video-PSG and suggestive clinical symptoms  | France    | 23 (9)                             | 73.4 (CPAP group)<br>77.6 (non-CPAP group)<br>72.1 | 4.1 years      | Not recorded   |
| Wang et al. (2020) [31] <sup>a</sup>    | Secondary analysis of Richards et al. (2019)      | MCI with OSA                 | AHI 10–14 diagnosed by PSG   | USA       | 17 (9)                             | 72.1   | 1 year         | Hidden sensors in CPAP machine   |

Abbreviations: AD = Alzheimer's disease; AHI = apnoea-hypopnoea index; CPAP = continuous positive airway pressure; HCPCS = Healthcare Common Procedure Coding System; ICD-9 = International Classification of Diseases-9; MCI = mild cognitive impairment; PSG = polysomnography.

<sup>a</sup> Secondary analysis data is not included in the main review analyses.

<sup>b</sup> Data from Dunietz et al. [34] is reported separate to the main review analyses.

Cohen's kappa inter-rater reliability calculation was 0.36 between the two reviewers which is classified as 'fair' agreement.

Risk of bias for all retained studies was also assessed using the Cochrane Collaboration's tool for assessing risk of bias, where signalling questions were followed to reach a consensus of "low", "moderate" or "high" bias [27]. Four reviewers (CO, VG, HL and DW) conducted this analysis independently before reaching joint consensus. For risk of bias, inter-rater reliability was calculated with Cohen's Kappa Coefficient which was 0.62 which is classified as a 'substantial' agreement.

Five reviewers (CO, AB, BB, HL and DW) cross-checked the data extracted by completing the data extraction table independently and coming to a joint consensus on the data.

## 2.9. Data synthesis and analysis

The diverse nature of the data across studies, in particular the reporting methods of adherence, resulted in a meta-analysis not being possible, therefore a narrative synthesis was performed.

## 3. Results

### 3.1. Search results

The search identified 1705 records in total. 136 full texts were reviewed and 125 were excluded. Excluded papers included predominantly review articles (N = 49) and studies with ineligible populations (N = 26). Relevant reviews were reference checked to ensure no relevant studies were missed out of this review. 11 articles were retained in the final review (see Fig. 1).

### 3.2. Study characteristics

The study characteristics are summarised in Table 1. Four of the retained articles were secondary analyses [28–31] of two other retained studies using participants from the same cohorts [32,33]. Only unique participants were analysed in the present review. The studies were conducted in four different countries (France, Italy, the United States and Australia). Data from Dunietz et al. is reported separately to the main analyses, due to the study not meeting all inclusion criteria stated in Sections 2.1 and 2.2 [34]. The study investigated all PAP treatment

**Table 2**  
Demographics and mean scores of cognitive and sleep assessments.

| Demographics        | Data available for total no. of participants | Value   |
|---------------------|--|---|
| Female gender n (%) | N = 278                                      | 100 (36%)   |
| Mean age (years)    | N = 255                                      | 72.1  |
| Race (%)            | N = 202                                      | 149 Caucasian (74%)<br>23 African American (11%)<br>1 Pacific Islander (0.5%)<br>29 other/unknown (14%) |
| MMSE (range 0–30)   | N = 159                                      | 26.5  |
| CDR (range 0–3)     | N = 120                                      | 1.38  |
| ESS (range 0–24)    | N = 174                                      | 9   |
| AHI (events/h)      | N = 255                                      | 27.7  |

Abbreviations: AHI = Apnoea-Hypopnoea Index; CDR = Clinical Dementia Rating; ESS = Epworth Sleepiness Scale; MMSE = Mini-Mental State Examination.

rather than CPAP exclusively.

There were 278 unique participants in this review: 187 MCI participants and 91 AD participants. Table 2 summarises the demographics and mean scores of cognitive and sleep assessments of the review population. A weighted mean is reported to account for the varying number of participants across the studies.

The mean age of 255 participants across retained studies was 72.1 years (excluding Troussiere et al., 2014 due to median age reported [35]). Baseline cognition was measured using the mini-mental state examination (MMSE) in five studies (excluding Troussiere et al., 2014 due to median score reported [35]) and the clinical dementia rating (CDR) in two studies. All retained studies reported the apnoea-hypopnoea index (AHI) for OSA severity and four studies reported baseline Epworth Sleepiness Scale (ESS) for subjective sleepiness.

Education was reported in all studies with varying methods. Ancoli-Israel et al., Liguori et al. and Hoyos et al. had a mean education of 13.2 years across their cohorts [32,36,37]. Skiba et al. and Richards et al., combined, reported 89/113 (79%) participants with education beyond high school level [17,33]. Finally, Troussiere et al. reported 10/23 participants with education beyond primary level [35].

### 3.3. Clinical characteristics

The mean BMI scores among 254 participants was 28.5 kg/m<sup>2</sup> (range: 25–30.3 kg/m<sup>2</sup>), thus on average participants were classified as overweight. Information on diabetes and hypertension was available for four studies – Richards et al.; Skiba et al.; Troussiere et al. and Hoyos et al. [17,33,35,37]. Collectively, they reported diabetes in 54 (27%) participants and hypertension in 176 (87%) participants. Furthermore, cardiovascular disease was reported by Richards et al., Troussiere et al. and Hoyos et al.; a total of 47 (44%) of participants were found to have cardiovascular disease [33,35,37].

### 3.4. Cognitive diagnosis criteria and severity

Cognitive diagnostic criteria and severity varied amongst studies, and the latter is summarised in Table 1. For the diagnosis of AD, the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) – Ancoli-Israel et al., the National Institute on Aging and Alzheimer's Association (NIA-AA) – Troussiere et al. and the core clinical and biomarker criteria – Liguori et al. were used [35,36]. The Peterson criteria – Richards et al. and Hoyos et al., the Clinical Dementia Rating scale (CDR) and Consortium to Establish a Registry for

Alzheimer's Disease (CERAD) modified with other tests – Skiba et al. and the core clinical and biomarker criteria – Liguori et al., were used to define MCI [17,33,36,37].

### 3.5. Adverse events

Adverse events were reported in two studies. Richards et al. stated 5 potential adverse events in their trial which occurred in the CPAP adherent group, but none were deemed related to CPAP treatment [33]. Hoyos et al. reported 3 serious adverse events and one non-serious adverse event, similarly, all events occurred in the treatment group [37].

### 3.6. Quality of studies and risk of bias

Tables 3 and 4 summarises the results of the quality appraisal and bias assessment. Three of the retained studies were found to have low quality for two or more questions on their appraisals, and three studies were found to have high risk of bias.

### 3.7. Outcome measurement

Most studies used hidden clocks or sensors in CPAP machines to record usage (see Table 1). CPAP use was reported in 3 studies as the average number of hours of use per night across the treatment period. Ancoli-Israel et al. reported average CPAP use in the therapeutic group as 5.8 h/night for 73% of the nights [32]. Skiba et al. demonstrated median CPAP use to be 3.9 h for the overall sample population [17]. Finally, Hoyos et al. reported average use as 3.2 h/night for the overall population and 6.3 h/night in the adherent group (additional information requested from authors) [37]. The remaining studies did not report any CPAP use metrics but reported the number of individuals adherent vs. non-adherent using 4 h/night as a cut-off (summarised in Table 5).

In the 5 studies using a binary cut-off for adherence, a total of 107 participants were adherent (MCI = 85 and AD = 22) and 89 participants were non-adherent (MCI = 78 and AD = 11). Therefore, out of 226 participants; 47.3% were adherent, 39.4% were non-adherent and 13.3% had no CPAP use due to participant refusal or treatment having never started. Of the 187 MCI participants, 85 (45%) were adherent, 78 (42%) were non-adherent and 24 (13%) had no CPAP use. Of the 39 AD participants, 22 (56.4%) were adherent, 11 (28.2%) were non-adherent and 6 (15.4%) refused CPAP.

Dunietz et al. included 1520 participants (443 MCI, 1077 AD), whereby bivariate analyses estimated 1048 participants were treated with PAP and 68% of participants (240 MCI, 469 AD) were adherent and 32% (77 MCI, 262 AD) were non-adherent [34]. The study utilised data derived from Medicare fee-for-service claim files. Participants were labelled as PAP treated if there were one or more PAP Healthcare Common Procedure Coding System (HCPCS) claims codes recorded, and they were further classified as adherent if two more HCPCS claims were recorded for PAP supplies, separated by at least 1 month during the 3-year study period.

### 3.8. CPAP adherence interventions

A detailed summary of studies incorporating additional adherence interventions is listed in Table 6. Ancoli-Israel et al., Hoyos et al. and Richards et al. all provided additional support to encourage adherence through various interventions [32,33,37]. Results on the effectiveness of interventions was not specifically investigated by studies.

## 4. Discussion

This study systematically reviewed CPAP use and adherence rates in participants with OSA and comorbid MCI or AD. Extensive searches across 8 electronic databases revealed only 6 studies containing 278 unique participants (187 MCI and 91 AD) and only half of these studies

**Table 3**  
Joanna Briggs Institute checklist results for quality appraisal.

|                |     |
|----------------|-----|
| Yes            |     |
| Unclear        |     |
| No             |     |
| Not applicable | N/A |

|    | Questions  | Ancoli-Israel | Richards | Troussiere | Skiba | Liguori | Hoyos |
|----|--|---------------|----------|------------|-------|---------|-------|
| 1  | Is it clear in the study what is the cause and what is the effect?   | N/A           |          |            | N/A   | N/A     | N/A   |
| 2  | Were the participants included similar at baseline?  |               |          |            |       |         |       |
| 3  | Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? | N/A           |          |            | N/A   | N/A     | N/A   |
| 4  | Was there a control group?   | N/A           |          |            | N/A   | N/A     | N/A   |
| 5  | Were there multiple measurements of the outcome both pre and post the intervention/exposure?   | N/A           |          |            | N/A   | N/A     | N/A   |
| 6  | Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?        |               |          |            |       |         |       |
| 7  | Were the outcomes of participants included in any comparisons measured in the same way?  | N/A           |          |            | N/A   | N/A     | N/A   |
| 8  | Were outcomes measured in a reliable way?  |               |          |            |       |         |       |
| 9  | Was appropriate statistical analysis used?   |               |          |            |       |         |       |
| 10 | Were the exposures measured similarly to assign people to both exposed and unexposed groups?   | N/A           | N/A      | N/A        |       |         | N/A   |
| 11 | Was the exposure measured in a valid and reliable way?   | N/A           | N/A      | N/A        |       |         | N/A   |
| 12 | Were confounding factors identified?   | N/A           | N/A      | N/A        |       |         | N/A   |
| 13 | Were strategies to deal with confounding factors stated?   | N/A           | N/A      | N/A        |       |         | N/A   |
| 14 | Were the groups/participants free of the outcome at the start of the study?  | N/A           | N/A      | N/A        |       |         | N/A   |
| 15 | Was the follow up time reported and sufficient to be long enough for outcomes to occur?  | N/A           | N/A      | N/A        |       |         | N/A   |
| 16 | Were strategies to address incomplete follow up utilized?  | N/A           | N/A      | N/A        |       |         | N/A   |
| 17 | Was true randomisation used for assignment of participants to treatment groups?  |               | N/A      | N/A        | N/A   | N/A     |       |
| 18 | Was allocation to treatment groups concealed?  |               | N/A      | N/A        | N/A   | N/A     |       |
| 19 | Were participants blind to treatment assignment?   |               | N/A      | N/A        | N/A   | N/A     |       |
| 20 | Were those delivering treatment blind to treatment assignment?   |               | N/A      | N/A        | N/A   | N/A     |       |
| 21 | Were outcome assessors blind to treatment assignment?  |               | N/A      | N/A        | N/A   | N/A     |       |
| 22 | Were treatment groups treated identically other than the intervention of interest?   |               | N/A      | N/A        | N/A   | N/A     |       |
| 23 | Were participants analyzed in the groups to which they were randomised?  |               | N/A      | N/A        | N/A   | N/A     |       |
| 24 | Were outcomes measure in the same way for treatment groups?  |               | N/A      | N/A        | N/A   | N/A     |       |
| 25 | Was the trial design appropriate, and any deviation from the standard RCT design accounted for in the conduct and analysis of the trial? |               | N/A      | N/A        | N/A   | N/A     |       |

Questions 1, 2, 3, 4, 5, 6, 7, 8 and 9 are for the Quasi experimental studies. Questions 2, 6, 8, 9, 10, 11, 12, 13, 14, 15 and 16 are for the Cohort studies. Questions 2, 6, 8, 9, 17, 18, 19, 20, 21, 22, 23, 24 and 25 are for Randomised studies.

**Table 4**  
Cochrane’s Risk of Bias for randomised and non-randomised studies.

|                |     |
|----------------|-----|
| Low bias       | ●   |
| Moderate bias  | ●   |
| High bias      | ●   |
| Not applicable | N/A |

|                  | Ancoli-Israel | Richards | Troussiere | Skiba | Liguori | Hoyos |
|------------------|---------------|----------|------------|-------|---------|-------|
| Allocation bias  | ●             | N/A      | N/A        | N/A   | N/A     | ●     |
| Selection bias   | ●             | ●        | ●          | ●     | ●       | ●     |
| Performance bias | ●             | N/A      | N/A        | N/A   | N/A     | ●     |
| Detection bias   | ●             | ●        | ●          | ●     | ●       | ●     |
| Attrition bias   | ●             | ●        | ●          | ●     | ●       | ●     |
| Reporting bias   | ●             | ●        | ●          | ●     | ●       | ●     |
| Confounding bias | N/A           | ●        | ●          | ●     | ●       | N/A   |
| Information bias | N/A           | ●        | ●          | ●     | ●       | N/A   |
| Other bias       | ●             | ●        | ●          | ●     | ●       | N/A   |

**Table 5**  
The total number of adherent and non-adherent participants in 5 of the retained studies.

| Author                                | No. of adherent participants | No. of non-adherent participants |
|---------------------------------------|------------------------------|----------------------------------|
| Hoyos et al. (2022) <sup>a</sup> [37] | 10 (34%)                     | 19 (66%)                         |
| Liguori et al. (2021) [36]            | 12 (50%)                     | 12 (50%)                         |
| Richards et al. (2019) [33]           | 29 (54%)                     | 25 (46%)                         |
| Skiba et al. (2020) [17]              | 42 (44%)                     | 30 (31%)                         |
| Troussière et al. (2014) [35]         | 14 (61%)                     | 3 (13%)                          |
| <b>Total</b>                          | <b>107</b>                   | <b>89</b>                        |

<sup>a</sup> Data requested from authors.

**Table 6**  
Adherence interventions incorporated by retained studies.

| Study                                   | Adherence intervention   |
|---|--|
| <b>Ancoli-Israel et al. (2008)</b> [32] | Research associate visited participant’s home weekly to encourage participation  |
| <b>Hoyos et al. (2022)</b> [37]         | CPAP therapist provided support to participants throughout the study   |
| <b>Richards et al. (2019)</b> [33]      | <i>CPAP Adherence Intervention (CAI)</i><br>Project staff provided CAI by phone and face-to-face for a total of 12–14 h over 1-year, involving patient education, motivational interviews and follow-up visits, as well as social support from study partner.<br><i>Attention Control Intervention</i><br>Administered by phone and face-to-face if patients chose not to continue CPAP or their CPAP was taken away by their insurance company for non-use. Involves patient education motivational interviewing, building rapport and social support from study partner. |

Abbreviations: CAI = CPAP adherence intervention.

reported adherence metrics. 5 studies reported approximately half of the participants were adherent to CPAP (using a cut-off of 4 h/night). Average nightly CPAP use ranged from 3.2 to 6.3 h/night in 3 studies.

Reporting adherence as a binary outcome using a cut-off of 4 h/night is commonly used across the literature, partly due to US insurance companies basing coverage of CPAP treatment on adherence  $\geq 4$  h/night for at least 70% of nights during a 30-day period during the first 3 months [38]. Given that adherence is not a binary outcome, reporting CPAP using this method alone may disregard important information on the strength of association between adherence and positive outcomes. Indeed, evidence suggests a dose-dependent response to exist between CPAP use and clinical improvement, with some studies reporting normalisation of ESS scores despite less than 4 h of CPAP usage [39,40]. Within the present review, Ancoli-Israel et al., along with Skiba et al. and Hoyos et al., all reported overall group adherence as the mean number of hours of CPAP use per night [17,32,37]. Overall, standardised criteria for reporting adherence, perhaps including both the number of adherent vs. non-adherent participants as well as overall duration of use would facilitate future comparison of data and subsequent meta-analyses [41].

Of the retained studies, adherence levels were low albeit consistent with the population of OSA patients treated with CPAP who are not known to have cognitive impairment. In studies using a 4 h/night cut-off, CPAP adherence rates in older adults have been reported to range between 38% and 69.7% [42–44]. When stratified by age group, a linear decline in adherence is seen with increasing age, with rates reaching as low as 23.8% in those 80 years and older [42]. Within clinical settings, data is somewhat limited, but from 5 sleep centres in the UK adherence at 3 months (as defined by 4 h/night) ranged between 27 and 51%, although we note that the age range in this study was much lower (38–65 years) [45].

Although variable, CPAP use in OSA has been linked to improved cognition [29,31,37]. This, along with the theoretical potential for CPAP to help prevent accumulation of AD pathology, highlights the need for tailored protocols to enhance OSA treatment. Perhaps through improving CPAP adherence and/or incorporating multimodal treatment plans, thereby facilitating long-term trials of OSA treatment in individuals with potentially progressive cognitive impairment. The papers included in the present review did not specifically assess the benefit of interventions to improve adherence. Within the general literature, adherence interventions including behavioural interventions, such as

### Practice points

1. CPAP is the gold standard treatment for OSA and should be considered in individuals with cognitive impairment and OSA.
2. OSA has been demonstrated to potentially affect cognitive function and cognitive trajectory and measures to enhance adherence such as telemedicine may improve adherence.
3. Reporting CPAP use as a continuous variable has more potential utility than just reporting adherence rates in MCI and AD groups.
4. This review has found that adherence is low amongst OSA patients with comorbid AD or MCI, albeit comparable to the general older population.

cognitive behavioural therapy (CBT) [46] and motivational enhancement therapy (MET) [47], telemonitoring [48], patient education [49], as well as peer buddy system (PBS) [50] have been extensively investigated. A recent meta-analysis assessed the effectiveness of adherence interventions and found telemedicine to improve mean hours of CPAP use with moderate certainty of evidence, both behavioural/supportive interventions and MET also had positive effects on adherence however the certainty of evidence was low [51]. Specific to the older population (mean age >60), Bakker et al. demonstrated MET to significantly improve adherence measured at 6 and 12 months [52]. Furthermore, both telemonitoring and telehealth (audio-/videotaped patient education content) demonstrated positive impact on adherence and serve as cost-effective strategies [53,54]. In fact, the use of telemonitoring has been proposed to reduce the cost of OSA management by 17% (estimated calculations from data based on the general Japanese population) [53]. Extrapolating from patients with OSA and cardiovascular disease, there are potentially large cuts to health-care related costs if future trials can improve adherence [55].

Specific to the present review, it is worth noting that 3 of the retained studies reported using additional interventions with varying methods, as detailed in Table 6. Therefore, an obvious confounder is the lack of controlled adherence interventions used across studies which very likely would affect levels of compliance reported. It is also worth considering that even in studies which did not utilise additional adherence interventions there is an inherently higher level of participant monitoring in research studies compared to typical clinical monitoring, which may have increased adherence, limiting real-world applicability.

We predicted CPAP use may be lower in individuals with cognitive impairment due to the behavioural and psychological symptoms which arise as a result of dementia including apathy, depression, irritability and anxiety [25]. Indeed, medication adherence in individuals with dementia, including MCI and AD, has been previously demonstrated to be very low; ranging from 17% to 42% [56]. Hence, it is not clear why CPAP adherence is not markedly lower in MCI/AD compared to populations without documented cognitive impairment. Although we note that cognition may not have always been tested in studies of OSA in older people, and given the prevalence of AD, it may be possible that these participants have undiagnosed cognitive impairment therefore contributing to less marked difference between groups. OSA underdiagnosis in the general population likely extends to dementia cohorts, which might in part be contributed by clinician apprehension in referring dementia patients for OSA investigation or treatment due to poor adherence as a limiting factor. However, data from the present review provides support for clinicians in referring individuals with dementia for OSA management. This is further supported by the fact that administration of CPAP carries little side effects, contrasted by the vast number of adverse effects caused by acetylcholinesterase inhibitors and memantine.

Encouragingly, a recent study by Richards et al., which was published after completion of our systematic review, revealed CPAP adherence rates in 174 participants with amnesic MCI and moderate to severe OSA to be 73.6%, with mean daily use of 5.15 h at 3 months. Factors including participation in a tailored CPAP adherence intervention, white race and moderate OSA were all associated with higher CPAP

use at 3 months. These results echo the findings of our review and add further support to prescribing CPAP for individuals with cognitive impairment [57].

Dunietz et al. found higher adherence rates compared to the retained studies, however it is crucial to note that the authors labelled participants as 'PAP treated' based on the presence of one or more Medicare claims codes, and defined adherence if 2 additional claims were made for PAP supplies during the study period [34]. Not only does the adherence criteria not allow for quantification of hours of CPAP use, their treatment and adherence criteria may result in misclassification of participants to adherent or non-adherent groups.

The retained studies also varied in the level of detail reported on various study outcomes and interventions. Adverse events were reported in only two studies and side effects experienced by CPAP use was not mentioned by any studies. Similarly, there was a lack of detail reported on CPAP equipment such as mask type and pressure setting, which are key factors that greatly affect adherence. Moreover, the retained studies differed in study duration, ranging from 6 weeks to 4.1 years. It is not clear how adherence may vary with treatment duration; hence, long-term, well-powered studies using standardised adherence reporting methods and clearly defined interventions and outcomes are needed.

### 5. Limitations

Limitations of the retained studies include small sample size, ranging from 23 to 96 participants, as well as high risk of bias found in four of the included studies. There was also a lack of racial diversity, as 74% of participants were white. Existing research has highlighted significant racial disparity which exists for both OSA and AD. Lower CPAP adherence rates are consistently reported amongst Black and Hispanic groups [58–60]. Hence, better representation is needed to accurately reflect adherence rates of the general population.

A further limitation of the present review is the variation in severity of OSA or MCI and AD recruited participants. Most studies used AHI for OSA diagnosis, however two studies used an AHI cut-off of 10, whereas three studies used a cut-off of 5, 15 and 30. This is particularly relevant as OSA severity has been demonstrated to affect adherence levels [61]. Regarding cognition, according to the MMSE and CDR assessments, participants with more severe dementia were generally not included in the studies, thereby limiting inference about those with more severe cognitive decline. Hence, future designs of clinical trials should include a wide range of both dementia and OSA severity.

### 6. Conclusion

Adherence to CPAP in individuals with OSA and comorbid MCI or AD is low, but perhaps not significantly lower than in older individuals without cognitive impairment. This review provides support for the notion that individuals with cognitive impairment or dementia should not be excluded from the consideration of initiating CPAP treatment. Given the potential to alleviate accumulation of proteins that lead to AD dementia and enhance cognition, normalizing sleep-related breathing and assessing the long-term impact on brain health should be a research priority. Future research into developing tailored treatment protocols by



## Research agenda

1. Short-term research should focus on whether CPAP improves cognition and quality of life on individuals with AD – and if so, what is the minimum adherence required for benefit in terms of average duration of use and number of nights  $\geq 4$  h use.
2. Long-term research studies should ask whether CPAP delays the accumulation of AD pathology and consequent cognitive/functional decline and if so, what is the minimum adherence required for benefit in terms of average duration of use and number of nights  $\geq 4$  h use.
3. Future research studies should also ensure to recruit patients of diverse backgrounds to address the racial and sex disparities which continue to exist in healthcare.

incorporating CPAP adherence interventions may be key to optimising OSA management.

## Data availability statement

Data available on request from the authors.

## Acknowledgements

This research was supported by Above and Beyond Charity.  
Thanks to Southmead Library, North Bristol NHS Trust.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.smr.2023.101869>.

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