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Effect of continuous positive airway pressure therapy on stroke risk and rehabilitation in population with obstructive sleep apnea: A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Previous studies reported inconsistent results regarding the effect of continuous positive airway pressure (CPAP) therapy on stroke risk and rehabilitation in population with obstructive sleep apnea (OSA). The present study aimed to make a meta-analysis to explore the effect of CPAP therapy on stroke risk and rehabilitation in OSA. *Methods:* Articles published in English before March 2021 in the databases as follows: PubMed, Medline, Web of Science, EMBASE and Google Scholar. For the effect of CPAP therapy on risk of stroke. We computed the results of relative risk (RR) or hazard ratio (HR) and 95% confidence intervals (CIs) regarding the effect of CPAP therapy on risk of stroke. For the effect of CPAP therapy on stroke rehabilitation, the standardized mean differences (SMD) in change rates of National Institute of Health stroke scale (NIHSS) or Canadian Neurological Scale (CNS) scores with a 95% CI was obtained with STATA 12.0 software to estimate the treatment effect. *Results:* The study indicated no significant effect of CPAP therapy on stroke risk in patients with OSA (RR/HR = 0.67, 95% CI 0.39 to 1.16, I^2 = 84.1%, $p < 0.001$). However, the study showed a better neurological outcome in OSA patients with stroke treated with CPAP plus usual care, compared to those treated with usual-care (SMD = 0.45, 95% CI 0.03 to 0.87, I^2 = 73.9%, $p = 0.001$). *Conclusion:* The present study showed that CPAP therapy did not prevent stroke in patients with OSA. However, the study showed a neurofunctional improvement with CPAP therapy in OSA patients with stroke.

Keywords: Continuous positive airway pressure, meta-analysis, obstructive sleep apnea, stroke.

INTRODUCTION

As known, obstructive sleep apnea (OSA) is related to cardiovascular diseases (CVD) such as coronary artery disease, arrhythmia, hypertension, heart failure and stroke.[1] At present, continuous positive airway pressure (CPAP) is the most effective therapy for OSA.[2] CPAP therapy could improve the breathing pattern during sleep, resulting in improvement of health status and depressive symptoms.[3] In addition, meta-analyses showed that treatment with CPAP was associated with a significantly lower risk of major adverse cardiovascular event (MACE). Regarding the effect of CPAP therapy on stroke risk in OSA, Molnar *et al*. reported that CPAP treated OSA-positive patients showed decreased risk of stroke, compared to untreated OSA-positive patients.[4] However, other studies showed no significant effect of CPAP therapy on stroke risk in OSA.[5,6] The present study aimed to make a meta-analysis to explore the effect of CPAP therapy on stroke risk in OSA.

In addition, the estimated prevalence of OSA is 38% to 70% in stroke patients.[7] Some studies showed that CPAP treatment improves neurologic outcomes of stroke patients with OSA.[8,9] However, some studies showed no significant effect of CPAP treatment on rehabilitation in OSA.[10,11] The present study aimed to make a meta-analysis to explore the effect of CPAP therapy on stroke rehabilitation in OSA.

METHODS

This study was based on the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline.[12]

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Search strategy and selection criteria

Articles published in English before March 2021 in the databases as follows: PubMed, Medline, Web of Science, EMBASE and Google Scholar. These search terms: ('continuous positive airway pressure' OR 'CPAP') AND ('stroke') were used. After eliminating duplicates, 645 studies were included. For the effect of CPAP therapy on risk of stroke in population with OSA, we included cohort studies and randomized controlled trials (RCTs), reporting relative risk (RR) or hazard ratio (HR) and 95% CI associated with CPAP therapy and risk of stroke. For the effect of CPAP therapy on stroke rehabilitation in population with OSA, we included studies with randomized clinical trials (RCTs) design and investigating the influence of CPAP therapy on scores of National Institute of Health stroke scale (NIHSS) or Canadian Neurological Scale (CNS). We excluded meta-analyses, reviews and case reports.

Data extraction and analysis

STATA 12.0 software was applied to compute results extracted from included studies. The following data were extracted from included studies: Author, publication year, study type, subgroups, numbers of participants, information of included participants (age and gender), body mass index (BMI), apnea-hypopnea index (AHI), CPAP use time, follow-up years, events for analysis, adjustment factor and results. We used Q test and I^2 to evaluate heterogeneities between studies. When the heterogeneity was high (p value for Q test ≤ 0.05), we used random effects models as pooling methods; with low heterogeneity (p value for Q test > 0.05), fixed effects models were used as pooling methods. For the effect of CPAP therapy on risk of stroke, we computed the results (RRs or HRs and 95% confidence intervals (CIs) regarding the effect of CPAP therapy on risk of stroke). For the effect of CPAP therapy on stroke rehabilitation, the standardized mean differences (SMD) in change rates of NIHSS or CNS scores with a 95% CI was obtained with STATA 12.0 software to estimate the treatment effect. In addition, we applied subgroup analyses and meta-regression analyses to investigate source of the heterogeneity. We used sensitivity analysis to assess the stabilization of the study. Finally, we used Begg's test, Egger's test and funnel plot to assess publication bias.

RESULTS

Study selection and characteristics

Figure 1 illustrated the selection procedures and results. Characteristics of the finally included 18 studies were showed in Supplementary Tables 1 and 2. For the effect of CPAP therapy on risk of stroke, the study included 4 cohort studies[4,13-15] (including 3,006 OSA patients with CPAP treatment and 25,857 OSA patients without treatment) and 7 RCTs[5,6,16-20] (including 3,006 OSA patients with CPAP plus usual care treatment and 23,158 OSA patients with usual-care). In addition, the study included 7 RCTs.[8-11,21-23] including 190 OSA patients with CPAP plus usual care treatment and 191 OSA patients with usual-care to evaluate the effect of CPAP therapy on stroke rehabilitation in population with OSA.

Meta-analysis results

The study indicated no significant effect of CPAP therapy on stroke risk in patients with OSA (RR/HR = 0.67, 95% CI 0.39 to 1.16, $I^2 = 84.1\%$, $p < 0.001$, Figure 2). In addition, subgroup study showed no significant effect of CPAP therapy on stroke risk in patients with OSA in both RCTs and cohort studies (RCTs: HR = 0.91, 95% CI 0.68 to 1.22, $I^2 = 0.0\%$, $p = 0.532$; cohort studies: RR = 0.60, 95% CI 0.28 to 1.30, $I^2 = 87.0\%$, $p < 0.001$; Figure 3). Subgroup study showed that therapy with CPAP did not prevent stroke in patients with OSA in both Caucasian and Asian populations (Caucasian: RR/HR = 0.67, 95% CI 0.34 to 1.34, $I^2 = 87.4\%$, $p < 0.001$; Asian: RR/HR = 0.73, 95% CI 0.45 to 1.19, $I^2 = 0.0\%$, $p = 0.402$; Figure 4). Meta-regression analysis showed that gender, age, AHI and follow-up time were not responsible for heterogeneity across studies (gender: $p = 0.992$; age: $p = 0.698$; AHI: $p = 0.959$; follow-up time: $p = 0.673$). Sensitivity analysis showed no changes in direction of effect when any one study was excluded in the meta-analysis (Supplementary Figure 1. A). No significant risk of publication bias was showed for the meta-analysis by Begg's test, Egger's test and funnel plot (Begg's test: $p = 0.213$; Egger's test: $p = 0.125$; Supplementary Table 2. A).

The study showed a better neurological outcome in OSA patients with stroke treated with CPAP plus usual care, compared to those treated with usual-care (SMD = 0.45, 95% CI 0.03 to 0.87, $I^2 = 73.9\%$, $p = 0.001$; Figure 5). Sensitivity analysis showed no changes in direction of effect when any one study was excluded in the

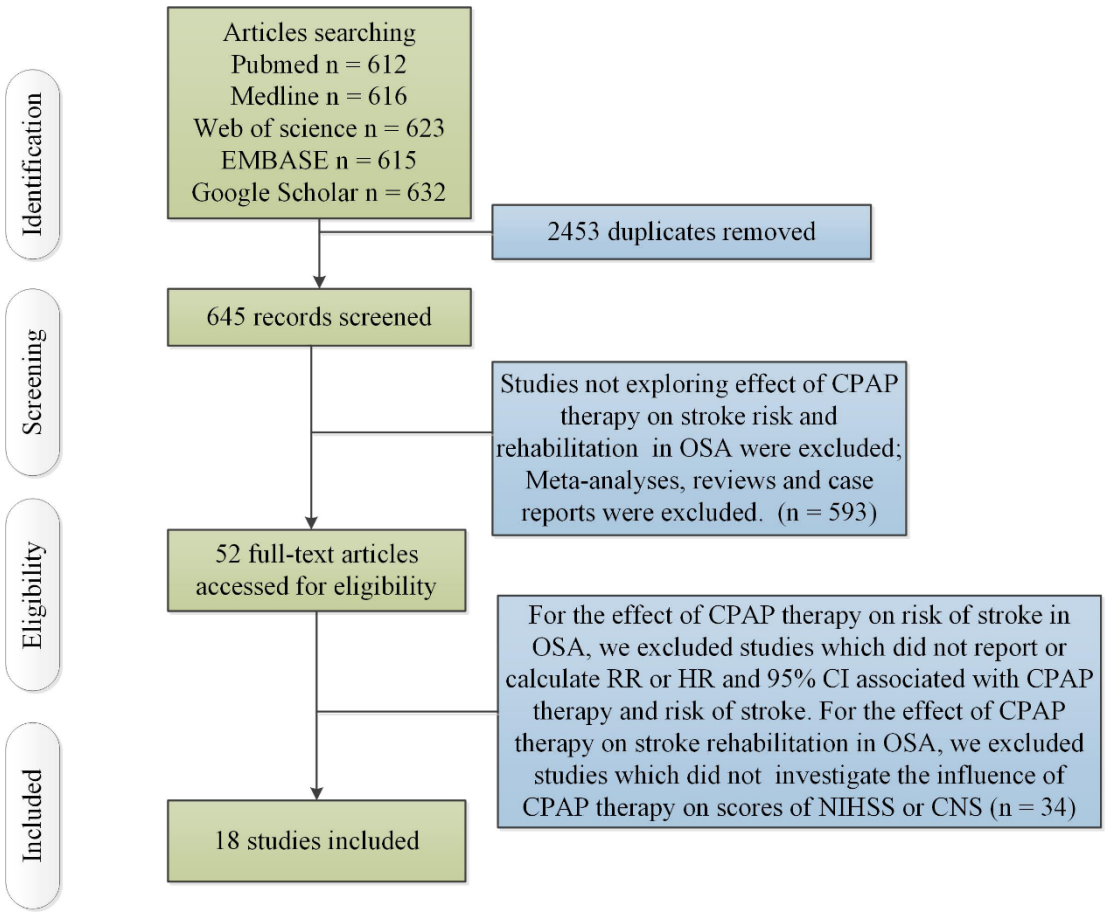

Figure 1. Flow of information through the different phases of a meta-analysis. Abbreviations: CI, confidence interval; CNS, Canadian Neurological Scale; CPAP, continuous positive airway pressure; HR, hazard ratio; NIHSS, National Institute of Health stroke scale; OSA, obstructive sleep apnea; RR, relative risk.

meta-analysis (Supplementary Figure 1. B). No significant risk of publication bias was showed for the meta-analysis by Begg's test, Egger's test and funnel plot (Begg's test: p = 0.881; Egger's test: p = 0.109; Supplementary Table 2. B).

DISCUSSION

The present study showed no significant effect of CPAP therapy on stroke risk in patients with OSA. However, the study showed a better neurological outcome in OSA patients with stroke treated with CPAP plus usual care, compared to those treated with usual-care.

Regarding the effect of CPAP therapy on stroke risk in OSA, the present study showed that CPAP therapy did not prevent stroke in patients with OSA. The present study included 4 cohort studies and 7 RCTs. A previous meta-analysis with cohort studies showed that treatment with CPAP was associated with a lower incidence of stroke (RR: 0.27, 95%CI: 0.14-0.5).[24] But this result could not be reproduced in the RCTs and the studies using administrative data.[24] Molnar *et al*. reported that CPAP treated OSA patients showed decreased risk of stroke, compared to untreated OSA patients in a cohort study.[4] RCTs were with shorter follow-up period than cohort studies and showed limited power to evaluate the effect of CPAP on stroke separately.[17] However, meta-regression analysis in the present study showed no effect of follow-up period on the heterogeneity between included studies. Additionally, in some studies, OSA patients with CPAP therapy might show more severe OSA, compared to untreated group.[25] Thus, more prospective studies were essential to explore the effect of CPAP therapy on stroke risk in OSA.

Additionally, this study showed a neurofunctional improvement with CPAP therapy in OSA patients with stroke. This result correspond to a recent meta-analysis including

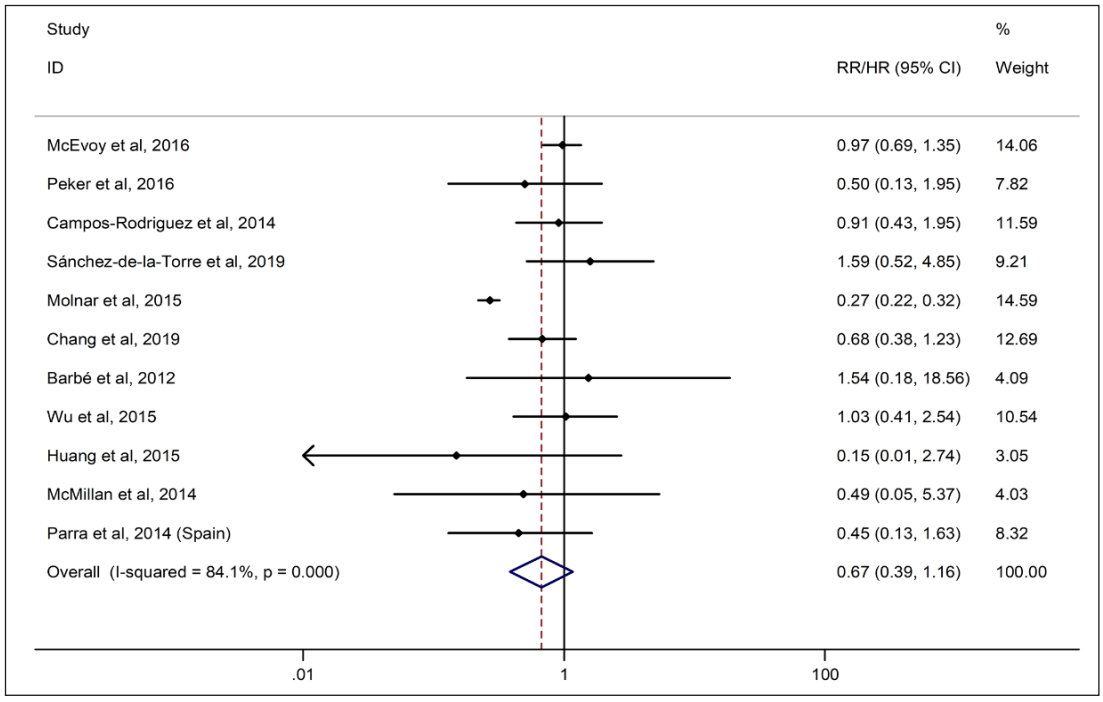

Figure 2. Forest plots regarding effect of CPAP therapy on stroke risk in patients with OSA. Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio; OSA, obstructive sleep apnea; RR, relative risk.

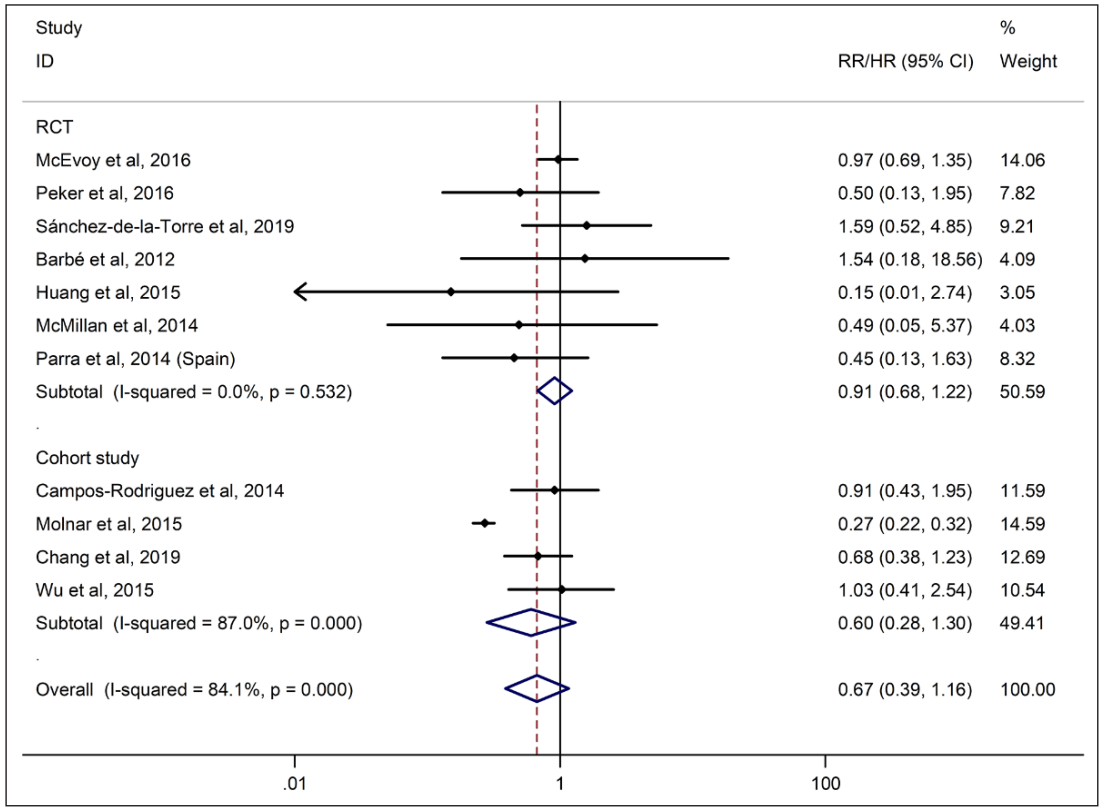

Figure 3. Subgroup studies regarding effect of CPAP therapy on stroke risk in patients with OSA in RCTs and cohort studies. Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio; OSA, obstructive sleep apnea; RR, relative risk.

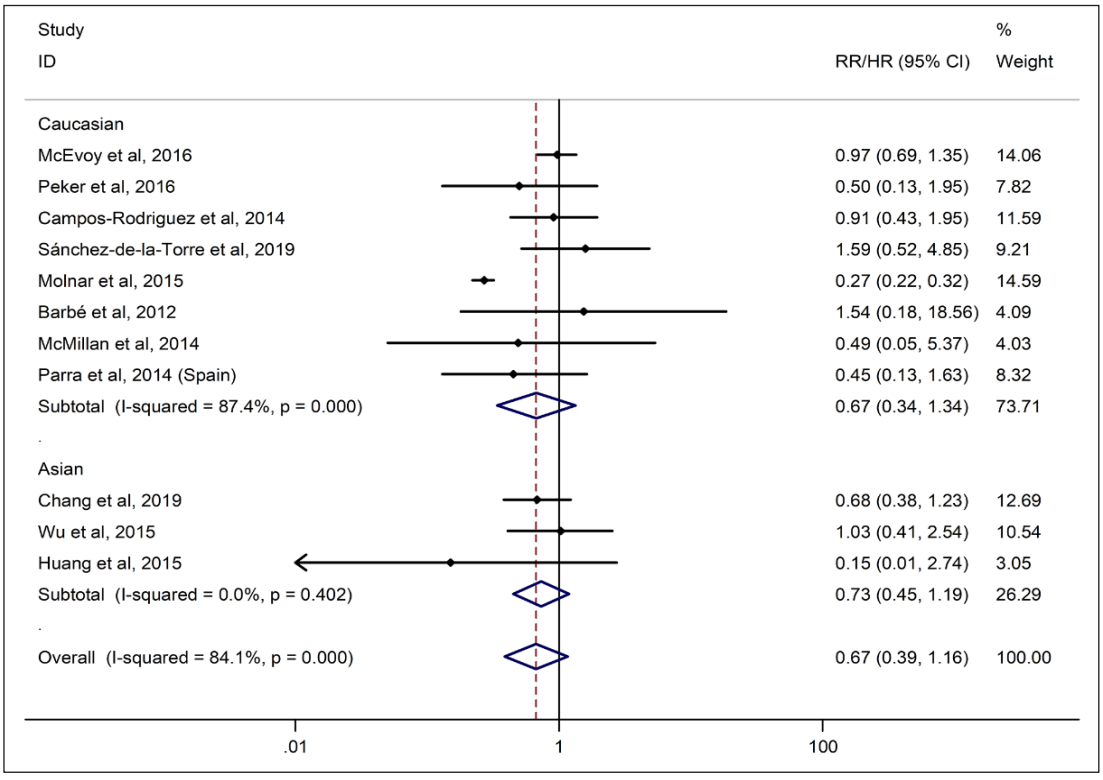

Figure 4. Subgroup studies regarding effect of CPAP therapy on stroke risk in patients with OSA in Caucasian and Asian populations. Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio; OSA, obstructive sleep apnea; RR, relative risk.

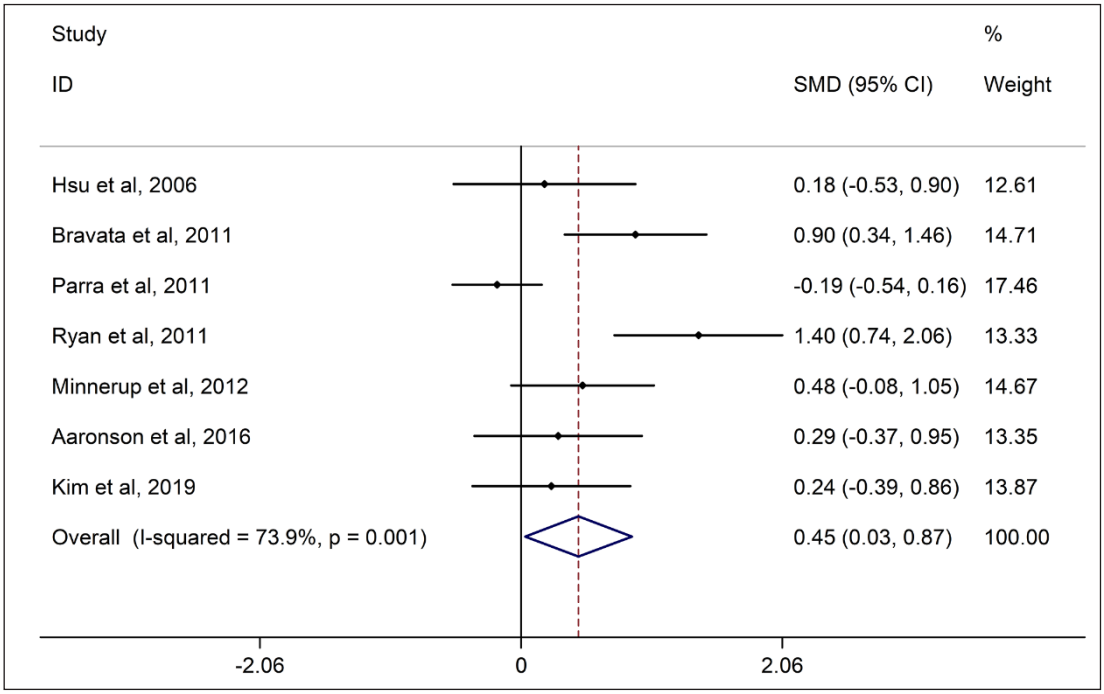

Figure 5. Forest plots regarding neurological outcome in OSA patients with stroke treated with CPAP plus usual care, compared to those treated with usual-care. Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; SMD, standardized mean difference.

6 RCTs, which showed that neurofunctional scales (NIHSS and CNS) showed an overall neurofunctional improvement with CPAP (SMD 0.5406, 95% CI 0.0263-1.0548) but with a considerable heterogeneity (I^2 = 78.9%, p = 0.0394) across the studies.[26] OSA after stroke might have an influence on oxygenation and perfusion of the penumbra, which might adversely affect stroke outcome.[26,27] The early use of CPAP might prolong survival of the penumbra, resulting in clinical and imaging improvement in stroke patients. Additionally, the use of continuous CPAP therapy could independently result in improving cognitive deficit and depression, leading to better participation of stroke patient in the rehabilitation program, which result in a more positive impact on recovery after stroke.[23]

There are some limitations in the present study. Firstly, regarding the effect of CPAP therapy on stroke risk in OSA, the amount of included studies was limited to explore the sources of heterogeneities. Secondly, regarding the effect of CPAP therapy on stroke rehabilitation in OSA, the number of included studies was small.

In conclusion, the present study showed that CPAP therapy did not prevent stroke in patients with OSA. However, the study showed a neurofunctional improvement with CPAP therapy in OSA patients with stroke.

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Supplementary Table 1. Characteristics of 11 studies regarding effect of CPAP therapy on stroke risk in patients with OSA

References (country)	Study type	Group	Sample Size (male %)	Mean Age	Apnea-hypopnea index/h, mean (SD)	Follow-up(years), median	Events for analysis	Cases	Adjustment factor	Results
McEvoy *et al.*[1] 2016, (Asia, Australia, Europe, North and South America)	RCT	CPAP	1346 (81.1%)	61.3	29.0 (15.9)	3.7	Incident stroke	67	NR	HR: 0.97 (0.69–1.35)
		Usual-Care	1341 (80.7%)	61.2	29.6 (16.4)			68		
Peker *et al.*[2], 2016 (Sweden)	RCT	CPAP	122 (82.0%)	65.5	28.3 (12.7)	4.75	Incident stroke	3	NR	HR: 0.50 (0.13-1.95)
		Usual-Care	122 (86.1%)	66.5	29.3 (14.0)			6		
Campos-Rodriguez *et al.*[3], 2014 (Spain)	Cohort study	AHI <10	258 (0)	52	4	6.8	Incident stroke	10	age, BMI, hypertension, type 2 diabetes mellitus, atrial fibrillation	RR: AHI ≥10 &Untreated: 2.76 (1.35-5.62) AHI ≥10 & CPAP: 0.91 (0.43-1.95)
		AHI ≥10 & Untreated	268 (0)	49	24			38		
		AHI ≥10 & CPAP	441 (0)	58	42.8			23		
Sánchez-de-la-Torre *et al.*[4], 2019 (Spain)	RCT	CPAP	629 (84%)	59.9	36.4 (18.6)	3.35	Incident stroke	8	NR	HR: 1.59 (0.52-4.85)
		Usual-Care	626 (85%)	60.7	35.5 (18.3)			5		
Molnar *et al.*[5], 2015 (USA)	Cohort study	OSA(-)	3056272 (93%)	61	NR	7.74	Incident stroke	50333	age, gender, race/ethnicity, baseline eGFR, comorbidities at baseline, measures of quality of care, income, marital status, BMI	HR: OSA(+)&Untreated: 3.48 (3.28-3.64) OSA(+)&CPAP: 3.50 (2.92-4.19)
		OSA(+)& Untreated	21764 (96%)	59				1601		
		OSA(+)& CPAP	1478 (96%)	57				122		

Supplementary Table 1. Characteristics of 11 studies regarding effect of CPAP therapy on stroke risk in patients with OSA

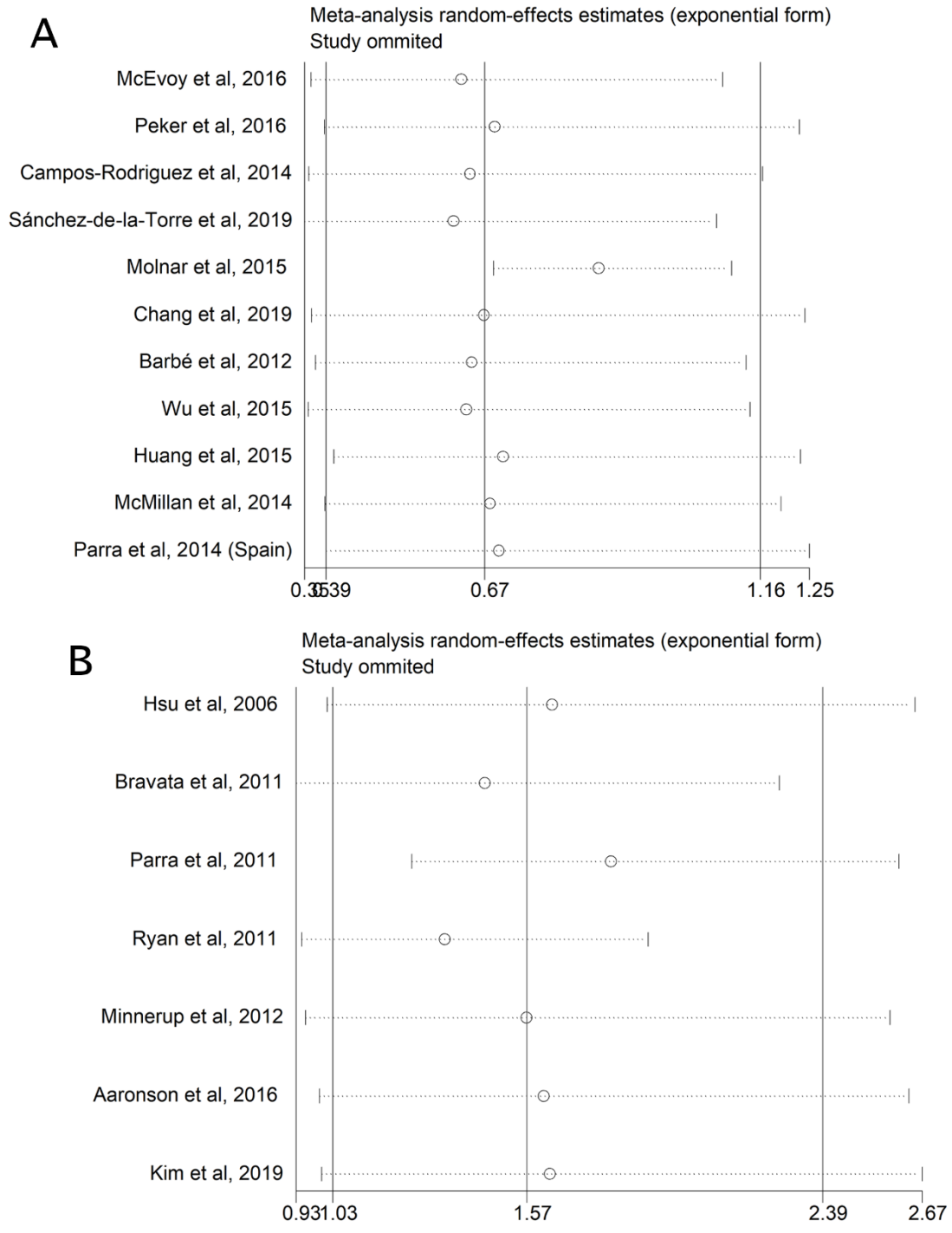
References (country)	Study type	Group	Sample Size (male %)	Mean Age	Apnea-hypopnea index/h, mean (SD)	Follow-up(years), median	Events for analysis	Cases	Adjustment factor	Results
Chang *et al.*[6], 2019 (China, Taiwan)	Cohort study	CPAP	959 (83.2%)	51.1	NR	4.97	Incident stroke	18	gender, age, urbanization degree, baseline comorbidities	RR: 0.68 (0.38-1.23)
		Usual-Care	959 (82.5%)	51.3		5.19		29		
Barbé *et al.*[7], 2012 (Spain)	RCT	CPAP	357 (87.7%)	52.0	42	4	Incident stroke	3	NR	HR: 1.54 (0.18-18.56)
		Usual-Care	366 (83.6%)	51.8	35			2		
Wu *et al.*[8], 2015 (China)	Cohort study	AHI ≥15 &Untreated	167 (85.6%)	56	40.1	4.8	Incident stroke	14	NR	RR: 1.03 (0.41-2.54)
		AHI ≥15 &CPAP	128 (82.8%)	54	46.3			11		
Huang *et al.*[9], 2015 (China)	RCT	Control	37 (86.5%)	62.7	28.7 (12.4)	3	Incident stroke	3	NR	HR: 0.15 (0.01-2.74)
		CPAP	36 (77.8%)	62.0	28.3 (13.0)			0		
McMillan *et al.*[10], 2014 (UK)	RCT	Control	138 (79%)	71.3	NR	1	Incident stroke	2	NR	HR: 0.49 (0.05-5.37)
		CPAP	140 (86%)	70.9				1		
Parra *et al.*[11], 2015 (Spain)	RCT	Control	69 (69.6%)	65.5	NR	4.53	Incident stroke	8	NR	HR: 0.45 (0.13-1.63)
		CPAP	57 (71.9%)	63.7				3		

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio; NR, not reported; OSA, obstructive sleep apnea; RCT, randomized clinical trial; RR, relative risk.

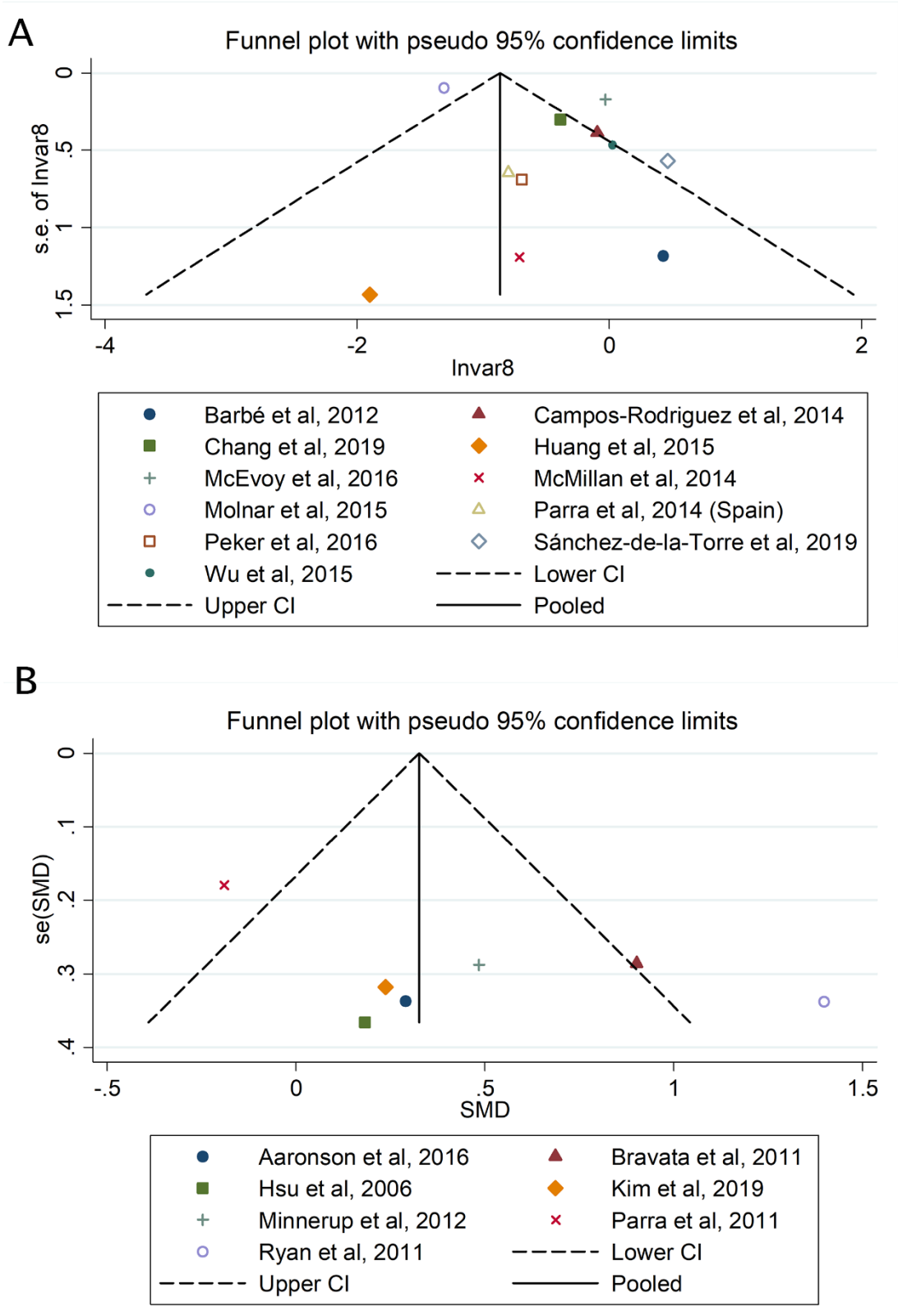
Supplementary Table 2. Characteristics of 8 studies regarding the effect of CPAP therapy on stroke rehabilitation in OSA

References (country)	Study type	Group	Sample Size (male %)	Mean Age	BMI, kg/m^2	Apnea-hypopnea index/h, mean (SD)	CPAP use, h/night	Follow-up(years), median	Events for analysis	Results
Hsu *et al.*[12], 2006 (UK)	RCT	CPAP	15 (73.3%)	74 (73-81)	26.8 (21.9-28.5)	43.1 (35.6-51.8)	1.4	6 mo	NIHSS	NIHSS: Baseline: 5 (4–9) vs. 6 (5–8) Outcome: 2 (1–4) vs. 3 (1–6);
		Usual-Care	15 (60%)	73 (65-77)	25.1 (22.1-33.1)	47.7 (36.5-60.2)	Median 0.16 over 8 wk			
Bravata *et al.*[13], 2011 (USA)	RCT	CPAP	31 (67.7%)	70.6 ± 9.4	26.8 ± 4.3	NR	5.10 (4.49–5.71)	30 d	NIHSS, recurrent events	NIHSS: 3.0↓vs. 1.0↓; recurrent events: 1 (3.2) vs. 3 (12.5)
		Usual-Care	24 (66.7%)	71.6 ± 13.3	29.4 ± 7.2	NR				
Parra *et al.*[14], 2011 (Spain)	RCT	CPAP	57 (71.9%)	63.7 ± 9.1	30.2 ± 4.6	NR	5.3 (4.99–5.61)	24 mo	RS Canadian Neurological Scale	RS↓: 90.9% vs. 56.3%; Canadian Neurological Scale: Baseline: 8.3 (1.6) vs. 8.0 (1.9); Outcome: 9.3 (1.3) vs. 9.5 (1.0)
		Usual-Care	69 (69.6%)	65.5 ± 9.1	28.8 ± 4	NR				
Ryan *et al.*[15], 2011 (Canada)	RCT	CPAP	22 (72.7%)	62.8 ± 12.8	28.8 ± 5.3	38.5 ± 18.1	4.96 (4.32-5.60)	4 wk	Canadian Neurological scale	Canadian Neurological scale: Baseline: 7.3 (1.9) vs. 7.7 (1.9) Outcome: 9.6 (1.7) vs. 8.4 (1.5);
		Usual-Care	22 (86.4%)	60.7 ± 10.3	27.3 ± 5.8	33.3 ± 16.4				
Minnerup *et al.*[16], 2012	RCT	CPAP	25 (36%)	68.6 (10.0)	27.8 (2.5)	NR	4.2 (3.79–5.61)	8 nights	NIHSS	NIHSS: 2.00 (0.82) ↓ vs. 1.40 (1.53) ↓
		Usual-Care	25 (40%)	63.4 (10.5)	26.7 (3.1)	NR				
Aaronson *et al.*[17], 2016	RCT	CPAP	20 (60%)	61.1 ± 8.2	28.1 ± 6.4	34.2 ± 14.8	2.50 (1.59–3.41)	2 mo	NIHSS	NIHSS: 3.50 (3.28) ↓ vs. 2.19 (2.71) ↓
		Usual-Care	16 (62.5%)	56.7 ± 8.8	25.8 ± 4.7	NR				
Kim *et al.*[18], 2019	RCT	CPAP	20 (65%)	63.3 ± 13.1	23.3 ± 3.7	44.4 ± 16.8	>4	3-week	NIHSS	NIHSS: 1.5 ± 1.3↓vs. 1.1 ± 1.5↓
		Usual-Care	20 (80%)	66.9 ± 12.3	24.4 ± 3.9	34.9 ± 17.2				

Abbreviations: BMI, body mass index; CI, confidence interval; CNS, Canadian Neurological Scale; CPAP, continuous positive airway pressure; NIHSS, National Institute of Health stroke scale; NR, not reported; OSA, obstructive sleep apnea; RCT, randomized clinical trial; RS, Rankin scale; SD, standard deviation.



Supplementary Figure 1. Sensitivity analysis regarding effect of CPAP therapy on stroke risk (A) and rehabilitation (B) in patients with OSA. Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.



Supplementary Figure 2. Funnel plots regarding effect of CPAP therapy on stroke risk (A) and rehabilitation (B) in patients with OSA. Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

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