BMJ Open

Effect of CPAP on cognitive function in stroke patients with obstructive sleep apnoea: a meta-analysis of randomised controlled trials

Yingxia Yang,[1] Weiqi Wu,[1] Honghong Huang,[1] Haining Wu,[1] Junying Huang,[1] Liya Li,[2] Lingxing Wang [1]

¹Department of Neurology, Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, China
²Department of Ultrasound, Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, China

Correspondence to
Dr Lingxing Wang;
15880718729@139.com and
Mrs Liya Li;
lly7473@fjmu.edu.cn

ABSTRACT

Objective To investigate the effect of continuous airway pressure (CPAP) treatment on cognitive function in stroke patients with obstructive sleep apnoea (OSA) by exploring randomised controlled trials (RCTs).

Methods Published RCTs that assessed the therapeutic effects of CPAP on cognition in stroke patients with OSA, compared with controls or sham CPAP, were included. Electronic databases, including MEDLINE, Embase and Cochrane library, were searched in October 2020 and October 2021. Risk of bias was assessed using the Cochrane collaboration tools. A random effects or fixed effects model was used according to heterogeneity. The outcomes were global cognitive gain, improvement in cognitive domain and subjective sleepiness.

Results 7 RCTs, including 327 participants, comparing CPAP with control or sham CPAP treatment were included. 6 RCTs with 270 participants reported results related to global cognition, and CPAP treatment had no significant effects on global cognitive gain in stroke patients with OSA (standardised mean difference (SMD), 0.18; 95% CI, −0.07 to 0.42; p=0.153). A subgroup analysis showed that an early start to (<2 weeks post stroke) CPAP treatment after stroke significantly improved global cognition (SMD, 0.66; 95% CI, 0.18 to 1.14; p=0.007), which was not found in the case of a delayed start to CPAP treatment. However, CPAP did not significantly help with memory, language, attention or executive function. Moreover, CPAP therapy significantly alleviated subjective sleepiness (SMD, −0.73; 95% CI, −1.15 to −0.32; p≤0.001).

Conclusions Early initiation of CPAP treatment might contribute to improvement in global cognition in stroke patients with OSA. This study had the following limitations: the sample size in each included study was relatively small; the scales related to cognitive assessment or subjective sleepiness were inconsistent; and the methodological quality was not high. Future trials should focus on including a greater number of stroke patients with OSA undergoing CPAP treatment.

PROSPERO registration number CRD42020214709.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a meta-analysis of the effect of continuous positive airway pressure (CPAP) therapy on cognitive function in stroke patients with obstructive sleep apnoea (OSA).
⇒ We question whether CPAP therapy can improve the cognitive function of poststroke patients with OSA, and further assess whether CPAP initiation time, treatment time or OSA severity influences the effect.
⇒ Due to limitations in the literature, such as difficulties with diagnosis of OSA and difficulties with acceptance of CPAP therapy in patients who had a stroke, the included sample size is relatively small, which limits the subgroup analysis of specific cognitive domains in our meta-analysis.

hypoxia and sleep fragmentation.[1] OSA can moderately or markedly affect cognition in many domains, including vigilance, attention, memory and executive function.[2] OSA is also related to a high risk of cardiovascular events, including coronary heart disease, heart failure and stroke.[3] It has been considered an independent risk factor for stroke.[4] Moreover, the prevalence of OSA in patients with stroke is about 50%–80%, which is four-fold to sixfold higher than that in the general population.[4 5] OSA is associated with exacerbated neurologic functions and impaired cognition after stroke, and with a high risk of recurrence of stroke.[6 7]

Continuous positive airway pressure (CPAP) is an effective treatment in OSA as it alleviates apnoea and hypopnea during sleep and decreases sleep fragment, hypoxia and daytime sleepiness. In addition, the effect of CPAP in OSA has been proved to be time dependent.[8] CPAP is also able to partially improve cognitive impairment in OSA, especially in attention and speed of information processing,[9] and severe OSA alone benefited from CPAP treatment, thereby indicating that

INTRODUCTION

Obstructive sleep apnoea (OSA) is characterised by repeated collapse of the upper airway, thereby leading to chronic intermittent

the effect of CPAP on cognition might be affected by the severity of OSA. On the other hand, studies[10 11] also show that CPAP treatment in patients who had a stroke may improve motor function and disability and reduce stroke severity; it is interesting that this effect was not affected by the initiation time of CPAP treatment after stroke. In 2014, the American Heart Association/American Stroke Association added the identification and treatment of OSA in stroke survivors to stroke guidelines as IIb recommendation and b level evidence.[12] Moreover, approximately one-third of stroke survivors have cognitive impairment[13] and stroke patients with OSA had more impairment in cognitive domains of attention, executive function or visuoperception.[6] However, the reported effect of CPAP on cognitive function in stroke patients with OSA has remained inconsistent. Several studies[14–16] have reported that CPAP treatment had cognitive improvement in stroke patients with OSA, and the increased cognitive domains included attention, executive function and calculation, but not memory, language, vigilance or orientation. Other studies[17–20] found negative cognitive improvement from CPAP therapy in stroke patients with OSA. Hence, we sought to systematically review and analyse the effects of CPAP therapy on cognitive function in patients with stroke who have OSA, and to further assess whether CPAP initiation time, treatment time or OSA severity influences the effect.

METHODS
Search strategy
We searched databases including PubMed, EMBASE and the Cochrane Library for randomised controlled trial (RCT) articles in English, published between 1980 and October 2020, and the search was repeated in October 2021 (online supplemental tables 1–3). The search words included (sleep disordered breathing OR sleep apnea OR upper airway resistance) AND (cognition OR cognitive OR dementia OR memory OR neuropsychological OR neuropsychology) AND (stroke OR cerebrovascular OR transient ischemic attack) AND (positive airway pressure OR PAP OR treatment OR therapy OR management). Reference lists of pertinent articles were also manually searched to further find research that could possibly be included. We also performed grey literature searches using a number of common websites, such as GreyNet International, Open Grey, Grey Literature Report and others, although none of the relevant grey literature was found. Two investigators (LW and YY) independently searched and screened the articles. Any discrepancy in selection was resolved by the third investigator (HW)

Inclusion/exclusion criteria
We included: (1) articles including adult patients diagnosed as having a transient ischaemic attack or stroke (by neurologists or using any recognised diagnostic criteria) with OSA (defined by apnoea hypopnea index, respiratory oxygen index or oxygen desaturation index); (2)

RCTs; (3) articles on comparison of CPAP therapy with control or sham CPAP treatment; (4) articles in which cognitive function, including global and specific cognitive domains, such as attention, memory, executive function or language, was effectively evaluated (the same cognitive assessment scales were used at the baseline and follow-up time points or the difference score was provided between the follow-up and baseline time points). Articles were excluded if there were no valid data, if data could not be transformed for appropriate calculations, meeting communications or duplicated articles were also excluded. This meta-analysis and systematic review was PROSPERO registered (CRD42020214709).

Data extraction and quality assessment
Two investigators (LW and YY) independently extracted the information. If there was any disagreement, consensus was reached by discussion or by consulting the third investigator (LL). The extracted information included the author, publication year, the country in which the research was conducted, participant numbers, clinical characteristics, CPAP initial time after stroke, baseline Apnea–Hypopnea Index (AHI), duration of follow-up, dropout, time period of CPAP use, main outcome (cognitive function including global cognition and specific cognitive domain) and additional outcome (subjective sleepiness). The main outcome was cognitive function and the additional outcome was the sleepiness-related scale.

The Cochrane collaboration's risk-of-bias tool[21] was used to assess the quality of included articles by LW and YY. The items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. The risk was graded as low, high or unclear. If every one of the above-mentioned domains was graded as unclear or low risk, the article was considered to have a low risk of bias. If one or more than one above domains were graded as high risk, the article was considered to have a high risk of bias.

Statistical analysis
The statistical analysis was performed using STATA software (StataCorp LLC, Texas, USA). A number of participants and mean values with SD were collected for continuous data. Gain of global cognition, specific cognitive domain (executive function, language) and sleepiness were assessed, and the gain of each variable was defined as the difference score between the follow-up and baseline time points. If a different scale was used to assess cognition or subjective sleepiness, results were expressed as a standardised mean difference (SMD). If the same scale was used, results were presented as a weighted mean difference. P value of <0.05 was considered statistically significant. If there were several follow-up time points, the longest follow-up period was used. An I^2 test was used to evaluate heterogeneity, and the values of $I^2>25\%$, 50%
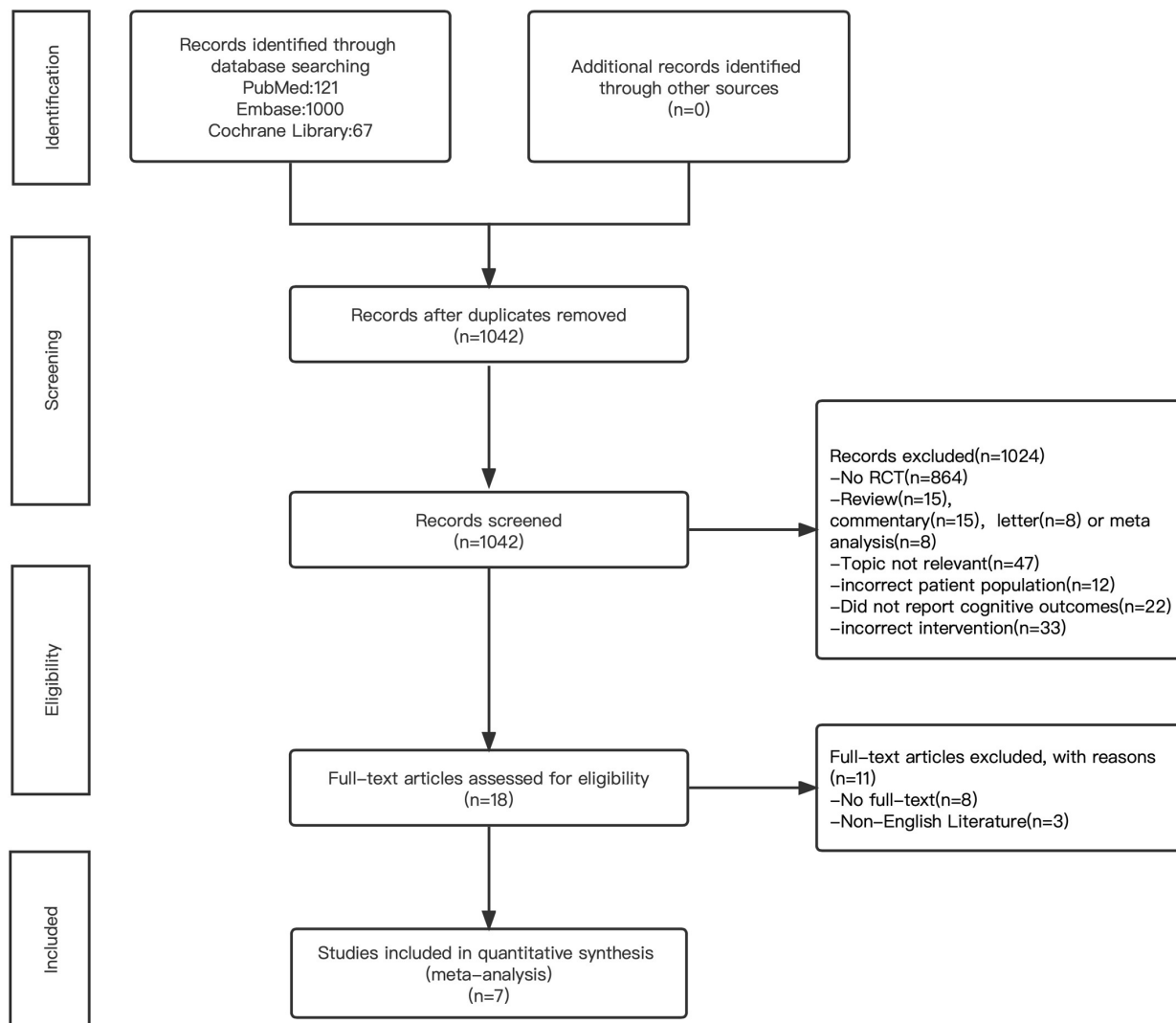
Figure 1 Flow diagram representing the literature search. RCT, randomised controlled trial.

and 75% were considered as low, moderate and high heterogeneity, respectively. When there was moderate or high heterogeneity, a DerSimonian-Laird random effect model was used, and a sensitivity analysis was performed to identify the source of heterogeneity. Otherwise, a fixed effect model was used. A subgroup analysis was performed based on CPAP treatment initiation after stroke, OSA severity, CPAP treatment time and CPAP duration. A funnel plot and Egger's test was used for publication bias, as appropriate.

Patient and public involvement
No patient involved.

RESULTS
Search results
The search process is shown in figure 1. A total of 1188 articles were identified after the initial search. After removing duplicate articles, 1042 articles were screened by reading the title and abstract, and 18 articles were selected for full-text assessment. Further exclusion of 11

articles was done and a final set of 7 articles was included for the analysis.

Study characteristics
The clinical characteristics of the included RCTs are shown in table 1. Among these studies, one each was published in 2001,[17] 2006[18] and 2011,[19] and the other four were published between 2016 and 2019.[14–16 20] The sample size in each RCT varied between 36 and 70 participants, and 327 participants were included in the end, with 167 in the CPAP group and 160 in the control/sham group. A total of six RCTs[14–17 19 20] distinguished between ischaemic and haemorrhagic strokes. A total of six studies[14 16–20] compared CPAP to the usual care and one[15] compared it to sham CPAP. Except for one study[15] which performed a sleep test for OSA after the initiation of sham or active CPAP treatment, the diagnosis of OSA in the other six studies[14 16–20] depended on polysomnography or a polygraphic monitor before treatment. Except for one study[15] which did not assess the mean baseline AHI, the AHI was >15 or ≥15[16 17 19 20] in four RCTs,

Table 1 Characteristics of included RCTs

Study	Country	Participants, N	CPAP group, n	Age, years	Sex male, n(%)	BMI (km/m²)	Hypertension, n (%)	Diabetes melitus, n (%)	Currently smoking, n (%)	Ischaemic stroke, n (%)	CPAP initial after stroke	Follow-up	Dropout, n (%)	AHI	CPAP hour/night	CPAP duration
Kim et al[14]	Korea	40	20	CPAP 63.3±13.1	CPAP 13 (65)	CPAP 23.3±3.7	CPAP 13 (65)	CPAP 4 (20)	–	CPAP 14 (70)	7 days–6 months	3 weeks	None	≥20	>4 hour/day	3 weeks
				Control 66.9±12.3	Control 16 (80)	Control 24.4±3.9	Control 15 (65)	Control 7 (35)		Control 16 (80)						
Gupta et al[20]	India	70	34	CPAP 53.41±9.85	CPAP 24 (80)	CPAP 24.85±4.98	CPAP 21 (70.00)	CPAP 8 (26.67)	CPAP 10 (33.33)	CPAP 23 (76.67)	6 weeks–6 months	3 months, 6 months, 12 months	None	>15	4.2±1.32 hour/night	3–6 months
				Control 52.69±13.23	Control 33 (82.5)	Control 25.57±3.26	Control 33 (82.50)	Control 8 (20)	Control 19 (47.50)	Control 33 (82.50)			None			
Hsu et al[18]	UK	30	15	CPAP 74 (73–81)	CPAP 11 (73.33)	CPAP 26.8 (21.9–28.5)	–	–	–	–	21–25 days	8 weeks, 6 months	None	≥30	8 weeks : 1.4 hour/night (median 0.16 hour/night)	8 weeks
				Control 73 (65–77)	Control (60)	Control 25.1 (22.1–33.1)							None			
Khot et al[15]	America	40	20	CPAP 55.9±12.1	CPAP 10 (50)	CPAP 31.0±5.7	CPAP 18 (90)	CPAP 6 (30)	CPAP 6 (30)	CPAP 12 (60)	10 (IQR 6–16)	28 days	CPAP 7 (35)	–	3.9±2.7	17 (±9.5) days
				Control 56.5±12.1	Control 12 (60)	Control 28.5±4.0	Control 15 (75)	Control 8 (40)	Control 3 (15)	Control 13 (65)			Control 3 (15)		3.9±1.8	
Ryan et al[19]	Canada	48	25	CPAP 62.8±12.8	CPAP 19 (16/22)	CPAP 28.8±5.3	CPAP 18 (81.8)	CPAP 10 (45.5)	CPAP 7 (32)	CPAP 21 (95.45)	21.5±8.7	4 weeks	CPAP 3 (12)	≥15	4.96±2.25	4 weeks
				Control 60.7±10.3	Control 19 (19/22)	Control 27.3±5.8	Control 15 (68.2)	Control 17 (31.8)	Control 11 (50)	Control 18 (81.82)			Control 1 (4.35)			
Sandberg et al[17]	Sweden	63	33	CPAP 78.1±6.4	CPAP 17 (17/31)	CPAP 24.5±4.1	CPAP 20 (64.52)	CPAP 10 (32.26)	–	CPAP 28 (90.32)	14–28 days	7 days, 28 days	CPAP 2 (6.06)	≥15	4.1±3.6 hour/night (range 0–10.9 hours)	7 days, 28 days
				Control 76.8±7.9	Control 15 (15/28)	Control 24.8±4.8	Control 17 (60.71)	Control 12 (42.86)		Control 23 (82.14)			Control 2 (6.67)			
Aaronson et al[16]	Nederlands	36	20	CPAP 61.1±8.2	CPAP 12 (60.0)	CPAP 28.1±6.4	–	–	–	CPAP 14 (70.0)	23.2 (±12.2)	4 weeks, 2 months	Control 6 (30)	≥15	2.5±2.8 (range, 0–9)	4 weeks
				Control 56.7±8.8	Control 10 (62.5)	Control 25.8±4.7				Control 10 (63.0)			Control 4 (25)			

All participants in the included RCTs had experienced stroke.
Data are presented as ranges, mean±SD or median (IQR) unless otherwise indicated.
AHI, Apnea–Hypopnea Index; BMI, body mass index; CPAP, continuous positive airway pressure; RCT, randomised controlled trial.

Table 2 Assessment of risk of bias

Study	Sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Aaronson et al[16]	Low	Unclear	High	Low	Low	Low	Low
Kim et al[14]	Low	Unclear	High	Low	Unclear	Low	Unclear
Hsu et al[18]	Unclear	Low	High	Low	Unclear	Low	Unclear
Sandberg et al[17]	Low	Low	High	High	Low	Unclear	Unclear
Ryan et al[19]	Low	Low	Low	Low	High	Low	Low
Khot et al[15]	Low	Low	Low	Low	Low	Unclear	Low
Gupta et al[20]	Low	Low	High	Low	Unclear	Low	Low

The risk in each item was graded as low, high or unclear according to Cochrane collaboration's risk-of-bias tool.[21]

≥20[14] in one RCT and ≥30[18] in another RCT. In all the studies, CPAP therapy was started more than 7 days after the stroke. The CPAP adherence time ranged from 1.4 to 4.96 hour per night, and lasted more than 4 hour per night in four studies[14 16 17 19] and less than 4 hour per night in the other three studies.[15 16 18] The CPAP treatment duration and follow-up varied from 1 week to 6 months and 1 week to 1 year, respectively. No dropout was seen in three studies.[14 18 20] In the other four studies,[14 15 17 19] dropout rates varied from 4.35% to 35%.

Risk-of-bias assessment

Table 2 shows the results of bias risk. In the included seven studies, one was considered to have a low risk of bias and the others were considered to have a high risk of bias. In all the included RCTs, only two studies[14 19] declared blinding of the participants and researchers. However, all studies except one[17] blinded the assessors to the outcomes. Egger's test showed no significant publication bias in our meta-analysis, and funnel plots of cognitive function were shown in figure 2.
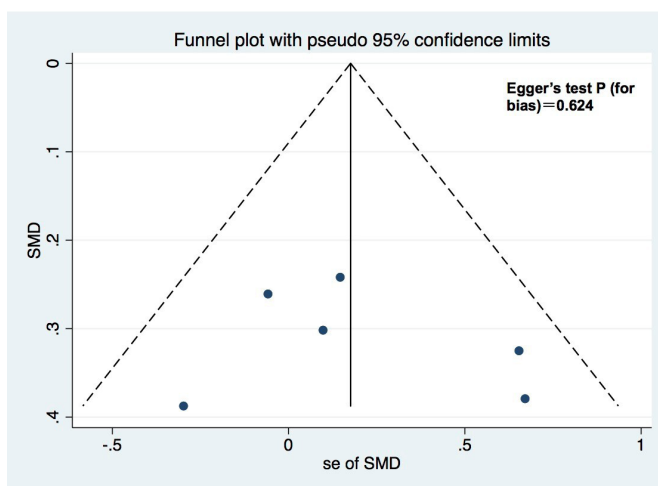

Figure 2 Funnel plot for global cognition in stroke patients with obstructive sleep apnoea. SMD, standardised mean difference.

Cognitive function and subjective sleepiness

Among the seven RCTs, one[15] did not provide results related to global cognition (online supplemental table 4). In the remaining six RCTs (participants=270), CPAP treatment had no significant effect on global cognitive function in stroke patients with OSA, compared with the control/sham group (SMD, 0.18; 95% CI, −0.07 to 0.42; p=0.153; I^2=20.0%; figure 3).

Two RCTs (participants=70) initiated CPAP treatment<2 weeks post stroke, while the other four trials (participants=200) ≥2 weeks post stroke. A subgroup analysis based on the initiation time of CPAP therapy after stroke found that early initiation of CPAP treatment (<2 weeks post stroke) significantly improved global cognition (SMD, 0.66; 95% CI, 0.18 to 1.14; p=0.007; I^2=0.0%; figure 4A), while no cognitive benefit was found in case of delayed (≥2 weeks post stroke) CPAP treatment (SMD, 0.01; 95% CI, −0.26 to 0.29; p=0.916; I^2=0.0%) (figure 4A); there was significant subgroup difference (χ^2=5.14, df=1, p=0.023). In three RCTs (participants=173), AHI was >15, while in the other two trials (participants=67) AHI was ≥20. A subgroup analysis of AHI indicated that no significant global cognitive improvement was found (figure 4B) in moderate (AHI≥15) or severe OSA (AHI≥20), with no significant difference between the subgroups (χ^2=0.08, df=1, p=0.783). Meanwhile, the CPAP usage was ≥4 hour/day in four trials (participants=213), and that in the other two (participants=57) was <4 hour/day. There were three RCTs with ≥4 weeks of CPAP duration and the other three with <4 weeks. Subgroup analysis also showed that neither CPAP usage (≥4 hour/day or <4 hour/day) (figure 4C) nor CPAP duration (≥4 weeks or <4 weeks) (figure 4D) had an impact on global cognition, with no significant difference between the subgroups (CPAP usage: χ^2=0.00, df=1, p=0.970; CPAP duration: χ^2=1.12, df=1, p=0.290).

Moreover, there were 3 RCTs (participants=113) performing attention test, 3 RCTs (participants=146) performing a memory test, 2 RCTs (participants=73) performing an executive function test and 2 participants RCTs (participants=76) performing a language test. No significant improvement was found in specific cognitive
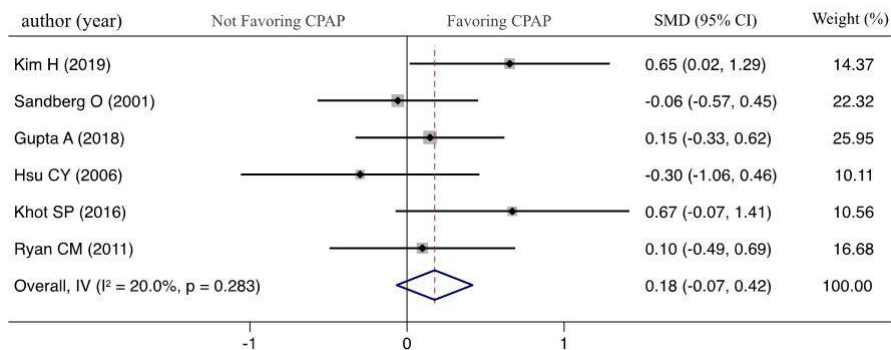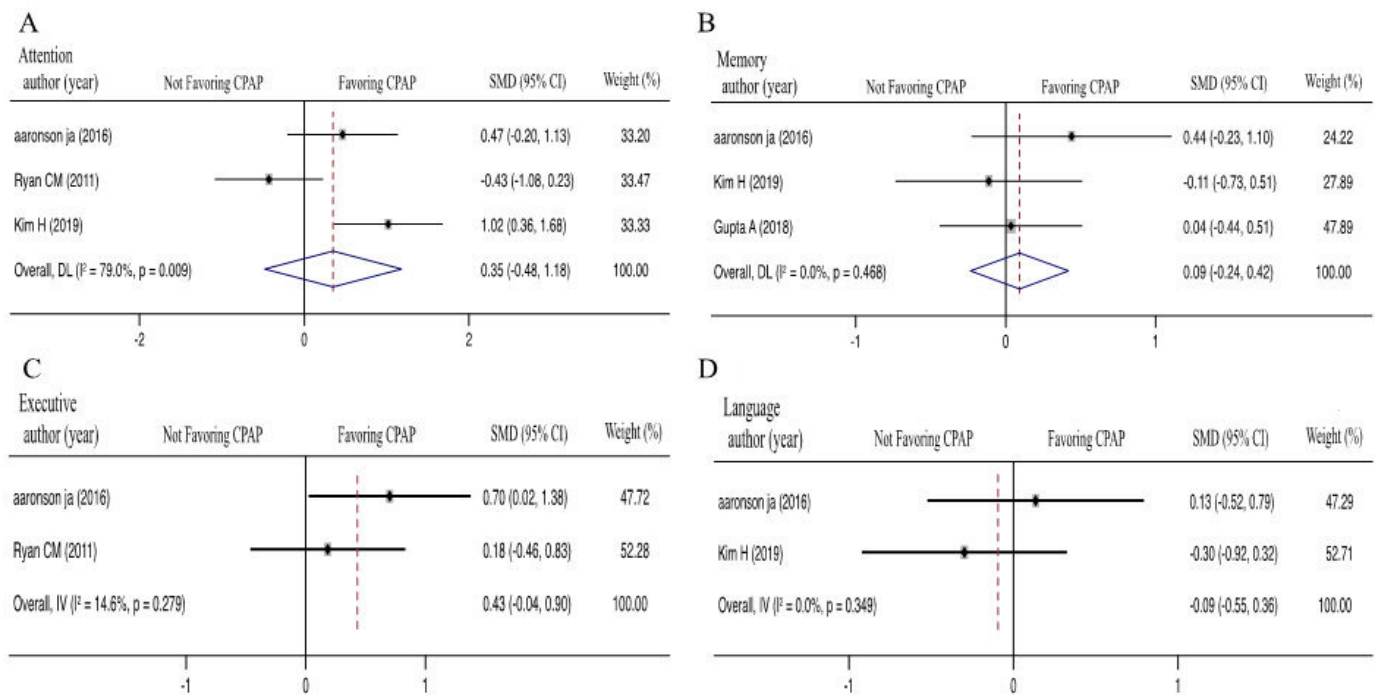
Figure 3 Forest plot of trials on the association of continuous positive airway pressure (CPAP) with global cognitive gain in stroke patients with obstructive sleep apnoea. SMD, standardised mean difference; IV, inverse variance.

domains (online supplemental table 5), including attention (SMD, 0.35; 95% CI, –0.48 to 1.18; p=0.409; I^2=79.0%; figure 5A), memory (SMD, 0.09; 95% CI, –0.24 to 0.42; p=0.583; I^2=0.0%; figure 5B), executive (SMD, 0.43; 95% CI, –0.04 to 0.90; p=0.071; I^2=14.6%; figure 5C) and language (SMD, –0.09; 95% CI, –0.55 to 0.36; p=0.685;

I^2=0.0%; figure 5D). As there was high heterogeneity in attention (I^2=79.0%), we performed a sensitivity analysis to assess the sources of heterogeneity, and found that, after removing the study by Ryan et al,[19] the heterogeneity was reduced from 79.0% to 25.2% without changing the null effect of CPAP therapy on attention. This heterogeneity
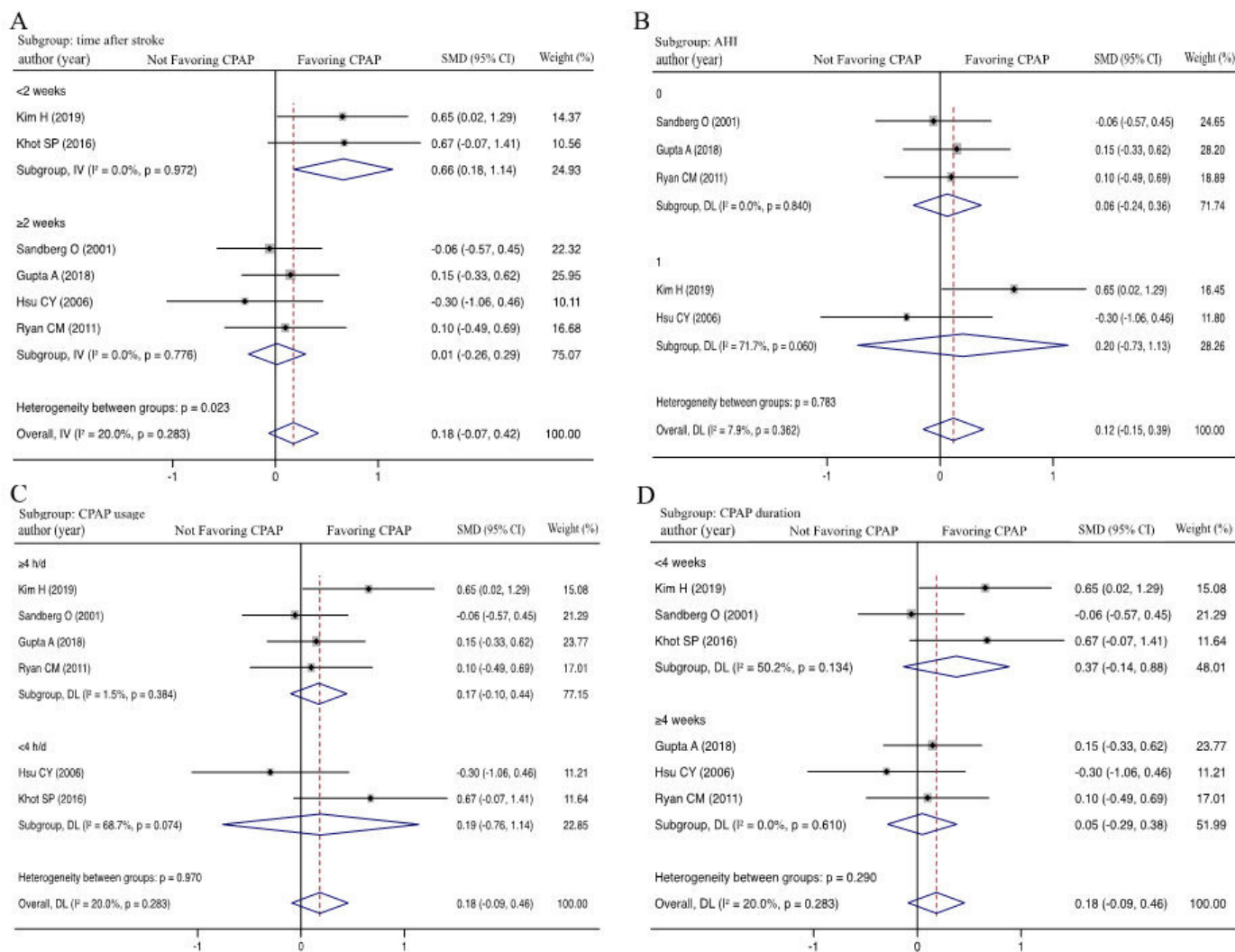
Figure 4 Forest plot of trials on the association of continuous positive airway pressure (CPAP) with global cognitive gain in stroke patients with obstructive sleep apnoea by subgroup analysis. SMD, standardised mean difference; IV, inverse variance; Dl, derSimonian-laird.

Figure 5 Forest plot of trials on the association of continuous positive airway pressure (CPAP) with specific cognitive domains in stroke patients with obstructive sleep apnoea. SMD, standardised mean difference; Dl, derSimonian-laird; IV, inverse variance.

might be due to methodologic differences (outcome parameters of attention testing).

Furthermore, 5 RCTs with 218 participants investigated subjective sleepiness. CPAP therapy significantly decreased the sleepiness scale score compared with that of the sham/control group (online supplemental table 6) (SMD, −0.73; 95% CI, −1.15 to −0.32; p≤0.001; I^2=52.5%; figure 6), which indicated improvement in subjective sleepiness by CPAP. A sensitivity analysis was performed to assess the source of heterogeneity. When the study by Aaronson *et al*[16] was removed, the heterogeneity decreased from 52.5% to 5.5% with a significant effect of CPAP on subjective sleepiness.

DISCUSSION

The effect of CPAP on global cognition after stroke

In this meta-analysis, CPAP treatment did not improve global cognition in stroke patients with OSA. However, a subgroup analysis indicated that CPAP therapy initiated within 2 weeks of stroke improved global cognitive functions, and this positive effect was not found when initiated after 2 weeks. More than 2 weeks from stroke onset was considered subacute or chronic stroke.[22] This result indicates that the initiation time of CPAP treatment may be related to global cognitive improvement in these patients. OSA can affect perfusion and oxygenation in the penumbra after stroke, which exacerbates neurological impairments and has adverse effects in poststroke outcomes.[10 23] It is possible that the early application of CPAP helps prolong the survival of the penumbra, which

leads to measurable cognitive improvements. In addition, delayed CPAP therapy could not have such positive effects on penumbra. Although the use of CPAP in the early stages of stroke is beneficial, many factors including the recognition and diagnosis of OSA or the acceptance of CPAP, limit its early use. In our meta-analysis, none of the included studies involved initiation of CPAP within 7 days after stroke, rendering it difficult for us to further explore the association of the CPAP initial time and cognitive effects. However, the severity of stroke could have restrained the early use of CPAP as it is possible that patients who started CPAP therapy after 2 weeks had more severe medical conditions, which limited the CPAP
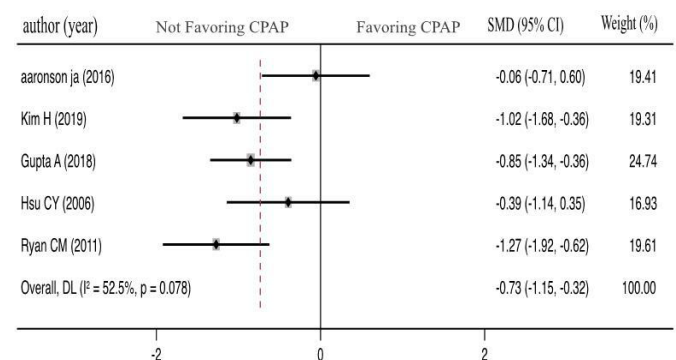
Figure 6 Forest plot of trials on the association of continuous positive airway pressure (CPAP) with subjective sleepiness in stroke patients with obstructive sleep apnoea. SMD, standardised mean difference; Dl, derSimonian-laird.

treatment within 2 weeks and led to inapparent improvements in global cognition.

Moreover, it is reported that the effectiveness of CPAP treatment in OSA is time dependent.[8 24] Previous studies have shown that continuous CPAP treatment for 3 months can increase the connectivity in the right middle frontal gyrus,[25] with limited effects in white matter.[8] In addition, after 6 months, the changes in white matter and cognition caused by OSA were observed to be fully reversed.[20] A previous study has also shown that whole night effectiveness could be achieved only when the duration of CPAP usage per night reached 6 hour.[26] These studies demonstrate that the more sufficient the treatment, the better the recovery. However, patients with stroke often have various neurological disabilities including hemiplegia, aphasia or neglect, which may reduce their tolerance and adherence to CPAP. In this meta-analysis, the median time of CPAP treatment in most trials was 4 hour/night and the duration was less than 3 months. The insufficient therapy time and duration may limit the benefits of CPAP. This may explain the null effects of CPAP on global cognitive gain in stroke patients with OSA and may be the reason for which the subgroup analyses of CPAP usage and duration were negative. Furthermore, a subgroup analysis based on OSA severity also showed no significant improvement in global cognition.

The effect of CPAP on specific cognitive domains after stroke

It has been proven that OSA can lead to impairment in many cognitive domains.[2] In several meta-analyses investigating the effect of CPAP therapy on OSA, CPAP treatment has been shown to only partially improve cognitive impairment in attention,[27] vigilance[28] or executive function[9 29] in OSA, and some effect is found only in populations with severe OSA.[9] However, in our meta-analysis, CPAP therapy had no significant improvement in executive function, attention, memory or language in stroke patients with OSA. It is known that in patients with stroke, the most common affected cognitive domains are attention and executive function[30] and the impairment of executive function might be persistent due to brain anoxia. As such, we speculate that the coexistence of stroke and OSA may counteract the therapeutic effect of CPAP on attention and executive functions in OSA alone. That said, it is worth noting that there are only a small number of studies included for each cognitive domain. In addition, a subgroup analysis could not be further performed, and the results as such should be interpreted with caution.

Implications for future research on the effect of CPAP on cognition after stroke

Although we found no significant improvement in global cognition and cognitive domains in stroke patients with OSA, we do not deny the role of CPAP treatment in stroke patients with OSA as the subgroup analysis showed that early initiation of CPAP had significant cognitive benefits. This sheds some light on the effect of CPAP on cognitive improvement in stroke with OSA. In this meta-analysis,

only 70 patients in 2 RCTs[14 15] initiated CPAP therapy within 2 weeks after stroke; this small proportion might conceal the positive effects on cognition. OSA is present in approximately 50%–75% of patients with stroke or transient ischaemic attack, and, despite the high prevalence, 70%–80% of OSA in stroke was not diagnosed and treated.[12] The included RCTs only represented a small portion of patients. The early use of polysomnography to identify these patients is important, as it can advance the use of CPAP treatment, including to hyperacute periods of stroke. Meanwhile, improving CPAP compliance to >4 hour/night and >3 months by respiratory care support should be considered in the future RCTs, as this might reveal the real effect of CPAP on cognition in stroke patients with OSA. Moreover, cognitive impairment has been reported in one-third of stroke survivors and there is no accepted consensus on cognitive assessment tools.[13]

Most of the included RCTs adopted the Mini-Mental State Examination (MMSE) or Addenbrooke's Cognitive Examination (ACE) to assess global cognition, while some used the cognitive component of the Functional Independence Measure. The latter, which is often adopted in patients who had a stroke, was simple and not as sensitive as MMSE or ACE, meaning potential cognitive improvement might have been missed. In addition, not all included RCTs have assessed specific cognitive domains. The nature of patients' cognitive alterations depends on the localisation of the lesion after stroke, and the evaluation of the specific cognitive domains may as such be more indicative. Moreover, in the RCTs, even for the same cognitive domain, different studies chose different tests for assessment according to the neuropsychological assessment categorisations. For example, the trail making test or sustained attention response time were suitable for attention assessment. In one RCT,[13] the author adopted two tests each to assess attention, memory and executive function, and combined the result in the analysis. We believe the different choices of tests for one domain did not affect the result of our meta-analysis and that the combined tests for one domain even increases the reliability of our study. However, in some cognitive domains, the related components of MMSE were used for analysis as no specific cognitive domain test was provided in the RCTs, which may have decreased the study accuracy. In the future, RCTs should focus on global cognition with more sensitive, available tools, fully assessing cognitive domains.

The effect of CPAP on subjective sleepiness after stroke

Daytime sleepiness is a common complaint of patients with OSA. CPAP treatment alleviates this symptom and helps with daytime function.[27] Similarly, our meta-analysis also showed that CPAP therapy decreases self-reported sleepiness in stroke patients with OSA. The improvement of subjective sleepiness might encourage these patients to participate in rehabilitation for stroke and lead to better outcomes, although we identified no global cognitive benefits. Moreover, the reduced daytime sleepiness might

increase the adherence to CPAP and finally contribute to cognitive improvement. Further study is necessary in this regard. In the future, not only subjective sleepiness but also objective sleepiness, quantified by the multiple sleep latency test and maintenance of wakefulness test, should be considered to minimise the influence of subjective feeling.

Limitations

There are some limitations to our meta-analysis. First, the sample size in each included study was relatively small and we could not carry out a subgroup analysis for specific cognitive domains. The recognition and diagnosis of OSA or acceptance of CPAP in patients who had a stroke may be difficult, and the evaluation of cognition in post stroke may be deficient, leading to a limited sample in each study. Second, a sensitive cognitive assessment scale, such as the MOCA, was not applied for global cognition, which could have masked the possible benefits of CPAP treatment in stroke patients with OSA. A previous study has shown that MOCA is more sensitive than MMSE, especially in mild cognitive impairment.[31] However, in the included RCTs, none had used MOCA to assess cognition. In addition, the scales related to cognitive assessment or subjective sleepiness were inconsistent between the RCTs. Third, in most RCTs, the screening sleep test for OSA was performed before CPAP treatment. However, one RCT conducted studies after the initiation of CPAP and combined the parameter of auto-titrating CPAP, which was a non-standardised method, although it is considered to have a similar accuracy as conventional polysomnography for diagnosing OSA.[32] Fourth, the included studies had a high risk of bias, especially regarding the blinding of participants and researchers and the inadequate description of other sources, which limited the methodological quality. Therefore, the results of this meta-analysis should be interpreted with caution.

CONCLUSION

In conclusion, our meta-analysis demonstrated that early initiation of CPAP therapy in poststroke patients with OSA could significantly improve global cognitive gain. However, the included data is not sufficient to draw a conclusion on the effect of CPAP on specific cognitive domains in these patients. Further trials should include higher number of stroke patients with OSA undergoing CPAP treatment and focus on prolonging CPAP therapy adherence.

ORCID iD
Lingxing Wang http://orcid.org/0000-0001-5208-1795

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